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Emotional and Behavioral Adjustment in 4 to 11-Year-Old Boys and Girls with Classic Congenital Adrenal Hyperplasia and Unaffected Siblings

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Summary

It has been suggested that atypical hormone environments during early development may contribute to subsequent development of psychopathology. Also, it has been suggested that individuals with the autosomal recessive genetic variant, classic congenital adrenal hyperplasia (CAH), might be at increased risk of psychopathology. The present study examined emotional and behavioral adjustment in young children with CAH and their unaffected siblings in the United Kingdom. The parent-reported version of the Strengths and Difficulties Questionnaire (SDQ) was employed to assess adjustment in children aged 4 to 11 years. There were 38 boys with CAH, 43 girls with CAH, 23 unaffected brothers, and 31 unaffected sisters. No differences in emotional or behavioral problems were found between boys or girls with CAH and unaffected same-sex siblings. In addition, affected and unaffected boys in the current sample generally did not differ from boys in the general population. However, compared with girls in the general population, girls with CAH had more difficulties related to conduct problems, hyperactivity/ inattention, and prosocial behavior, and unaffected sisters had more difficulties related to peer problems, conduct problems, and prosocial behavior. These findings suggest that both girls with CAH and unaffected sisters of girls or boys with CAH may be at increased risk of developing behavioral problems. Potential influences related to the early hormone environment, familial process, and social stigma are considered.

Highlights

- First study on this topic in young children with CAH and unaffected siblings.
- No differences in difficulties between children with CAH and unaffected siblings.
- Boys in families with a child with CAH did not show increased difficulties.
- Girls with and without CAH in these families showed increased difficulties.
- Stigma or parental stress may contribute to the increased difficulties in girls.

Keywords: disorder of sex development; externalizing; family; gender; hormones; internalizing

1. Introduction

Classic congenital adrenal hyperplasia (CAH) is an autosomal recessive genetic condition, which occurs in approximately 1 in 16,000 to 1 in 20,000 births (White, 2009). More than 90% of cases are caused by 21-hydroxylase deficiency, resulting in cortisol insufficiency and steroid precursors being converted to adrenal androgens (Pasterski & Hughes, 2016; White et al., 1994). Although females with classic CAH are exposed to elevated concentrations of androgens prenatally, prenatal androgen exposure in males with classic CAH appears to be within the normal male range (Pang et al., 1980; Wudy et al., 1999). Females with classic CAH are usually born with ambiguous external genitalia, while there is no genital ambiguity in males with classic CAH. Females with the condition are typically identified at birth or during early infancy and reared as girls in Western countries, and may undergo feminizing genital surgeries (Vidal et al., 2010). For both males and females, classic CAH involves long-term hormonal replacement therapy and careful medical monitoring (Speiser et al., 2010). Conversely, individuals with non-classic CAH have mild enzyme deficiency and often show no apparent clinical symptoms at birth; females with non-classic CAH do not have virilized external genitalia and many individuals with non-classic CAH do not need treatment (Merke & Bormstein, 2005). In recent years, increasing attention has been drawn to psychosocial adjustment and mental health of individuals with CAH and their need for psychological support (Speiser et al., 2010). It has also been suggested that atypical early hormone environments associated with classic CAH (cortisol insufficiency and/or heightened androgen exposure) may contribute to mental health problems (Mueller et al., 2013, 2014).

Various psychological and behavioral outcomes have been examined in individuals with CAH. Research has shown increased male-typical childhood play behavior, sexual orientation, and gender identity in females with classic CAH and generally unaltered psychosexual development in males with classic CAH (for a review, see Hines, 2011). Recent studies suggest that working memory may be reduced in males and females with classic CAH (Browne et al., 2015; Collaer et al., 2016). Inconsistent results have been reported in studies focusing on some other outcomes such as quality of life (e.g., Arlt et al., 2010; Johannsen et al., 2006; Kuhnle et al., 1995; Reisch et al., 2011).

Previous studies examining rates of psychiatric diagnoses in children, adolescents, and adults with CAH recruited from clinics have sometimes, but not always, reported increased rates of psychiatric disorders (e.g., Liang et al., 2008; Meyer-Bahlburg et al., 2008; Morgan et al., 2005; Mueller et al., 2010). Two recent studies in Sweden employed nation-wide population-based registers of CAH and psychiatric diagnosis to investigate if mental health outcomes differed between individuals with CAH and age- and sex-matched controls (Engberg et al., 2015; Falhammar et al., 2013). Elevated rates of alcohol misuse, substance use disorders, and stress-related and adjustment disorders were found in females with CAH (Engberg et al., 2015), and elevated rates of suicidality and alcohol misuse were found in males with CAH (Falhammar et al., 2013).

Nonetheless, the several prior studies on psychiatric disorders included mostly adolescents and adults. Also, because of their focus on psychiatric disorders, these studies provided limited information about less severe forms of emotional or behavioral problems that may require psychological support or benefit from early intervention. In addition, these studies compared individuals with CAH to age-matched controls, patients with other clinical conditions, or general populations, instead of unaffected relatives, and thus had little control over genetic or familial influences. Furthermore, some of the studies either included individuals with non-classic CAH or reported insufficient information on CAH diagnosis, so that they may not adequately reflect the adjustment of individuals experiencing classic, as opposed to the less severe non-classic, CAH.

Research on emotional and behavioral adjustment in young children with classic CAH and their unaffected relatives of similar age may be particularly important, because it could shed light on how early any CAH-related adjustment differences emerge and whether the adjustment of children (both affected and unaffected) in families with a child with classic CAH differs from that of children in the general population. However, prior research on this topic has produced inconsistent results and included participants aged up to 18 years (Berenbaum et al., 2004; Idris et al., 2014). Berenbaum et al. (2004) studied 82 individuals with classic CAH (30 boys, 52 girls) and 82 unaffected relatives (48 brothers, 3 male cousins, 30 sisters, 1 female cousin) in the United States. Within each sex, it was found that there were no CAH-related group differences in emotional or behavioral problems. Another study conducted by Idris et al. (2014) studied 49 individuals with classic CAH (20 boys, 29

girls) and 42 unaffected relatives (17 brothers, 25 sisters) in Malaysia. It was found that children with CAH had more emotional and behavioral problems than did their unaffected relatives. Regarding comparisons with general populations, both affected and unaffected children's adjustment was described as "close to the population averages" in Berenbaum et al. (2004) and as "within the normal population range" in Idris et al. (2014). It is unclear if the descriptions were based on significance tests; no test procedures or results were reported.

The present study investigated emotional and behavioral adjustment in young boys and girls with classic CAH and their unaffected siblings, aged 4 to 11 years old, in the United Kingdom. Atypical early hormone environments, as well as familial stress, have been proposed to adversely affect many aspects of mental health (e.g., Mueller 2013, 2014; Goodman et al., 2011; Zegaczewski et al., 2016). Therefore, several key aspects of child adjustment were examined in the present study, using the parent-reported version of the Strengths and Difficulties Questionnaire (SDQ), which assesses emotional symptoms, peer problems, conduct problems, hyperactivity/inattention, and prosocial behavior. Children with CAH and their unaffected siblings were compared to assess CAH/endocrine-related differences. In addition, both affected children and unaffected siblings in the present study were compared with children in a general UK population sample to assess family-related differences. Previous studies from our research team examining other outcomes in the same sample (e.g., Hines, 2016; Pasterski et al., 2015) have used all unaffected relatives recruited (siblings and cousins) as controls. The present study focused on unaffected siblings to enable stronger implications for potential familial influences. However, for consistency and completeness, both analyses based on unaffected siblings only and those based on all unaffected relatives will be reported.

2. Method

2.1. Samples

Families of children with CAH were recruited via 11 endocrine clinics and a national CAH support group in the UK. A total of 153 children, aged 4 to 11 years (M = 7.40, SD = 2.30), participated. All children with CAH had classic CAH with 21-hydroxylase enzyme deficiency. Unaffected relatives of these children with CAH were recruited as controls. There were 38 boys with

CAH (35 salt-wasting, 3 simple-virilizing), 43 girls with CAH (37 salt-wasting, 6 simple-virilizing), 23 unaffected brothers, and 32 unaffected sisters. In addition, there were 17 unaffected first cousins (8 boys, 9 girls). Medical background interviews were conducted with parents to obtain diagnostic information, which was confirmed by information on medications being taken. None of the children had been treated prenatally with dexamethasone, a type of steroid medication used in some cases to treat pregnancies where CAH is suspected, with the aim of reducing physical virilization.

Sample characteristics, including ethnicity, parental education, and family structure, are summarized in Table 1. There were no significant differences among boys and girls with and without CAH in ethnicity, family structure, or parental education. Children's age at assessment and verbal intelligence, as measured by the vocabulary subtest of the Wechsler Intelligence Scale for Children (4th ed.) (WISC-IV) (Wechsler, 2003) or the Wechsler Preschool and Primary Scale of Intelligence (3rd ed.) (WPPSI-III) (Wechsler, 2002), as age-appropriate, were recorded. Children's age at assessment and verbal intelligence are also summarized in Table1. There were no significant differences among the subgroups in age or age-scaled verbal intelligence scores. In addition, 47% of the unaffected sisters had a same-sex sibling with CAH and 45% of the unaffected brothers had a same-sex sibling with CAH. There were no significant differences between unaffected sisters and brothers in terms of their affected siblings' sex. The sociodemographic structure and verbal intelligence of the sample remained similar when the unaffected cousins were also included as controls (for details, see Hines et al., 2016; Kung et al., 2016).

To assess potential familial influences on emotional and behavioral adjustment of affected children and unaffected siblings, published SDQ data of a general UK population sample consisting of 2901 boys and 2954 girls aged 5 to 10 years (Goodman, 2001; Meltzer et al., 2000) were used for comparison.

2.2. Procedures and Measures

Assessment procedures were 2.5 to 3 hours long and included measures of cognitive, behavioral, and psychological outcomes. Data for other outcomes have been (Browne et al., 2015; Hines et al., 2016; Kung et al., 2016; Pasterski et al., 2015, Spencer et al., 2017), or will be, reported

separately. Parents provided informed consent for their own and their child's participation in the study. The study protocols were approved by national and institutional research ethics committees.

The parent-reported version of the Strengths and Difficulties Questionnaire (SDQ; Goodman 1997, 2001) was employed to assess emotional and behavioral adjustment. The parent-reported SDQ was developed and validated in children aged 4 to 16 years old in the UK (Goodman et al., 1997). It is a 25-item questionnaire with five subscales: emotional symptoms, peer problems, conduct problems, hyperactivity/inattention, and prosocial behavior (Goodman et al., 2001). This five-subscale structure is confirmed by factor analysis (Stone et al., 2010). Each subscale comprises five questions with 3-point response scales ('Not true' = 0, 'Somewhat true' = 1, 'Certainly true' = 2), with a subscale score range of 0–10. Of the 25 items, 10 are positively worded 'strengths'; these are reversed scored if they contribute to the emotional symptoms, peer problems, conduct problems, or hyperactivity/inattention subscales. The mean test-retest reliability of the subscales after 4 to 6 months is 0.65 (Goodman, 2001). Cut-off points of the subscales (emotional ≥ 5; peer ≥ 4; conduct ≥ 4; hyperactivity ≥ 7; prosocial ≤ 6) can be used to identify children who show "high difficulties" and are at substantially elevated risks of developing psychiatric disorders (Goodman et al., 2001; Bourdon et al., 2005). The SDQ has been found to be at least as good as the Child Behavior Checklist (CBCL) at predicting psychiatric cases in the UK (Goodman & Scott, 1999). The SDQ also is one of the most widely employed measures of child mental health in both clinical and research settings across the globe; it has been translated into more than 60 languages and psychometrically validated in more than 15 countries (Stone et al., 2010). In the current sample, internal consistencies of the subscales were satisfactory (emotional: $\alpha = .61$; peer: $\alpha = .61$; conduct: $\alpha = .66$; hyperactivity: $\alpha = .79$; prosocial: $\alpha = .73$) and comparable to those in previous research (Goodman, 2001). For 98% of the children, mothers completed the SDQ; for 2%, fathers completed it. SDQ scores were available for all children, except 1 girl with CAH and 1 unaffected brother.

3. Results

3.1. Analytical Approach

All statistical tests were conducted within each sex for three reasons: (1) CAH influences genital structure and gender-related behavior in girls, but not boys; (2) some prior research either

focused on only one sex or reported statistics separately for each sex; (3) distributions and means of SDQ scores generally differ by sex. All tests were two-tailed, with alpha set at .05. In the current sample, both histograms and Kolmogorov-Smirnov tests showed that SDQ scores were not normally distributed and were generally skewed towards the low difficulties end. This was consistent with the non-normal distribution in the general population sample. Therefore, non-parametric tests were employed. Median tests were used to assess the significance of group differences between boys and girls with and without CAH in the current sample. In addition, Fisher's exact tests were used to assess if proportions of high difficulties scores (having a score in the high difficulties band) significantly differed between boys and girls with and without CAH in the current sample. Regarding comparisons with the general population sample, non-parametric tests could not be used because median scores for the general population sample were not available. Instead, independent samples t-tests were used to compare mean scores between the current and the general population samples. Proportions of high difficulties scores between the current and the general population samples were compared using Fisher's exact tests. All analyses were first conducted in samples including unaffected siblings only (reported in this results section) and then repeated in samples including both unaffected siblings and cousins (reported in Appendix). To complement the above analyses and provide a stronger control for potential familial differences, non-parametric related-samples sign tests were also conducted to see if there were significant group differences in median scores between matched pairs of boys and girls with and without CAH in the current sample (reported in Appendix for samples including unaffected siblings only and samples including both unaffected siblings and cousins). Analyses comparing subgroups within the current sample were conducted using SPSS version 20.0 and analyses comparing the current sample and the general population sample were conducted using GraphPad Prism version 7.0. Descriptive statistics and test results for median and mean scores and for proportions of high difficulties scores are summarized in Table 2 and Table 3, respectively.

3.2. Children with CAH and Unaffected Siblings

No significant differences were found on any SDQ subscales between girls with CAH and unaffected sisters in median scores (p = .14–.72) or proportions of high difficulties scores (p = .52–1). Similarly, in boys, there were also no significant differences (median scores: p = .34–.97; proportions

of high difficulties scores: p = .53–1), although differences in emotional symptoms between unaffected brothers and boys with CAH approached conventional levels of significance, with boys with CAH having higher emotional symptoms (median scores: p = .09; proportions of high difficulties scores: p = .08).

3.3. Current Sample and General Population Sample

Descriptive statistics show that girls in the current sample (both with CAH and unaffected) had more difficulties on all SDQ subscales than did girls in the general population, whereas the pattern in boys was less consistent (see Tables 2 and 3). Compared with girls in the general population sample, girls with CAH had significantly higher mean scores on conduct problems and hyperactivity/inattention, as well as significantly lower mean scores on prosocial behavior (all p < .05). Unaffected sisters had significantly lower mean scores than girls in the population sample on prosocial behavior (p < .05), and differences between these two groups in peer problems approached conventional levels of significance (p < .10) with unaffected sisters having higher mean scores. In terms of proportions of high difficulties scores, compared to girls in the general population sample, girls with CAH were more likely to have high difficulties scores on conduct problems and prosocial behavior (all p < .05), and unaffected sisters were more likely to have high difficulties scores on conduct problems (p < .10) and prosocial behavior (p < .05). By contrast, neither boys with CAH nor unaffected brothers differed significantly from boys in the general population sample on any SDQ subscales (p > .10 for both mean scores and high difficulties scores), except that unaffected brothers had significantly lower mean emotional symptoms scores (p < .05).

The above analyses were repeated in samples including both unaffected siblings and cousins. These analyses yielded similar results (see Appendix).

4. Discussion

The present study examined emotional and behavioral adjustment in 4 to 11-year-old boys and girls with classic CAH and their unaffected siblings in the UK. No significant differences were found between children with and without CAH for either boys or girls within the current sample. Regarding within-sex comparisons to the general population sample, descriptive statistics show that both girls with CAH and unaffected sisters consistently had more difficulties on all the SDQ subscales

both in terms of mean scores and proportions of high difficulties scores. On average, affected and unaffected girls in the current sample had significantly higher levels of externalizing problems (conduct problems) as well as psychosocial problems (peer problems and low prosocial behavior). Descriptive statistics indicate a less consistent pattern in boys. There was only one significant difference - unaffected brothers had lower mean scores on the emotional symptoms subscale than did boys in the general population. Findings were similar for both boys and girls when unaffected cousins were included in the analyses. The current findings suggest that, in families with a child with CAH, adjustment of affected and unaffected boys generally does not differ from that of boys in the general population, whereas both affected and unaffected girls may be at increased risk of developing behavioral problems compared with girls in the general population.

Prior studies examining emotional and behavioral adjustment in children with classic CAH and their unaffected relatives aged up to 18 years have produced inconsistent results (Berenbaum et al., 2004; Idris et al., 2014). The current findings are consistent with those reported in Berenbaum et al. (2004), which found no differences between boys or girls with CAH and unaffected same-sex relatives in an American sample using the parent-reported version of the CBCL for younger participants and the self-reported version of the Self-Image Questionnaire for Young Adolescents (SIQYA) for older participants. On the other hand, Idris et al. (2014) found that Malaysian children with CAH had more emotional and behavioral problems than did their unaffected relatives, as indicated by parent-reported CBCL scores. These inconsistent findings between the Western samples (the present study and Berenbaum et al., 2004) and the Malaysian sample (Idris et al., 2014) might reflect cultural differences in medical care and psychological and social support provided to individuals with CAH, although further research is needed to investigate whether these differences exist between the cultures. In addition, both the present study and Berenbaum et al. (2004) employed age-appropriate measures developed and validated in the countries where the samples were recruited and assessed. By contrast, Idris et al. (2014) used a translated version of the parent-reported CBCL, which had not been validated in Malaysia. Regarding comparisons with the general populations, it is unclear whether the two prior studies conducted statistical tests comparing their samples to general population samples, and so we cannot compare this aspect of our results to theirs.

4.1. Familial Processes and Social Stigma

In the present study, compared with children in a general population sample, on average, girls with CAH, as well as unaffected sisters of children with CAH, exhibited increased psychosocial and externalizing problems, while boys with CAH and unaffected brothers did not. CAH is a condition that requires long-term medical care in both affected boys and girls. The current findings for unaffected siblings are consistent with prior research suggesting that girls are sometimes more susceptible than boys to psychological distress associated with having a sibling with a severe illness. A review shows that healthy female siblings of children with certain chronic health conditions, such as cancer, are more likely to experience psychological difficulties than are healthy male siblings (Zegaczewski et al., 2016).

It is also possible that psychosocial challenges facing parents may play a role in the increased behavioral difficulties in both girls with CAH and unaffected sisters. Parents of children with a disorder of sex development (DSD), such as CAH, may experience DSD-related stigma (Rolston et al., 2015) and have high subjective needs for psychological support (Bennecke et al., 2015). Parents also may show significant levels of post-traumatic stress (Pasterski et al., 2014), depressive and anxiety symptoms (Suorsa et al., 2015), parenting stress (Duguid et al., 2007) and negative parenting practices (Kirk et al., 2011). Reduced parental psychological well-being can negatively influence children's adjustment (Silberg & Rutter, 2002). The negative influences can be stronger for girls than boys, because girls have been found to be more sensitive to parental distress (Hammen, 2002; Hankin et al., 2007). For example, a meta-analysis has shown that maternal depression is more strongly associated with psychological difficulties in girls than in boys (Goodman et al., 2011).

The susceptibility to psychological distress in affected and unaffected girls may be further increased by exposure to sex/gender-related stigma that may be associated with females with CAH. Unlike males with CAH, females with CAH are typically born with ambiguous external genitalia and show increased male-typical gender role behavior, gender identity, and sexual orientation (Hines, 2011). Females with CAH also tend to have suboptimal psychosocial outcomes (Strandqvist et al., 2014). In particular, females with CAH have reported experiences of sex/gender-related stigma, such as stigma about body image and gender typicality, during childhood and adolescence in medical

settings (Meyer-Bahlburg et al., 2017a) and in general social environments (Meyer-Bahlburg et al., 2017b). The stigma can be conveyed by family members and the media or enacted by peers (Meyer-Bahlburg et al., 2017b). It is possible that the stigma does not only impact females with CAH, but also unaffected sisters in families with a child with CAH. While prior research has focused on the stigma experienced by females with CAH, further research can test if unaffected female siblings' CAH-related knowledge and experiences are related to their psychological adjustment.

4.2. Endocrine Influences

Both males and females with CAH have reduced cortisol production prenatally (White et al., 1994). In addition, females with CAH are exposed to elevated concentrations of androgens prenatally (Pang et al., 1980; Wudy et al., 1999). It has been suggested that the overproduction of androgens and/or underproduction of cortisol prenatally may contribute to the development of psychopathology (Mueller et al., 2013; Mueller et al., 2014). However, in the present study, no CAH/endocrine-related group differences were found between boys or girls with CAH and unaffected same-sex siblings, suggesting that there are no strong prenatal influences of elevated androgen exposure or cortisol deficiency on subsequent development of emotional or behavioral problems in young children, at least as assessed with the SDQ. This implication of the present study concurs with a prior study showing no strong or consistent relationships between umbilical cord blood testosterone and emotional or behavioral problems in typically-developing young children (Robinson et al., 2013) and also concurs with prior research showing no differences in emotional or behavioral problems between children and adolescents with CAH and their unaffected relatives (Berenbaum et al., 2004). Moreover, on average, both girls with CAH and unaffected sisters in the current study showed increased externalizing and psychosocial problems in comparison with girls in the general population, suggesting that social influences, such as familial processes or social stigma, play a stronger role than endocrine influences in the development of psychological difficulties in these children.

4.3. Strengths, Limitations, and Further Research

The strengths of the present study include having a relatively large sample of young children with CAH, using an age-appropriate and psychometrically validated measure of emotional and behavioral adjustment, and making comparisons based on both unaffected siblings and children in the

general population. A limitation is that the present study relied on a parent-reported measure. It is possible that parental stress and knowledge of CAH may influence the parents' reports on their children's adjustment. Further research may usefully explore whether or not the same results can be found when information is obtained directly from the child and when clinical assessments and multiple informants are used. To empirically elucidate whether the current observations are specific to families with a child with CAH, further research also can include a control group consisting of families with a child with another chronic health condition.

The present study did not statistically control for any potential age or socio-economic differences between the current sample and the general population sample due to the lack of access to the relevant information for the general population sample. Nevertheless, the current findings show that girls with CAH and unaffected sisters had higher SDQ scores than did girls in the general population, whereas boys with CAH and unaffected brothers generally did not differ from boys in the general population. It is unlikely that this gender-specific pattern can be explained by any potential differences in age or socio-economic background between the samples. There were no gender differences in age or socio-economic background in the current sample and no such gender differences were reported in the general population sample. Also, large-scale studies employing the SDQ in the UK have not reported any interactions between gender and age or between gender and socio-economic background in predicting SDQ scores (e.g., Goodman, 2001; Meltzer et al., 2000; O'Connor et al., 2003).

4.4. Conclusions

The present study assessed emotional and behavioral adjustment in young children with and without CAH in the UK. No differences in emotional or behavioral problems were found between boys or girls with CAH and unaffected same-sex siblings. However, on average, both girls with CAH and unaffected sisters exhibited more psychosocial and externalizing problems than did girls in the general population. These findings suggest that psychological support is important not only for children with CAH, but also for their unaffected siblings, especially female siblings. Both affected and unaffected children in these families may benefit from early monitoring and prevention programs. Reducing the stress experienced by parents of children with CAH and the social stigma facing

individuals with CAH may also help alleviate the risk that girls in families with children with CAH will develop mental health difficulties.

Conflicts of Interest

The authors declare no conflict of interest.

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KTFK performed data analysis and drafted the manuscript. MH designed the study. DS, VP, and SASN oversaw data acquisition and management. PCH, IAH, and CLA contributed to access to some of the participants through clinical resources. All authors provided critical revisions and approved the final version of the manuscript.

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Table 1. Sample characteristics of boys and girls with and without CAH.

	Male Siblings *n* = 23	Boys with CAH *n* = 38	Female Siblings *n* = 32	Girls with CAH *n* = 43
	Means (Standard Deviations)			
Age	7.58 (2.24)	7.15 (2.04)	7.37 (2.71)	7.13 (2.28)
Vocabulary	10.22 (2.49)	10.82 (2.72)	11.50 (2.92)	10.16 (3.32)
	n (%)			
Ethnicity				
Caucasian	20 (87.0%)	33 (86.8%)	30 (93.8%)	38 (88.4%)
Mixed	1 (4.3%)	3 (7.0%)	1 (3.1%)	2 (4.7%)
	2 (8.7%)	1 (2.6%)	1 (3.1%)	1 (2.3%)
Indian/Pakistan/Bangladeshi				
Middle Eastern	–	1 (2.6%)	–	1 (2.3%)
African/African-Caribbean	–	–	–	1 (2.3%)
Family Structure				
Live with two parents	22 (95.7%)	37 (97.4%)	31 (96.9%)	41 (95.3%)
Live with mother only	1 (4.3%)	1 (2.6%)	1 (3.1%)	2 (4.7%)
Parental Education				
Both parents with no post-secondary education	7 (30.4%)	7 (18.4%)	7 (21.9%)	13 (30.2%)
At least one parent with vocational training or degree	15 (65.2%)	23 (60.5%)	20 (62.5%)	24 (55.8%)
At least one parent with postgraduate degree	1 (4.3%)	8 (21.1%)	5 (15.6%)	6 (14.0%)

Table 2. Statistics of Strengths and Difficulties Questionnaire (SDQ) scores in the current sample and in the general population sample.

	Male Siblings *n* = 22	Boys with CAH *n* = 38	UK Boys *n* = 2901	Female Siblings *n* = 32	Girls with CAH *n* = 42	UK Girls *n* = 2954
	Medians Means (Standard Deviations)					
Emotional Symptoms	0.00 **.86 (1.08)** [*]	2.00 2.29 (1.96)	- 1.8 (2.0)	2.00 2.28 (1.71)	2.00 2.40 (2.21)	- 2.0 (1.9)
Peer Problems	1.00 1.09 (1.51)	1.00 1.38 (1.85)	- 1.5 (1.7)	1.00 **1.81** **(2.15)** [†]	0.50 1.31 (1.83)	- 1.3 (1.6)
Conduct Problems	1.00 1.31 (1.46)	1.00 1.55 (1.45)	- 1.8 (1.8)	1.00 1.63 (1.77)	1.50 **2.05** **(1.97) ***	- 1.5 (1.5)
Hyperactivity/Inattention	4.00 3.90 (1.87)	3.50 3.76 (2.45)	- 4.1 (2.8)	2.50 3.31 (3.05)	3.00 **4.13** **(2.81) ****	- 3.1 (2.5)
Prosocial Behavior[a]	8.50 8.00 (1.75)	9.00 8.08 (1.95)	- 8.4 (1.7)	9.00 **8.16** **(1.92) ****	8.00 **8.00** **(1.93)** ****	- 8.9 (1.4)

-Medians not available for the general population sample.

[a]Unlike scores on other subscales, lower scores on prosocial behavior indicate more difficulties.

Note. In the current sample, within each sex, there were no significant differences in median scores between children with and without congenital adrenal hyperplasia (CAH), except that unaffected brothers had marginally significantly lower median emotional symptoms scores than did boys with CAH. Bolded statistics indicate significant or marginally significant differences in mean scores found in within-sex comparisons between subgroups in the current sample and the general population sample. [†]$p < .10$ *$p < .05$ **$p < .01$ ***$p < .001$.

Table 3. Prevalence of high difficulties scores in the current sample and in the general population sample.

	Male Siblings $n = 22$ % (n) ≥ cut-off	Boys with CAH $n = 38$	UK Boys $n =$ 2901	Female Siblings $n = 32$ % (n) ≥ cut-off	Girls with CAH $n = 42$	UK Girls $n =$ 2954

		% (n) ≥ cut-off	% ≥ cut-off		% (n) ≥ cut-off	% ≥ cut-off
Emotional Symptoms	0% (0)	15.8% (6)	10.8%	12.50% (4)	16.7% (7)	10.7%
Peer Problems	9.1% (2)	15.8% (6)	12.8%	18.8% (6)	11.9% (5)	9.2%
Conduct Problems	14.3% (3)	7.9% (3)	15.8%	**21.9% (7) †**	**23.8% (10) ***	10.4%
Hyperactivity/Inattention	9.1% (2)	10.5% (4)	21.0%	15.6% (5)	19.0% (8)	11.3%
Prosocial Behavior[a]	18.2% (4)	21.1% (8)	13.7%	**21.9% (7) ****	**21.4% (9) *****	6.7%

[a]Unlike other subscales, lower scores on prosocial behavior indicate more difficulties; numbers indicate proportions of children scoring at or below the cut-off.

Note. In the current sample, within each sex, there were no significant differences in probabilities of being in the high difficulties bands between children with and without congenital adrenal hyperplasia (CAH), except that unaffected brothers were marginally significantly less likely to have high difficulties scores on emotional symptoms than were boys with CAH. Bolded statistics indicate significant differences or differences that approached significance found in within-sex comparisons between subgroups in the current sample and the general population sample. $^{\dagger}p < .10$ $*p < .05$ $**p < .01$ $***p < .001$.

Appendix

Descriptive statistics and test results for mean and median scores and for proportions of high difficulties scores in children with CAH and their unaffected relatives (siblings and cousins) are summarized in Table A1 and Table A2, respectively.

Children with CAH and Unaffected Relatives (Siblings and Cousins)

No significant differences were found on any SDQ subscales between girls with CAH and unaffected female relatives in median scores (p = .14–.75) or proportions of high difficulties scores (p = .55–1). Similarly, in boys, there were also no significant differences in SDQ scores (median scores: p = .67–.99; proportions of high difficulties scores: p = .12–1), although differences in emotional symptoms between unaffected male relatives and boys with CAH approached conventional levels of significance, with boys with CAH having higher emotional symptoms (p = .08 for both median scores and proportions of high difficulties scores).

Current Sample (Siblings and Cousins) and General Population Sample

Descriptive statistics show that girls in the current sample had more difficulties on almost all SDQ subscales than did girls in the general population, whereas the trend in boys was less consistent (see Tables A1 and A2). Compared with girls in the general population sample, girls with CAH had significantly higher mean scores on conduct problems and hyperactivity/inattention, as well as significantly lower mean scores on prosocial behavior (all $p < .05$). Unaffected female relatives had significantly lower mean scores than girls in the population sample on prosocial behavior ($p < .05$), and differences between these two groups in peer problems approached conventional levels of significance ($p < .10$) with unaffected female relatives having higher mean scores. In terms of proportions of high difficulties scores, compared with girls in the general population sample, girls with CAH were more likely to have high difficulties scores on conduct problems and prosocial behavior (all $p < .05$), and unaffected female relatives were more likely to have high difficulties scores on conduct problems ($p < .10$), peer problems ($p < .10$), and prosocial behavior ($p < .05$). By contrast, neither boys with CAH nor unaffected male relatives differed significantly from boys in the general population sample on any SDQ subscales ($p > .10$ for both mean scores and high difficulties

scores), except that unaffected male relatives had marginally significantly lower mean emotional symptoms scores ($p < .10$).

Matched-Pair Analyses Within the Current Sample

In terms of same-sex matched sibling pairs, 15 of the 32 unaffected sisters had a sister with CAH and 10 of the 22 unaffected brothers had a brother with CAH. For the whole control sample including both siblings and cousins, 18 of the 41 unaffected females had a female relative with CAH and 15 of the 30 unaffected males had a male relative with CAH. Median SDQ scores for the children included in the matched-pair analyses are summarized in Table A3 and Table A4.

Paired difference tests found no significant differences in median SDQ scores between children with CAH and unaffected siblings in either sex ($p > .10$). Similarly, paired difference tests found no significant differences between children with CAH and unaffected relatives (both siblings and cousins) in either sex ($p > .10$).

Table A1. Statistics of Strengths and Difficulties Questionnaire (SDQ) in the current sample and in the general population sample.

	Control Boys *n* = 30	Boys with CAH *n* = 38	UK Boys *n* = 2901	Control Girls *n* = 41	Girls with CAH *n* = 42	UK Girls *n* = 2954
	Medians Means (Standard Deviations)					
Emotional Symptoms	0.00 **1.10** **(1.69)** †	2.00 2.29 (1.96)	- 1.8 (2.0)	2.00 2.24 (1.80)	2.00 2.40 (2.21)	- 2.0 (1.9)
Peer Problems	1.00 1.33 (1.60)	1.00 1.38 (1.85)	- 1.5 (1.7)	1.00 **1.73** **(2.03)** †	0.50 1.31 (1.83)	- 1.3 (1.6)
Conduct Problems	1.00 1.40 (1.65)	1.00 1.55 (1.45)	- 1.8 (1.8)	1.00 1.49 (1.73)	1.50 **2.05** **(1.97) ***	- 1.5 (1.5)
Hyperactivity/Inattention	4.00 4.00 (1.82)	3.50 3.76 (2.45)	- 4.1 (2.8)	2.00 3.26 (2.92)	3.00 **4.13** **(2.81) ****	- 3.1 (2.5)
Prosocial Behavior[a]	8.50 8.17 (1.64)	9.00 8.08 (1.95)	- 8.4 (1.7)	9.00 **8.10** **(1.83) *****	8.00 **8.00** **(1.93)** *****	- 8.9 (1.4)

-Medians were not available for the general population sample.

[a]Unlike scores on other subscales, lower scores on prosocial behavior indicate more difficulties.

Note. In the current sample, within each sex, there were no significant differences in median scores between children with and without congenital adrenal hyperplasia (CAH), except that unaffected male relatives had marginally significantly lower median emotional symptoms scores than did boys with CAH. Bolded statistics indicate significant or marginally significant differences in mean scores found in within-sex comparisons between subgroups in the current sample and the general population sample. †$p < .10$ *$p < .05$ **$p < .01$ ***$p < .001$.

Table A2. Prevalence of high difficulties scores in the current sample and in the general population sample.

	Control Boys *n* = 30 % (n) ≥ cut-off	Boys with CAH *n* = 38 % (n) ≥ cut-off	UK Boys *n* = 2901 % ≥ cut-off	Control Girls *n* = 41 % (n) ≥ cut-off	Girls with CAH *n* = 42 % (n) ≥ cut-off	UK Girls *n* = 2954 % ≥ cut-off
Emotional Symptoms	3.3% (1)	15.8% (6)	10.8%	14.63% (6)	16.7% (7)	10.7%
Peer Problems	13.3% (4)	15.8% (6)	12.8%	**17.1% (7)** †	11.9% (5)	9.2%
Conduct Problems	16.7% (5)	7.9% (3)	15.8%	**19.5% (8)** †	**23.8% (10) ***	10.4%
Hyperactivity/Inattention	10.0% (3)	10.5% (4)	21.0%	12.2% (5)	19.0% (8)	11.3%
Prosocial Behavior[a]	13.3% (4)	21.1% (8)	13.7%	**19.5% (8) ****	**21.4% (9) *****	6.7%

[a]Unlike other subscales, lower scores on prosocial behavior indicate more difficulties; numbers indicate proportions of children scoring at or below the cut-off.

Note. In the current sample, within each sex, there were no significant differences in the probabilities of being in the high difficulties bands between children with and without congenital adrenal hyperplasia (CAH), except that unaffected male relatives were marginally significantly less likely to have high difficulties scores on emotional symptoms than were boys with CAH. Bolded statistics indicate significant differences or differences that approached

significance found in within-sex comparisons between subgroups in the current sample and the general population sample. $^{\dagger}p < .10$ $^{*}p < .05$ $^{**}p < .01$ $^{***}p < .001$.

Table A3. Median SDQ scores for same-sex matched pairs of children with CAH and unaffected siblings.

	Unaffected Brothers *n* = 10	Boys with CAH *n* = 10	Unaffected Sisters *n* = 15	Girls with CAH *n* = 15
	Medians			
Emotional Symptoms	0.00	2.50	2.00	1.50
Peer Problems	0.50	0.50	1.00	0.00
Conduct Problems	1.00	1.50	0.75	1.50
Hyperactivity/Inattention	4.50	3.00	1.50	3.50
Prosocial Behavior	8.50	8.50	9.00	7.50

Table A4. Median SDQ scores for same-sex matched pairs of children with CAH and unaffected controls including siblings and cousins.

	Control Boys n = 15	Boys with CAH n = 15	Control Girls n = 18	Girls with CAH n = 18
	Medians			
Emotional Symptoms	0.00	3.00	2.00	2.00
Peer Problems	1.00	1.00	1.00	0.00
Conduct Problems	1.00	2.00	1.00	2.00
Hyperactivity/Inattention	5.00	3.00	3.00	4.00
Prosocial Behavior	9.00	9.00	9.00	7.00