



# Good overall behavioural adjustment in children and adolescents with classic congenital adrenal hyperplasia

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## Abstract

**Purpose** Patients with classic congenital adrenal hyperplasia (CAH) are treated postnatally with life-long glucocorticoid (GC) replacement therapy. Although prolonged exposure to GCs may have a negative impact on behaviour, few studies have studied this issue. We therefore investigated behavioural outcomes in male and female children and adolescents with CAH.

**Methods** An observational study in which Swedish and Italian children and adolescents with CAH identified through neonatal screening for CAH ( $n = 57$ , age range 7–17 years) were compared with healthy population controls matched for age and sex ( $n = 72$ , age range 7–17 years). Thirteen (eight females) of the fifty-seven children and adolescents with CAH had been treated prenatally with dexamethasone (DEX). Standardised questionnaires for parents and self-report scales for children/adolescents were used to assess behavioural and emotional problems, social anxiety, temperament and scholastic competence.

**Results** There were no statistically significant differences between CAH patients (not prenatally treated with DEX) and controls on most of the scales measuring adaptive functioning or behavioural problems. However, children with CAH were rated by their parents to have more social problems than controls (Child Behaviour Checklist, CBCL social problems,  $p = 0.032$ ). In the small group ( $n = 13$ ) of prenatally DEX-treated cases parents rated their children/adolescents to have more mood problems compared with non-DEX-treated children/adolescents with CAH (CBCL-withdrawn/depressed,  $p = 0.019$ ).

**Conclusion** Children/adolescents with CAH showed good overall adjustment. The clinical significance of the parentally perceived increase in social problems in children/adolescents with CAH requires further investigation. The findings underline the importance of psychological support for children/adolescents with a chronic condition.

**Keywords** Behaviour · Cognition · Congenital adrenal hyperplasia · Glucocorticoid · Dexamethasone · Prenatal treatment

## Abbreviations

CAH	Congenital adrenal hyperplasia
DEX	Dexamethasone
21OHD	21-Hydroxylase deficiency
GC	Glucocorticoid
GR	Glucocorticoid receptor
SW	Salt-wasting
SV	Simple virilising
HC	Hydrocortisone

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## Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorder. The most common variant, caused by 21-hydroxylase deficiency, occurs in 1:10,000–1:15,000 live births. CAH is characterised by impaired synthesis of cortisol and aldosterone in the adrenal cortex with a

consequent increase in adrenal androgens [1, 2]. In the more severe classic CAH (salt-wasting, SW and simple virilising, SV) the increased production of androgens leads to virilisation of external genitalia in affected girls already in utero [3, 4].

Neonatal screening programmes for CAH have been instituted in Sweden and in many other countries worldwide to facilitate early diagnosis and prevent salt-losing crises and death in neonates [5–7]. Consequently, life-long replacement therapy with hydrocortisone (HC) and mineralocorticoid is already started in the second week of life [1, 8]. However, because of difficulties in mimicking the normal circadian cortisol rhythm with conventional glucocorticoid (GC) treatment, there is a risk of both over- and under-treatment during an individual's lifespan. A dysregulated or flattened rhythm may be related to behavioural changes and mental health symptoms in children during childhood and early adolescence [9–12].

GCs act via the mineralocorticoid receptor and glucocorticoid receptor. These receptors are highly expressed in the prefrontal cortex, which is linked to regions of the brain (e.g. amygdala, hippocampus and cerebellum) involved in emotional behaviour and stress responses [13, 14]. A few studies investigating structural brain differences in adolescents and adult patients with CAH have reported white matter impairment in the corpus callosum, cerebellum and amygdala, regions that play an important role in emotional regulation. These studies have also reported abnormalities in the hippocampus, a brain region also involved in the regulation of stress and the hypothalamic–pituitary–adrenal axis [15, 16]. A functional magnetic resonance imaging study of the brain reported altered amygdala function in response to negative stimuli (angry and fearful facial expression) in girls with CAH, suggesting impairments in social cognition that may negatively affect social interactions [17].

Studies on behavioural outcomes in children and adolescents with CAH are scarce but the few studies that exist have focused on the effects of prenatal androgen exposure on behaviour in girls and women with CAH. Females with CAH spend more time in male-typical activities in adolescence [18, 19]. Moreover, they are reported by their mothers to be more aggressive and active than their unaffected sisters [20]. These studies support the view that prenatal androgen exposure has a direct organisational effect on the human brain to determine certain aspects of sex-typed behaviour. The majority of girls with CAH, however, have a female-typical gender identity [21].

In addition, epidemiological studies have shown that girls and women with CAH [22], but also men with CAH [23], have substance misuse, mood and anxiety disorders and an increased risk of psychiatric disorders. An increased rate of suicide or suicide attempts has also been reported in men with CAH [24].

Depression [25] and anxiety [26] have been reported in children and adolescents with Cushing's syndrome, a disease characterised by prolonged exposure to elevated levels of GCs [27]. Of note, the incidence of mood-related problems in patients with Cushing's syndrome seems to correlate with the degree and timing of GC exposure [28]. Patients with Cushing's syndrome showed significant improvement in depression and anxiety scores after a reduction of cortisol levels.

Another aspect of the clinical management of CAH concerns prenatal treatment. Since the mid-1980s, in many medical centres worldwide prenatal treatment of CAH with dexamethasone (DEX) has been practised to reduce the in utero virilisation in affected girls. Although effective, the treatment is still controversial because of uncertainties regarding its long-term safety [29–31]. In our previous work on a cohort of DEX-treated children and adolescents in the age range of 7–17 years (with and without CAH) no differences were found in parent-reported behavioural problems compared with population controls. However, DEX-treated children and adolescents scored themselves as having more social anxiety [32, 33]. Conversely, we found that healthy children and adolescents treated during the first trimester with DEX were well adjusted [34].

Living with a child with a chronic condition may also affect parenting behaviour and the parent–child relationship, both of which play an important role in the psychological development of the child. Parental overprotection has been related to poor child adjustment and negative health outcomes (decrease in autonomy, depression and anxiety) [35–37]. Studies on women with CAH show that the disease had an influence on their upbringing with a feeling of being overprotected by their parents and that it may affect their schooling because of frequent hospital visits and the inability to attend physical education classes [38].

Thus, the primary purpose of this study was to assess the behavioural outcomes in a cohort of girls and boys with classic CAH who were diagnosed through national neonatal screening programmes for CAH in Sweden and Italy. In addition, we sought to determine some behavioural outcomes in a small cohort of children and adolescents with CAH who were prenatally treated with DEX.

## Methods

### Recruitment and participants

This study is part of a longitudinal study investigating short- and long-term effects of prenatal treatment with DEX in fetuses at risk of CAH and effects of postnatal chronic GC treatment in patients with CAH (PREDEX study) [31, 34, 39–41]. In this study we include patients from both

Sweden and Italy. We focus on the behavioural outcome of children and adolescents with classic CAH and also observe a small group of patients with CAH who were treated prenatally with DEX (boys during the first trimester and girls during the entire gestational period).

All individuals were initially contacted by letter along with information about the study. All those willing to participate gave their written informed consent to take part in the study. Swedish patients were recruited throughout Sweden to minimise selection bias; healthy controls were enlisted from Stockholm County through the Swedish population registry. All the Swedish participants received reimbursement of 50 euros. Italian patients were recruited from the Emilia-Romagna region and the controls from a group of healthy siblings to patients with CAH. All patients and controls were matched for sex and age. The study was approved by the Regional Ethics Committee in Stockholm and the Ethic Committee of the University of Bologna. The participation rate was 81% for the CAH cohort and 55% for the controls.

In total, the CAH cohort comprised 44 children and adolescents with CAH not prenatally treated with DEX (CAH: 22 boys (seven Italian), 22 girls (five Italian)) and 13 children/adolescents with CAH prenatally treated with DEX (CAH-DEX: five boys and eight girls (two Italian)). The control group included 72 individuals (34 boys (one Italian), 38 girls (one Italian)); of these, eight were healthy siblings of five patients with CAH included in the study). All participants were between 7 and 17 years old.

All patients with CAH were identified through the Swedish or Italian neonatal screening programmes for CAH (30 had SW CAH and 14 SV CAH). Among the patients with CAH, 14 had a null genotype (completely abolished 21-hydroxylase activity). All patients were treated with HC.

Group-specific demographic data are presented in Table 1. Age and parental education did not differ between the CAH, CAH-DEX and control groups. We show length in centimetres (cm) and birth weight in grams (g), adjusted for country of origin. Moreover, length and weight at birth were converted into *z*-scores according to the Swedish and Italian population-based longitudinal reference values [42, 43]. Children and adolescents with CAH (without prenatal treatment) were longer at birth than population controls ( $p = 0.022$ ); girls treated with DEX during the entire gestational period were born significantly smaller ( $p = 0.019$ ) than CAH girls not treated prenatally (Table 1).

## Outcome measures

The questionnaires were completed by the parents and their children when visiting the clinical psychologists.

Consequently, they had the opportunity to ask for clarification of items, as recommended in the manual [44].

## Parent-completed questionnaires

Data to assess behavioural problems, social phobia and temperament were obtained using three parental ratings: The Child Behaviour Checklist for ages 4–18 years (CBCL/4–18), the Social Phobia and Anxiety Inventory for Children—Parent Report (SPAI-C-P) and the Emotionality–Activity–Sociability–Shyness Temperament Survey for children (EAS).

The CBCL/4–18 is an 113-item standardised parental–child instrument for psychiatric screening providing both broadband and narrowband scales. It was used to quantify not only internalising and externalising problems, as well as specific subscales, such as depressive, social and attention problems, but also delinquent and aggressive behaviours [44]. The CBCL total competence score, which measures adaptive functioning, is a sum of scores from three subscales: (1) Activities scale—the number, amount and quality of the child’s participation in different leisure activities and everyday tasks; (2) Social scale—participation in social activities, number of close friends and weekly contact with them; and (3) School scale—(e.g. academic performance and need for a special class or support) [44].

The SPAI-C-P is a 26-item parent-report measure covering cognitive, physiological and behavioural symptoms of social phobia according to the DSM-IV classification system [45, 46]. The SPAI-C-P includes subscales for ‘Public Performance’, ‘Assertiveness/General Conversation’ and ‘Traditional Social Encounters’.

Temperament was quantified using the parent-reported EAS with subscales describing four dimensions of temperament: Sociability, Activity, Shyness and Emotionality [47].

## Child-completed questionnaires

The Social Anxiety Scale for Children Revised (SASC-R), a self-reported scale for children, was used to assess children’s self-perception of social anxiety and avoidance [48, 49]. The scale is divided into three subscales: Fear of Negative Evaluation (SASC-FNE)—fear of negative evaluation from peers; Social Avoidance and Distress in new social situations or with unfamiliar peers (SAD-New); and Social Avoidance and Distress in general situations (SAD-General).

Children and adolescents also estimated their scholastic ability by completing the Scholastic Competence subscale from the Self-Perception Profile for Children [50]. The questionnaire includes school-related items reflecting the children’s perception of their competence at school.

**Table 1** Demographic data for the three study groups: patients with CAH not treated prenatally with DEX (CAH), patients with CAH treated prenatally with DEX (CAH-DEX) and population controls (C)

	Females			Males			<i>p</i> (CAH) CAH vs. C	<i>p</i> (DEX) CAH-DEX vs. CAH (f)	<i>p</i> (DEX) CAH-DEX vs. CAH (m)
	CAH	CAH-DEX	C	CAH	CAH-DEX	C			
Number of participants	22 <sup>a</sup>	8 <sup>b</sup>	38 <sup>c</sup>	22 <sup>d</sup>	5	34 <sup>e</sup>			
Age (Mean (SD))	10.8 (3.1)	11.1 (3.5)	10.7 (2.8)	12.3 (3.0)	11.5 (0.9)	10.7 (2.2)	0.099	0.852	0.561
Parental higher education (%) <sup>f</sup>	33.3	42.9	64.9	70.6	40.0	62.5	0.218	0.647	0.218
Birth length <sup>g</sup> (cm)	50.6 (3.5)	46.7 (4.0)	49.1 (3.1)	51.5 (2.1)	51.6 (3.2)	50.1 (2.8)	<b>0.022</b>	<b>0.016</b>	0.949
Birth weight <sup>h</sup> (g)	3496.0 (733.0)	2743.7 (757.0)	3245.2 (616.7)	3606.9 (399.1)	3663.0 (752.0)	3488.2 (678.1)	0.092	<b>0.019</b>	0.988
Mean (SD)									
Birth length (z-score)	0.6 (1.9)	-1-1 (1.5)	-0.2 (1.3)	0.4 (1.3)	-0.2 (1.6)	-0.4 (1.5)	<b>0.010</b>	<b>0.030</b>	0.410
Birth weight (z-score)	0.3 (0.6)	-0.4 (0.7)	-0.2 (0.6)	0.1 (0.6)	-0.1 (0.5)	0.0 (0.7)	<b>0.019</b>	<b>0.015</b>	0.562
Gestational week (SD)	39.1 (2.2)	37.5 (2.6)	39.1 (2.2)	39.7 (2.0)	40.3 (1.1)	39.7 (2.0)	0.505	0.300	0.322
HC (mg/m <sup>2</sup> ) (Mean (SD))	12.5 (3.9)	11.5 (4.0)	NA	13.6 (4.7)	14.6 (2.5)	NA		0.576	0.531

Significant *p* values are marked in bold*HC* hydrocortisone dose, *SD* standard deviation, *N/A* not applicable<sup>a</sup>Five Italian<sup>b</sup>Two Italian<sup>c</sup>One Italian<sup>d</sup>Seven Italian<sup>e</sup>One Italian<sup>f</sup>Education at the university level (%)<sup>g,h</sup>*p* values adjusted for country of origin. Statistical analyses for differences between groups were calculated using Fisher's exact test (two-sided)

## Statistical analysis

Multiple linear regression analyses were applied to analyse the role of diagnostic status (CAH, CAH-DEX, control), sex, age, parental education and city of origin on behavioural outcomes (dependent variables). The alpha level was set at  $p < 0.05$ . Interactions ( $p < 0.10$ ) between sex and group (CAH, control) were followed up by separate post hoc analyses between patients and controls of the same sex. Effect sizes were calculated using Cohen's  $d$  based on group differences adjusted for parental education and country of origin in the linear model. In the model a positive effect size represents higher scores in the CAH cohort and negative values represent higher scores in the controls. Effect sizes were categorised as large ( $d \geq 0.80$ ), moderate ( $d \geq 0.50$ ) and small ( $d \geq 0.20$ ). We did not control for multiple comparisons in order not to miss small, though potentially clinically relevant, effects.

Two multiple regression analyses were performed to determine the effect of genotype (null vs. non-null) and phenotype (SW vs. SV) on social problems within the CAH group. To investigate which factors contributed to an increased risk of social problems we included sex, age and GC dose at the time of testing in both of these regression analyses.

Finally, we performed a multiple linear regression analysis to compare behavioural outcomes in children/adolescents with CAH who were prenatally treated with DEX with those with CAH not exposed to DEX in utero. SPSS version 24 (IBM, Armonk, NY, USA) was used for statistical analysis.

## Results

Here, we present adaptive functioning, behavioural and temperamental outcomes for children and adolescents with CAH treated with HC from birth and the impact of prenatal DEX treatment. Group averages for all completed questionnaires, regression coefficients ( $\beta$ ),  $p$  values for the main effects of CAH, CAH by sex interactions as well as effect sizes are summarised in Table 2; the main effect of DEX, DEX by sex interactions as well as effect sizes are summarised in Table 3.

### Parent-completed questionnaires

There were no significant differences between the groups or a significant interaction between sex and diagnostic status in the parental ratings of children's problems on the scales measuring adaptive functioning (CBCL total competence score). In addition, we found no significant differences in behavioural problems when the CBCL subscales were

grouped on the level of two broad groupings (Internalising and Externalising problems). Finally, there were no significant differences between the groups on the Total problem score (all  $ps > 0.05$ , Table 2).

However, the CAH group was significantly different from the controls on the CBCL subscale Social problems ( $\beta = 0.60$ ,  $t(105) = 2.05$ ,  $p = 0.042$ ,  $d = 0.26$ ) (Table 2). We also found a significant interaction between CAH and sex in Social problems ( $\beta = -0.85$ ,  $t(105) = -2.17$ ,  $p = 0.032$ ) and the post hoc analyses revealed that girls with CAH were scored by their parents to have significantly more problems than control girls ( $F(1,56) = 4.3$ ,  $p = 0.043$ ). In contrast, boys with CAH did not differ significantly from control boys ( $F(1,49) = 3.5$ ,  $p = 0.067$ ).

The analysis of parental estimations of their children's social anxiety using the three factors of the SPAI-C-P did not reveal any significant differences between the groups.

In the Temperament Survey for children (EAS) none of the four aspects of temperament analysed showed a significant difference between the groups ( $p > 0.05$ , Table 2).

### Child-completed questionnaires

In the children's self-reports of social anxiety, as measured by SASC-R, we did not identify any significant difference between the groups ( $p > 0.05$ , Table 2).

In the comparison of the children and adolescence's ratings on scholastic competence in the Self-Perception Profile for Children there were no significant differences between the groups ( $p > 0.05$ , Table 2).

### Effects of prenatal treatment with DEX

In the parental ratings of children's behavioural problems (CBCL) we found a significant difference between the groups (CAHDEX vs. CAH) for the main effect of DEX on the subscale Withdrawn/Depressed ( $\beta = 1.10$ ,  $t(40) = 1.90$ ,  $p = 0.014$ ,  $d = 0.40$ ) and a significant interaction between DEX and sex ( $\beta = -1.41$ ,  $t(40) = -2.4$ ,  $p = 0.014$ ) (Table 3). However, separate post hoc analyses did not reach statistical significance in girls ( $F(1,20) = 1.3$ ,  $p = 0.266$ ) or boys ( $F(1,17) = 1.7$ ,  $p = 0.210$ ).

We also observed a significant interaction between DEX and sex ( $\beta = 1.43$ ,  $t(48) = 2.55$ ,  $p = 0.015$ , Table 3) in the Social problems subscale of the CBCL. The post hoc analyses revealed more social problems in CAHDEX-treated boys compared with boys with CAH that had not received prenatal DEX therapy ( $F(1,17) = 11.5$ ,  $p = 0.003$ ).

There were no significant differences between the groups in the analysis of parental estimations of their children's social anxiety using the three factors of the SPAI-C-P ( $p > 0.05$ , Table 3).

**Table 2** Results of parent-completed and children's self-report questionnaires showing group means and standard deviations for patients with CAH not prenatally treated with DEX (CAH) and population controls (C)

	Females			Males			CAH			CAH×SEX		
	CAH	C	Cohen's <i>d</i>	CAH	C	Cohen's <i>d</i>	β (CI lower, CI upper)	Cohen's <i>d</i>	β (CI lower, CI upper)	Cohen's <i>d</i>	β (CI lower, CI upper)	<i>p</i>
	<i>n</i> = 22	<i>n</i> = 38		<i>n</i> = 22	<i>n</i> = 34							
<b>CBC<sup>a</sup></b>												
Total competence scale	17.6 (4.3)	16.9 (3.0)	0.26	17.7 (3.8)	17.1 (2.8)	0.25	0.3 (-2.4, 6.0)	0.400	0.26	0.400	0.26	0.598
Withdrawn/Depressed	1.6 (1.5)	1.1 (1.1)	0.50	1.4 (1.7)	1.7 (2.1)	-0.23	0.1 (-1.6, 2.6)	0.627	0.08	0.627	0.08	0.495
Somatic complaints	1.2 (1.5)	1.1 (1.4)	0.05	1.0 (1.1)	0.9 (1.4)	0.12	-0.1 (-2.2, 1.4)	0.644	0.07	0.644	0.07	0.647
Anxious/Depressed	4.9 (5.1)	3.4 (3.5)	0.50	2.0 (2.6)	2.9 (4.1)	-0.39	0.3 (-2.5, 7.5)	0.316	0.08	0.316	0.08	0.292
Social problems	2.1 (2.2)	0.7 (1.4)	1.05	0.9 (1.0)	1.5 (2.5)	-0.50	0.6 (0.1, 4.6)	<b>0.042</b>	0.26	<b>0.042</b>	0.26	<b>0.032</b>
Thought problems	0.9 (1.7)	0.3 (0.6)	0.63	0.5 (1.1)	0.9 (2.6)	-0.30	0.2 (-1.0, 2.5)	0.441	0.06	0.441	0.06	0.213
Attention problems	2.7 (3.2)	1.6 (2.1)	0.57	1.7 (2.5)	3.3 (3.9)	-0.69	0.3 (-1.6, 5.6)	0.266	-0.11	0.266	-0.11	0.095
Delinquent behaviour	1.8 (3.2)	0.7 (1.1)	0.64	1.2 (1.6)	1.0 (1.5)	0.18	0.4 (-0.8, 3.7)	0.193	0.46	0.193	0.46	0.267
Aggressive problems	3.9 (4.7)	4.8 (4.6)	-0.27	4.1 (5.4)	5.3 (5.2)	-0.32	-0.2 (-8.6, 4.2)	0.505	-0.29	0.505	-0.29	0.742
Internalising problems	7.5 (7.0)	5.5 (4.3)	0.50	4.5 (3.9)	5.9 (6.9)	-0.35	0.2 (-4.7, 9.6)	0.498	0.06	0.498	0.06	0.414
Externalising problems	5.1 (5.7)	5.5 (5.4)	-0.12	5.3 (6.4)	6.5 (6.6)	-0.26	-0.1 (-9.5, 6.0)	0.666	-0.19	0.666	-0.19	0.907
Total problems	25.9 (21.2)	15.9 (13.1)	0.80	16.5 (12.8)	19.5 (19.6)	-0.26	0.4 (-6.0, 36.5)	0.157	0.28	0.157	0.28	0.177
<b>SPAI-C<sup>b</sup></b>												
Assertiveness/General conversation (AGC)	3.8 (3.2)	4.0 (2.6)	-0.10	2.6 (2.4)	3.5 (3.0)	-0.50	-0.0 (-3.8, 3.6)	0.954	-0.30	0.954	-0.30	0.778
Traditional social encounters (TSE)	0.9 (1.5)	1.0 (1.2)	-0.04	0.5 (1.0)	0.9 (1.4)	-0.49	-0.0 (-1.6, 1.7)	0.941	-0.26	0.941	-0.26	0.556
Public performance (PP)	4.7 (3.0)	3.1 (2.8)	0.79	2.2 (2.4)	2.3 (2.7)	-0.06	0.4 (-1.4, 5.5)	0.213	0.35	0.213	0.35	0.232
Total	10.2 (8.1)	9.0 (6.3)	0.23	5.9 (5.4)	7.7 (6.9)	-0.43	0.1 (-7.1, 10.3)	0.717	-0.09	0.717	-0.09	0.500
<b>EAS<sup>c</sup></b>												
Emotionality	2.6 (0.9)	2.9 (0.8)	-0.43	2.4 (0.8)	2.6 (1.0)	-0.30	-0.2 (-1.5, 0.7)	0.484	-0.37	0.484	-0.37	0.627
Activity	3.1 (0.7)	3.4 (0.7)	-0.53	3.0 (0.7)	3.4 (0.7)	-0.82	0.0 (-0.8, 0.9)	0.876	-0.67	0.876	-0.67	0.598
Shyness	2.4 (0.8)	2.2 (0.8)	0.30	2.0 (0.9)	1.9 (0.9)	0.11	0.2 (-0.8, 1.4)	0.567	0.19	0.567	0.19	0.536
Sociability	3.3 (1.0)	3.5 (0.8)	-0.38	3.3 (1.0)	3.4 (0.7)	-0.11	-0.0 (-0.9, 0.8)	0.887	-0.25	0.887	-0.25	0.597
<b>SASC-R<sup>d</sup></b>												
Fear of negative evaluation (FNE)	14.2 (5.1)	14.8 (5.2)	-0.15	13.0 (5.5)	15.7 (7.7)	-0.57	0.1 (-7.3, 9.2)	0.823	-0.38	0.823	-0.38	0.509
Social avoidance and distress (SAD) New	14.0 (3.9)	13.3 (4.3)	0.24	11.6 (3.4)	13.7 (6.0)	-0.61	0.3 (-3.6, 8.7)	0.408	-0.21	0.408	-0.21	0.302
Social avoidance and distress (SAD) General	7.4 (2.9)	6.8 (2.4)	0.32	5.8 (1.6)	7.7 (3.7)	-0.97	0.4 (-1.6, 5.9)	0.258	-0.32	0.258	-0.32	0.127
Total	35.6 (9.3)	34.8 (9.6)	0.12	30.4 (8.5)	37.2 (14.6)	-0.80	0.2 (-9.2, 20.5)	0.450	-0.38	0.450	-0.38	0.237
Self-Perception Profile for Children												
Total school competence	3.1 (0.6)	3.4 (0.4)	-0.63	3.3 (0.4)	3.3 (0.4)	0.15	-0.5 (-1.0, 0.2)	0.150	-0.28	0.150	-0.28	0.212

Regression coefficients ( $\beta$ ) with 95% confidence intervals (CI lower, CI upper), *p* values for the main effect of CAH and interaction between CAH and SEX and effect size (Cohen's *d*) adjusted for parental education and country of origin are listed for all findings. Significant *p* values are marked in bold

<sup>a</sup>Child Behaviour Checklist (CBCL)

<sup>b</sup>Social Phobia and Anxiety Inventory for Children—Parent Report (SPAI-C-P)

<sup>c</sup>Emotionality—Activity—Sociability—Shyness Temperament Survey for children (EAS)

<sup>d</sup>Social Anxiety Scale for Children Revised (SASC-R)



**Table 3** Results of parent-completed and children’s self-report questionnaires showing group means and standard deviations for patients with CAH not prenatally treated with DEX (CAH) and patients with CAH prenatally treated with DEX (CAH-DEX)

	Female		Male		DEX		DEX × SEX				
	CAH-DEX n = 8	CAH n = 22	d	CAH-DEX n = 5	CAH n = 22	d	β (CI lower, CI upper)	p	β (CI lower, CI upper)	p	
<b>CBCL<sup>a</sup></b>											
Total competence scale	14.2 (5.2)	17.6 (4.3)	-1.02	14.1 (2.9)	17.7 (3.8)	-1.49	-0.5 (-13.2, 3.7)	0.263	-1.20	0.2 (-4.5, 7.0)	0.660
Withdrawn/Depressed	3.1 (2.5)	1.6 (1.5)	1.04	0.4 (0.5)	1.4 (1.7)	-1.12	1.1 (1.0, 8.5)	<b>0.014</b>	0.40	-1.4 (-5.6, -0.5)	<b>0.019</b>
Somatic complaints	2.1 (1.5)	1.2 (1.5)	0.91	1.2 (1.3)	1.0 (1.1)	0.18	0.5 (-1.3, 4.7)	0.253	0.69	-0.5 (-2.8, 1.2)	0.428
Anxious/Depressed	2.9 (2.5)	4.9 (5.1)	-0.72	2.4 (2.3)	2.0 (2.6)	0.26	-0.4 (-11.8, 4.6)	0.379	-0.29	0.4 (-3.7, 7.4)	0.506
Social problems	1.3 (2.2)	2.1 (2.2)	-0.54	2.6 (1.7)	0.9 (1.0)	1.79	-0.7 (-6.7, 0.5)	0.093	0.23	1.1 (0.1, 5.0)	<b>0.047</b>
Thought problems	1.3 (1.9)	0.9 (1.7)	0.32	0.2 (0.4)	0.5 (1.1)	-0.42	0.3 (-1.5, 3.3)	0.435	0.19	-0.2 (-2.0, 1.4)	0.703
Attention problems	3.6 (4.1)	2.7 (3.2)	0.35	2.6 (3.2)	1.7 (2.5)	0.43	0.2 (-4.9, 8.0)	0.626	0.45	-0.1 (-4.6, 4.1)	0.901
Delinquent behaviour	1.4 (1.6)	1.8 (3.2)	-0.21	3.0 (4.6)	1.2 (1.6)	0.72	-0.4 (-8.3, 2.9)	0.338	0.27	0.8 (-1.4, 6.2)	0.216
Aggressive problems	6.9 (7.8)	3.9 (4.7)	0.64	8.8 (8.9)	4.1 (5.4)	0.91	0.1 (-11.7, 14.4)	0.836	0.77	0.2 (-7.4, 10.3)	0.747
Internalising problems	8.1 (5.7)	7.5 (7.0)	0.13	4.0 (2.5)	4.5 (3.9)	-0.21	0.2 (-8.8, 15.3)	0.585	0.16	-0.3 (-10.4, 6.0)	0.582
Externalising problems	8.3 (9.0)	5.1 (5.7)	0.60	11.8 (13.4)	5.3 (6.4)	0.87	-0.0 (-16.9, 16.0)	0.961	0.73	0.4 (-7.8, 14.6)	0.540
Total problems	25.6 (22.2)	25.9 (21.2)	-0.02	23.6 (22.3)	16.5 (12.8)	0.55	-0.1 (-44.4, 36.4)	0.842	0.28	0.2 (-22.3, 32.5)	0.709
<b>SPAI-C<sup>b</sup></b>											
Assertiveness/General conversation (AGC)	3.9 (3.0)	3.8 (3.2)	0.08	2.7 (2.1)	2.6 (2.4)	0.05	0.1 (-5.3, 7.2)	0.762	0.14	-0.2 (-4.9, 3.6)	0.767
Traditional social encounters (TSE)	1.4 (1.6)	0.9 (1.5)	0.40	1.6 (2.4)	0.5 (1.0)	0.85	0.0 (-3.2, 3.2)	0.984	0.67	0.3 (-1.7, 2.7)	0.643
Public performance (PP)	4.6 (4.5)	4.7 (3.0)	-0.04	4.5 (3.6)	2.2 (2.4)	1.05	-0.3 (-8.8, 4.7)	0.543	0.45	0.6 (-2.3, 2.3)	0.328
Total	12.6 (8.5)	10.2 (8.1)	0.41	9.4 (8.7)	5.9 (5.4)	0.69	0.1 (-13.7, 18.8)	0.757	0.60	0.0 (-10.7, 11.3)	0.956
<b>EAS<sup>c</sup></b>											
Emotionality	3.2 (1.2)	2.6 (0.9)	0.79	2.8 (1.1)	2.4 (0.8)	0.57	0.4 (-1.1, 2.9)	0.356	0.76	-0.3 (-1.7, 1.0)	0.620
Activity	2.7 (0.8)	3.1 (0.7)	-0.77	3.3 (0.9)	3.0 (0.7)	0.47	0.6 (-2.5, 0.4)	0.153	-0.25	0.6 (-0.4, 1.5)	0.259
Shyness	2.1 (0.7)	2.4 (0.8)	-0.50	2.0 (1.0)	2.0 (0.9)	0.06	-0.3 (-2.4, 1.0)	0.437	-0.18	0.5 (-0.7, 1.6)	0.416
Sociability	3.5 (0.6)	3.3 (1.0)	0.33	3.7 (0.6)	3.3 (1.0)	0.63	0.1 (-1.3, 1.6)	0.831	0.45	-0.1 (-1.0, 0.8)	0.822
<b>SASC-R<sup>d</sup></b>											
Fear of negative evaluation (FNE)	16.5 (6.9)	14.2 (5.1)	0.53	13.4 (5.6)	13.0 (5.5)	0.10	0.4 (-6.7, 17.1)	0.384	0.36	-0.5 (-11.2, 5.0)	0.445
Social avoidance and distress (SAD) New	16.2 (4.3)	14.0 (3.9)	0.74	14.4 (5.9)	11.6 (3.4)	0.81	0.4 (-4.2, 11.6)	0.348	0.82	-0.3 (-6.7, 3.9)	0.599
Social avoidance and distress (SAD) General	6.2 (2.6)	7.4 (2.9)	-0.61	5.4 (3.1)	5.8 (1.6)	-0.21	-0.3 (-6.9, 3.2)	0.453	-0.41	0.3 (-2.6, 4.2)	0.641
Total	38.8 (12.5)	35.6 (9.3)	0.42	33.2 (14.0)	30.4 (8.5)	0.34	0.3 (-13.5, 27.4)	0.495	0.41	-0.3 (-17.5, 10.2)	0.596
Self-Perception Profile for Children											
Total school competence	3.3 (0.5)	3.1 (0.6)	0.41	3.3 (0.2)	3.3 (0.4)	0.01	0.3 (-0.7, 1.5)	0.485	0.25	-0.3 (-0.9, 0.5)	0.596

Regression coefficients (β) with 95% confidence intervals (CI lower, CI upper), p values for the main effect of CAH, interaction between CAH and SEX and effect size (Cohen’s d) adjusted for parental education and country of origin are listed for all findings. Significant p values are marked in bold

<sup>a</sup> Child Behaviour Checklist (CBCL)

<sup>b</sup> Social Phobia and Anxiety Inventory for Children—Parent Report (SPAI-C-P)

<sup>c</sup> Emotionality–Activity–Sociability–Shyness Temperament Survey for children (EAS)

<sup>d</sup> Social Anxiety Scale for Children Revised (SASC-R)

In the Temperament Survey for children (EAS) none of the four aspects of temperament analysed showed a significant difference between the groups ( $p > 0.05$ , Table 3).

There were no significant differences between the groups in the children's self-reports of social anxiety, as measured by SASC-R nor on scholastic competences in the Self-Perception Profile for Children ( $p > 0.05$ , Table 3).

### Social problems regression analyses

Neither genotype, phenotype nor GC dosage contributed to the prediction ( $p > 0.5$ ).

## Discussion

In the present study we investigated the behavioural outcomes in a group of children and adolescents with CAH who were diagnosed early via neonatal screening programmes for CAH in Sweden (nationwide) and Italy (Emilia-Romagna region). We also describe the behavioural outcomes in a small group of children and adolescents with CAH who were treated prenatally with DEX. To investigate behavioural problems, adaptive functioning and temperament a battery of questionnaires was completed by parents and children and adolescents. The result of a good overall adjustment was expected, as we previously observed normal intelligence, executive functioning, learning and long-term memory in the current Swedish cohort. Indeed, our patient cohort seems to be well adjusted. Such positive adjustment may be attributed in part to close monitoring and access to continuity of care and psychological support.

The only significant group difference in the parental questionnaires was the higher incidence of social problems among CAH children and adolescents compared with the population controls. Moreover, comparing children and adolescents with CAH who were prenatally treated with DEX with children and adolescents with CAH who had not received such treatment, our results indicate more withdrawn-depressed problems in DEX-treated children and adolescents and more social problems in DEX-treated boys, as reported by their parents (CBCL).

The CBCL Social problems subscale assesses socially immature behaviours and difficulties in establishing close relationships with peers, as assessed with such items as 'Act too young for his or her age', 'Clings to adults or too dependent' and 'Does not get along with other kids'. Systematic studies focusing on the possible causes of social problems in children with CAH are scarce. Our results may not be surprising given that it is known that children with a chronic medical condition display less prosocial behaviour with peers [51]. A chronic medical disease may have a negative influence on psychosocial development, especially if promoting positive

adaptation is challenging for the parents. Evidence from the literature suggests that the parental emotional state and parenting styles impact the child's developmental trajectory. Parenting an ill child may lead to high parental stress and associated less effective parental strategies [52].

A systematic review found that parental psychological distress in parents of children with Type 1 diabetes mellitus was associated with more problematic behaviour in children [53], although the causal direction of this association is not clear. Thus, our findings underline the importance of screening and the need for counselling and emotional and psychological support for parents with ill children. Finally, further factors associated with social functioning in girls with CAH may be specific issues, such as body image, sexual functioning and self-stigma.

Of note, studies on behavioural outcome in children with CAH are scarce and those that are available have mostly focused on sex-specific issues (mainly in females) based on the hypothesised link between androgen effects and behavioural development. Previous studies investigating CAH in girls reported a higher level of aggression and a preference for masculine, physical sports and behaviours compared with unaffected females [54, 55]. However, in our cohort we did not observe any difference between girls with CAH and control girls in the subscale of CBCL assessing aggressive behaviour. Aggressive behaviour was assessed using a subscale of the CBCL questionnaire containing such items as 'Argues a lot', 'Cruelty', 'Bullying or meanness to others' and 'Destroys things belonging to his or her family'.

Some studies have also shown a significant increase in anxiety disorders in boys and girls with CAH [56]. In our study the children and adolescents with CAH did not report more social anxiety compared with the control children and adolescents. Likewise, we did not observe any between-group differences on the Scholastic Competence subscale for self-rated scholastic competence. Thus, there was good agreement between the parental ratings and the children's and adolescents' self-ratings, indicating a good overall psychological adjustment in children and adolescents with CAH. Medical treatment with HC and rapid initiation of therapy after neonatal screening may be important factors in helping to maintain psychological well-being.

Our study cohort also included a small number of children and adolescents who had been treated prenatally with DEX. The parents of these children and adolescents reported more social problems in males and more withdrawn/depressed problems in girls. However, because the analyses of these data were limited by poor statistical power, we were not able to draw any formal conclusions. Consequently, we suggest the use of multi-source assessment in larger studies.

In conclusion, our results on behavioural outcomes in patients with CAH confirm previous findings of good overall psychological adjustment in boys and girls with



CAH [57, 58]. Using parental questionnaires and children's self-reports, we did not identify any major behavioural problems. Our results indicate, however, more social problems in children and adolescents with CAH, as well as possibly more withdrawn-depressed problems in DEX-treated children/adolescents and more social problems in DEX-treated boys, as reported by their parents (CBCL). These findings highlight the importance of follow-up until adult age and screening of mental well-being. Integrating emotional and psychological support into the overall clinical management of CAH should be an integral part of the care process.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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