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Endocrine, cardiac and neuropsychological aspects of adult congenital adrenal hyperplasia

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Abstract

Objective: To investigate the metabolic, cardiovascular, and neuropsychological phenotype, quality of life (QoL), and hormonal regulation in individuals with congenital adrenal hyperplasia (CAH), a group of autosomal recessive disorders characterized by impaired synthesis of cortisol in the adrenal cortex and, if untreated compensatory hyperandrogenism. CAH is associated with an increased cardiovascular and metabolic morbidity, possibly due to overtreatment with glucocorticoids, leading to weight gain, insulin resistance, and metabolic syndrome.

Design, Participants, Measurements: Thirty-seven individuals with CAH and 33 age- and sex-matched controls were evaluated at a single centre at Aarhus University Hospital with echocardiography, electrocardiogram, 24-h blood pressure, biochemistry, anthropometrics, and autism spectrum, anxiety, depression, personality, cognitive failures, and QoL were assessed using questionnaires.

Results: CAH individuals had lower height than controls (170.5 vs. 182.9 cm in males and 160.2 vs. 170.1 cm in females, $p < 0.01$). Compared with female controls, females with CAH had higher haemoglobin (8.8 vs. 8.2 mmol/L, $p = 0.003$) and BMI (29.7 vs. 25.5 kg/m^2, $p = 0.006$), reduced insulin sensitivity (HOMA-IR): 2.7 vs. 1.9, $p = 0.018$), prolonged E-wave deceleration time (193 vs. 174 cm, $p = 0.015$), and E/é ratios (5.4 vs. 4.5, $p = 0.017$), and lower self-reported QoL. Males with CAH had more cognitive complaints ($p = 0.034$) and higher autistic scores (19.9 vs. 14.9; $p = 0.068$) compared with male controls. More individuals with CAH than controls reported writing problems.

Conclusion: A sex-specific comorbidity profile is evident in CAH, with females presenting with decreased metabolic and overall self-reported health, whereas males with CAH presented with increased cognitive complaints and autistic traits.

KEYWORDS

cardiology, congenital adrenal hyperplasia, endocrinology, neuropsychology, quality of life

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1 | INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders characterized by impaired synthesis of cortisol in the adrenal cortex. The most common cause of CAH is 21-hydroxylase deficiency (21-OHD) caused by bi-allelic pathogenic variants in the *CYP21A2* gene. The clinical presentation of CAH depends on sex, underlying genotype, and the preserved activity of 21-hydroxylase (21-OH). CAH is phenotypically classified into three groups, ranging from the most severe salt-wasting (SW), to simple virilizing (SV), and the milder nonclassical (NC). In NC, symptoms may include irregular menstruation, hirsutism, reduced final height, and infertility.[1] In SV, common symptoms are virilisation of the external genitalia at birth or later in infancy and early childhood, accelerated growth, and premature sexual maturation can be seen.[2] SW is characterized by complete impairment of 21-hydroxylase activity. Early symptoms in SW may include failure to thrive and salt wasting and genital virilisation of females.[3] However, all categories of CAH can potentially lead to adrenal crisis.[2,4] The reported prevalence of CAH among newborns in the Danish population is 15 per 100,000 females and 9 per 100,000 males,[5] whereas the newborn prevalence from other countries is reported to vary from 4 to 16 per 100,000 for females and males combined.[6,7] Based on carrier frequencies, the estimated prevalence of NC CAH in the US Caucasian population may be as high as 500 per 100,000 individuals.[2,8]

Reduced synthesis of 21-OH leads to excess production of androgen precursors such as 17-hydroxyprogesterone (17-OHP), androstenedione (A4), and the 11-oxygenated C19 steroids (11β-hydroxyandrostenedione (11-OHA4), 11-ketoandrostenedione (11-KA4), 11-ketotestosterone (11-KT), and 11β-hydroxytestosterone (11-OHT)).[9] Among these, 17-OHP is the most commonly used biomarker for monitoring treatment of CAH. However, there is potential for utilization of other androgen precursors, suggesting exploration of alternative androgen precursors beyond 17-OHP.

CAH is associated with an increased cardiovascular and metabolic morbidity, likely due to requirement for supraphysiological dose of glucocorticoid to suppress excessive androgen production with glucocorticoids, leading to weight gain, insulin resistance, diabetes, hypertension, dyslipidemia, and general metabolic syndrome.[10] Balancing between glucocorticoid excess and androgen excess and their respective roles in the development of cardiovascular and metabolic comorbidity is of great importance in future improvement of treatment in individuals with CAH.[10,11]

A potential link between CAH and cognitive impairments, especially impaired executive functions has been suggested.[12] In addition, an association between CAH and autism spectrum disorder (ASD) traits, such as social communication difficulties and stereotypic behaviours has been described.[13] Overall, increased autistic traits seem largely driven by impaired social skills and imagination.[6,13] Previous research has suggested that prenatal exposure to androgens in girls with CAH may be associated with alterations in personality towards male-typical traits, as well as an increased interest in male-typical toys, playmates, and activities.[14] Women with CAH have been reported to display less tender-mindedness and more aggression, while men with CAH show reduced dominance, increased tender-mindedness, and less aggression, but, overall, individuals with CAH tend to have more similar personality traits to controls of the same sex.[14–16] Understanding the impact of CAH on cognitive function, personality, and quality of life (QoL) is important for the improvement of treatment and follow-up regimens for individuals with CAH.

The aim of the present study was to investigate the metabolic, cardiovascular and neuropsychological phenotype, the biochemical profile—including the synthesis of 11-oxygenated C19 steroids, and QoL of adult females and males with CAH in comparison to an age- and sex-matched controls. Currently, the natural history of CAH is not clear and especially adult part of life with CAH is still not well characterized. Thus, there is a gap in knowledge concerning which kind of co-morbidity is seen with increased frequency in CAH. This in-depth study design is unique due to the diversity of the clinical and QoL data included, which expands the knowledge of the natural history of CAH and leads to a more detailed description of the phenotype of CAH.

2 | MATERIALS AND METHODS

2.1 | Participants

CAH individuals were recruited between 2016 and 2022 from the Department of Endocrinology at Aarhus University Hospital and the Department of Endocrinology at Odense University Hospital, Denmark. Blood-samples, echo-cardiography and clinical examinations were done in the same day. Age- and sex-matched controls (males: $n = 9$, females: $n = 24$) were recruited through advertisement. Participants were examined after an overnight fast in the morning between 8 and 9 AM before taking their medication. Individuals aged between 18 and 70 years were eligible for inclusion. Exclusion criteria for controls were a history of bone disease other than osteoporosis, active thyroid disease, as well as long-term treatment with corticosteroids, defined as a daily dose of ≥5 mg for more than 3 months.

2.2 | Ethics

All participants received oral and written information about the study before written consent was obtained. The study was approved by the local ethics committee (Region Midtjylland, Denmark (1-16-02-307-14).

2.3 | Methodology

2.3.1 | Demographics

Obtained demographics included age, age at diagnosis, CAH phenotype (SW, SV, NC) and genotype. Information regarding genotype was obtained from the Department of Clinical Genetics, Rigshospitalet,

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Copenhagen University Hospital, who perform all diagnostic analysis of CAH in Denmark.

Total daily cortisol dose was calculated after conversion using dosing equivalency of glucocorticoids.[17]

2.4 | Biochemistry and hormone analyses

We selected biomarkers that are most commonly used in clinical practice to ensure widespread usability. 17-OHP, A4, testosterone and dehydroepiandrosterone sulphate (DHEAS) were measured using an in-house Liquid Chromatography tandem mass spectrometry (LC-MS/MS) assay (Sciex). The assay was calibrated using a commercially available 6-point calibration curve (Chromsystems) accredited according to the DS/EN ISO 15189. 11-ketoandrostenedione (11-KA4), 11β-hydroxyandrostenedione (11-OHA4), 11-ketotestosterone (11-KT), and 11β hydroxytestosteron (11-OHT) were also measured using an in-house LC-MS/MS assay (Sciex). The assay was calibrated using a 3-point calibration curve made from Charcoal stripped Fetal Bovine Serum (Sigma-Aldrich) and spiked with weighed-in pure compounds (Steraloids).

Fasting routine measurements of serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH), anti-Müllerian Hormone (AMH), sex hormone-binding globulin (SHBG), sodium, potassium, creatinine, alkaline phosphatase, alanine transaminase, thyroid stimulating hormone (TSH), 25-hydroxy vitamin D, parathyroid hormone (PTH), ionized calcium, phosphate, and glucose concentrations in serum were performed.

Homoeostatic model assessment (HOMA) was used to calculate HOMA-IR (Homoeostatic model assessment for insulin resistance) by the following formula: (insulin*glucose)/22.5. This formula adjusts for fasting serum levels of insulin and glucose, and the resulting value can be used to assess the degree of insulin resistance.[18] Specifically, higher values of HOMA-IR indicate greater insulin resistance. The use of HOMA-IR provides a noninvasive and practical method for assessing insulin resistance, which is a key factor in several metabolic disorders.[18]

2.5 | Anthropometrics

Anthropometric measurements included height, body weight, and hip and waist measurements. Height was measured using a Raven magnetometer, while hip and waist measurements were obtained using tape measure. Body weight was measured to the nearest 0.1 kg, and height, hip, and waist measurements were measured to the nearest millimetre.

2.6 | Transthoracic echocardiography (TEE), blood pressure and electrocardiography (ECG)

TEE included measurement of ventricular septum thickness (cm), left ventricular internal diameter at end-diastole (LVIDD, cm), left ventricular internal diameter at end-systole (LVIDS, cm), left ventricular posterior wall diameter (LVPWD, cm), left ventricular outflow tract (LVOT) diameter (mm), aortic sinus diameter (mm), ejection fraction (%), deceleration time (E-DEC), aortic sinus calcification (ASC), carotid artery thickness (mm), peak early diastolic velocity E (m/s), peak late diastolic velocity A (m/s), mitral annular velocities, é: left ventricular filling pressure, E/A ratio and E/E' ratio. A 24-h ambulatory blood pressure (AMBP) and pulse were recorded with oscillometric measurements every 20 min (SpaceLabs 91207) using an appropriate cuff size placed on the left arm. Day and nighttime was set according to diary registered bedtime and waking up time. The nocturnal systolic (sys) blood pressure fall was calculated by dividing the difference between AMBPsys day and AMBPsys night with AMBPsys day. A 12-lead ECG was performed.

2.7 | Assessment of socioeconomic status, medication and health

Socioeconomic status was assessed by the highest level of education and current employment status. Health-related behaviours were evaluated by self-reported information about alcohol consumption, smoking, and daily medication intake.

Evaluation of overall health status was performed by clinical assessment and collection of medical history of each participant, undertaken by a physician. Data included assessment of co-morbidities, medication use, and any symptoms or complaints reported by the participants. Any relevant medical history, such as previous illnesses or surgeries were collected as well.

2.8 | Autism, anxiety, depression, personality, cognitive failures, and QoL

The questionnaires were selected based on current knowledge of CAH-associated impairments, including ASD, affective disorders, personality, and QoL.[19,20] The Autism Spectrum Quotient (AQ) questionnaire was utilized.[21] This questionnaire measures various aspects of social engagement, including attention to detail (10 items), attention switching (10 items), imagination (10 items), communication (10 items), and general social skills (10 items). Participants were asked to rate how well each statement correlated to their self-description on a 4-point scale ranging from 1 ("definitely disagree") to 4 ("definitely agree"). Negatively worded items were reverse-coded to ensure that higher scores reflected greater engagement in each aspect of social behaviour. Scores for each measure were computed by combining item responses, resulting in five scores for each participant. Scores above 29–32 were considered compatible with autism, although no formal clinical diagnosis was established.[21,22]

For symptoms of anxiety and depression, a short version of the symptom Checklist-90-Revised (SCL-90) was used, which is a self-reported questionnaire assessing anxiety (SCL-ANX), depression (SLC-DEP), somatization, and interpersonal sensitivity. The questionnaire

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contains 13 items scored on a scale of 0–4, with higher scores indicating more severe symptoms.[23]

Personality traits were assessed using the Revised NEO Personality Inventory (NEO PI-R) short form[24] including measures of neuroticism (12 items), extraversion (12 items), agreeableness (12 items), conscientiousness (12 items), and openness to experience (12 items). For all items, participants indicated how well each statement described them on a scale from 1 ("very inaccurate") to 5 ("very accurate"). Items responses within each personality measure were combined to create five personality scores for each participant.

The Cognitive Failures Questionnaire (CFQ) is a self-report instrument that measures an individual's cognitive errors and lapses in daily life.[25,26] The CFQ consists of 25 items, and respondents are asked to indicate the frequency of these errors on a 5-point Likert scale, where 0 represents "never" and 4 represents "very often." The items on the CFQ relate to a range of cognitive failures, including forgetting appointments, losing track of conversations, and misplacing objects. Higher scores on the CFQ indicate more frequent cognitive failures in daily life.

QoL was assessed using the SF-36 Health Survey,[27] a validated questionnaire assessing health-related QoL across eight domains; physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Each domain was scored on a scale of 0–1, with higher scores indicating better health-related QoL.

2.9 | Statistics

Descriptive statistics were computed for all study variables. To assess the psychometric properties of the questionnaires, internal consistency reliability coefficients (Cronbach's α) and examined intercorrelations among the questionnaire scores were computed. The Cronbach's α scores of all questionnaires used in the study ranged from 0.85 to 0.95, indicating high internal consistency reliability.

All statistical analyses were conducted using the Stata software programme (version 17, StataCorp LLC). For normal distributed data, Student's *t* test was used to compare means, and results were expressed as means with standard deviations. For nonnormal distributed data, the Wilcoxon rank-sum test was used, and results were expressed as medians with ranges. Fischer's exact test was used to assess categorical data with small sample sizes. To analyse the relationship between C19 steroids, steroid hormones, and cholesterol levels, we used linear regression models adjusted for age, sex, and BMI.

3 | RESULTS

3.1 | Demographics

A total of 37 individuals with CAH (males: $n = 11$; females; $n = 26$) and 33 controls (males: $n = 9$, females: $n = 24$) were included. Mean age of males with CAH was 31.4 ± 8.1 years and of females 35.4 ± 11.0 years. Phenotypes were distributed as follows in CAH males; SW: $n = 5$, SV: $n = 4$, and NC: $n = 2$, and in CAH females; SW: $n = 13$, SV: $n = 2$, and NC: $n = 11$. Mean age at diagnosis for females with CAH was for SW 0.0 ± 0.0 years, SV 5.5 ± 0.5 years, and NC 16.9 ± 2.6 years. For males with CAH, age at diagnosis was for SW 0.0 ± 0.0 years, SV 5.3 ± 1.8 years, and for NC 10 ± 2.0 years. *CYP21A2* genotype was available for 25 participants. NM_000500.9(CYP21A2):c.332_339del (p.Gly111fs) and NM_000500.9(CYP21A2):c.293-13 C > G (I2 splice) were the most frequent observed variants (Supporting Information: Appendix 1). Steroid use showed that males with CAH received a higher dose of hydrocortisone than females with CAH (Table 1).

3.2 | Biochemistry and hormone analyses

SW females had similar biochemical parameters to NC females, except for lower DHEAS (0.2 ± 0.1 μmol/L vs. 1.5 ± 1.5 μmol/L, $p = 0.006$) and aldosterone (128 ± 58 μmol/L vs. 211 ± 102 μmol/L, $p = 0.02$). CAH was associated with significantly higher levels of 17-OHP and lower levels of DHEAS in both sexes. Aldosterone levels were significantly lower in males with CAH compared with male controls. Females with CAH had a significantly higher haemoglobin level than female controls as well as a higher insulin levels and HOMA-IR (Table 2). There were significant differences between individuals with CAH and controls in terms of HDL-cholesterol, but not in total cholesterol or LDL cholesterol. There was a negative correlation between DHEAS and HDL-cholesterol in individuals with CAH: (β: −2.6 95%CI [−3.7; −1.5]), this correlation was not seen in controls. Regression analysis adjusted for other steroid hormones, age, sex, and BMI indicated that DHEAS was the only contributing factor to this (results not shown). There was a strong correlation ($R^2 > 86\%$) between 11-oxygenated C19 steroids and 17-OHP in CAH individuals but not in controls (Supporting Information: Figure 2). Hormone analyses (ACTH, estradiol, A4, testosterone, SHBG, AMH, LH, FSH, 11-OHA4, 11-KA4, 11-KT, and 11-OHT) and analysis of routine serum biomarkers showed no significant differences between individuals with CAH and controls (all $p > .05$) (Table 2).

Total daily cortisol dose was not correlated with 17-OHP, A4, LH, E2, testosterone or any anthropometric values. However, total daily cortisol dose was positively correlated with the natural logarithm of FSH ($p = 0.001$) but negatively associated with TSH, T3, and T4.

3.3 | Anthropometrics, socioeconomic status, medication use and education

Mean height of both males and females with CAH was lower compared with controls of the same sex (Table 1). CAH females had a significantly higher BMI compared with female controls, while there was no statistical difference in BMI between males with CAH and male controls (Table 1). There were no differences in weight, waist or hip measurements between CAH individuals and their respective sex-matched controls.

The proportion of participants currently working or studying among individuals with CAH (80.1% CI [64%–91%]) and among

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TABLE 1 Anthropometrics, descriptive indices and steroid use in all CAH participants.

	Female			Male		
	CAH	Control	*p* Value	CAH	Control	*p* Value
N	26	24		11	9	
Height (cm)	160.2 ± 6.5	170.1 ± 5.5	**<0.001**	170.5 ± 9.1	182.9 ± 7.9	**0.005**
Weight (kg)	75.7 ± 11.6	73.5 ± 13.1	0.5	80.6 ± 16.3	92.4 ± 25	0.2
Waist (cm)	87.6 ± 14.2	82.5 ± 13.2	0.2	91.2 ± 10.1	91.7 ± 14	0.9
Hip (cm)	107 ± 9.8	102 ± 12.4	0.1	102.3 ± 9.2	105 ± 13	0.6
Hip/waist	1.24 ± 0.2	1.26 ± 0.2	0.8	1.13 ± 0.10	1.15 ± 0.1	0.6
BMI	29.7 ± 5.4	25.5 ± 4.9	**0.006**	27.5 ± 3.3	27.7 ± 7.8	0.9
Age (years)	35.4 ± 11.0	33.3 ± 18.1	0.6	31.4 ± 8.1	32.9 ± 8.1	0.7
Alcohol[a]	2.9 ± 4.4	2.7 ± 2.3	0.8	4.46 ± 4.6	2.0 ± 1.5	0.1
Hydrocortisone, *N* (%)	24 (92)			10 (90)		1.0
Mean daily dose, mg [95%CI]	20 [17–24]			27 [21–34]		**0.04**
Prednisolone, *N* (%)	1 (4)			2 (18)		//
Median daily dose, mg (Range)	10 (NA)			2.5 (NA)		//
Fludrocortisonacetat, *N* (%)	11 (42)			4 (36)		//
Mean daily dose, mg [95%CI]	0.09 [0.04–0.1]			0.1 [0.07–0.2]		//
Dexamethasone, *N* (%)	3 (12)			3 (27)		//
Median daily dose, mg (Range)	0.2 (0.05–0.25)			0.1 (0.1–0.25)		//
Mean daily steroid dose, mg [95%CI]	21 [18–25]			27 [19–34]		0.15

Note: Data are presented as a means ± standard deviation or median (range). Daily steroid dose is calculated based on the combined corticosteroid effect, see text for detail, patients could receive more than one steroid. Fischer's exact test and Student's *T* test are used to calculate *p* values. *P* values < 0.05 are considered significant.

[a]Units per week (unit = 12 g alcohol).

controls (97% CI [81%–100%]) was not different ($p = 0.056$). More individuals with CAH than controls reported difficulties with writing in school or later in life (22.9% CI [12%–40%] vs. 3.0% CI [0%–20%, $p = 0.03$). Many CAH individuals (55.5%) and controls (66.7%) were living with a spouse. There was no significant difference in educational level between the two groups (Table 3).

There were no differences in alcohol consumption, and smoking habits between CAH individuals and their respective controls. Nor were there any differences between CAH individuals and controls regarding self-reported medication use of psycholeptics, psychoanaleptics, or analgesics. CAH individuals reported a significantly higher use of D-vitamin than controls. Use of birth control pills and antihypertensives did not differ between CAH individuals and controls (Table 3). The use of birth control pills correlated with SHBG ($p < 0.001$).

Joint pain was the only health complaint that individuals with CAH reported more frequently than controls (18.0% vs. 0.0%, $p = 0.01$). Whereas symptoms such as tiredness, headaches, reflux, bloating, and abnormal uterine bleeding were equally reported for both CAH individuals and controls. Diabetes mellitus type 2, hypothyroidism, hyperthyroidism, and gynaecomastia were not more frequent among individuals with CAH than among controls (Supporting Information: Appendix 3).

3.4 | Cardiovascular indices

There were no significant differences between individuals with CAH and controls in terms of, AMBP, pulse rate, QTc-interval, and most echocardiographic measures (Supporting Information: Table 4). However, there was a statistically significant difference between females with CAH and controls in terms of PR-interval, E-DEC and E/é. ASC and diastolic blood-pressure was lower in males with CAH than in controls (Supporting Information: Table 4).

3.5 | Autism, anxiety, depression, personality, cognitive failures, and QoL

3.5.1 | Autism

When combining males and females, individuals with CAH scored significantly higher on the Attention Switching subscale than

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TABLE 2 Hormones and additional biochemistry in CAH individuals versus controls.

	Female			Male		
Participants	**CAH**	**Control**	***p* Value**	**CAH**	**Control**	***p* Value**
N	26	24		11	9	
Pituitary hormones						
ACTH (ng/L)	13 (3–236)	15 (7–48)	0.7	33 (9–278)	16 (9–61)	0.3
LH (IU/L)	5.2 (0.3–58.0)	7.0 (0.3–48.2)	0.5	3.3 (0.3–9.4)	4.1 (2.7–5.2)	0.3
FSH (IU/L)	4.7 (0.3–86.0)	6.4 (0.3–113.5)	0.4	7.4 (0.3–12.7)	3.9 (3.0–7.7)	0.4
Sex and adrenal hormones						
Testosterone (nmol/L)	1.0 (0.1–4.1)	1.1 (0.3–2.1)	0.7	14.7 (4.5–27.0)	21 (9.9–25.0)	0.1
Estradiol (nmol/L)	166 (15–3080)	165 (15–1790)	0.9	79 (45–195)	79 (48–135)	0.6
Aldosterone (pmol/L)	133 (102–460)	126 (102–312)	0.9	110 (102–479)	280 (162–557)	**0.002**
A4 (nmol/L)	3.1 (0.3–11.7)	3.1 (0.9–5.2)	0.9	3.4 (1.2–50.2)	3 (1.8–3.9)	0.3
17-OHP (nmol/L)	14.9 (0.4–145.0)	1.0 (0.4–6.6)	**<0.001**	22.0 (5.5–802.0)	3.2 (0.9–4.3)	**<0.001**
DHEAS (μmol/l)	0.3 (0.1–4.5)	3.0 (0.4–7.5)	**<0.001**	1.6 (0.5–9.7)	4.2 (2.7–9.7)	**0.005**
11KA4 (nmol/L)	0.6 (0.1–3.0)	0.6 (0.3–1.3)	0.6	0.9 (0.2–12.7)	0.8 (0.5–2)	1.0
11-OHA4 (nmol/L)	2.3 (0.3–12.7)	2.9 (1.3–6.8)	0.5	4.6 (0.6–91.4)	4.9 (2.3–9.7)	0.8
11KT (nmol/L)	0.4 (0.0–4.1)	0.8 (0.2–2.4)	0.1	1.1 (0.1–28.8)	0.9 (0.4–2.0)	0.7
11-OHT (nmol/L)	0.2 (0.0–1.5)	0.3 (0.1–0.9)	0.1	0.6 (0.6–15.4)	0.5 (0.1–0.9)	0.5
P-SHBG (nmol/L)	71 (9–333)	69 (25–200)	0.9	40 (12–59)	46 (22–56)	0.7
P-AMH (pmol/L)	13.6 (0.2–105.0)	15.1 (0.2–72.0)	0.6	28.5 (0.8–36.5)	33.7 (4.3–76.4)	0.3
Glucose metabolism						
Insulin (pmol/L)	80 (32–515)	58 (14–193)	**0.029**	64 (27–651)	63 (37–190)	0.8
Glucose	5.5 ± 0.6	5.2 ± 0.4	**0.025**	5.3 ± 0.7	5.5 ± 0.5	0.4
HOMA_IR	2.7 (1.0–18.8)	1.9 (0.4–7.7)	**0.018**	2.1 (0.8–27.4)	2.2 (1.2–7.1)	1.0
Additional biochemistry						
PTH (nmol/L)	5.0 ± 1.6	4.9 ± 1.4	0.8	4.3 ± 1.5	5.1 ± 1.3	0.2
Haemoglobin (mmol/L)	8.8 ± 0.8	8.2 ± 0.6	**0.003**	9.5 ± 0.5	9.3 ± 0.2	0.1
Hba1c (mmol/mol)	35.5 ± 7.7	33.2 ± 3.6	0.2	34.5 ± 2.8	33.7 ± 2.2	0.5
TSH (int.U/L)	1.9 (0.0–7.1)	1.6 (0.2–6.9)	0.1	2.1 (0.9–2.9)	1.9 (1.4–5.6)	0.8
T3 (nmol/L)	1.8 (1.3–7.6)	1.6 (1.3–2.3)	0.05	1.9 (1.3–2.4)	1.7 (1.1–2.5)	0.3
T4 (nmol/L)	90 (70–227)	91 (68–141)	0.9	88 (53–102)	83 (64–98)	0.4

Note: Data are represented as mean ± SD or median (range) and compared using Student's *T* test or Wilcoxon-rank sum. *p* Values are bold if <0.05.
Abbreviations: A4, Androstenedione; ACTH, adrenocorticotropic hormone; AMH, anti-Müllerian hormone; DHEAS, dehydroepiandrosterone sulphate; FSH, follicle-stimulating hormone; Hba1C, haemoglobin A1C; HOMA-IR, Homoeostatic Model Assessment for Insulin Resistance; LH, luteinizing hormone; PTH, Parathyroid hormone; SHBG, sex hormone-binding globulin; TSH, Thyroid-Stimulating Hormone; T3, Triiodothyronine; T4, thyroxine; 11-KT, 11-ketotestosterone; 11-KA4, 11-ketoandrostenedione; 11-OHA4, 11β-hydroxyandrostenedione; 17-OHP, 17-hydroxy-progesterone; 11-OHT, 11β-Hydroxytestosterone.

controls (4.3 vs. 3.0, $p = 0.017$), Social scores (3.3 vs. 2.2, $p = 0.015$) and total AQ-scores (17.7 vs. 14.3, $p = 0.012$) (Table 4). Autistic traits did not correlate with any clinical traits or hormones, in males, females or combined (results not shown).

Males with CAH had a significantly higher mean Autism Spectrum Quotient (AQ) total score than male controls and scored significantly higher than male controls on the Social and Attention Switching subscales but not on the Imagination, Attention to detail, or Communication subscales (Table 4). There was no difference in mean AQ total score between females with CAH and controls, nor on any of the AQ subscales (Table 4, Figure 1).

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TABLE 3 Socioeconomic measures in CAH individuals versus controls.

	CAH N = 37	Control N = 33	p Value*
Medication			
Psychiatric medication[a]	6 (16.0%)	3 (9.0%)	0.4
Morphine use	3 (8.1%)	1 (3.0%)	0.4
Paracetamol use	3 (8.1%)	1 (3.0%)	0.4
NSAID use	4 (10.8%)	1 (3.0%)	0.2
Sumatriptan	1 (2.7%)	4 (12.1%)	0.1
D-vitamin supplementation	9 (24.3%)	1 (3.0%)	**0.011**
Birth control pills	4 (10.81%)	4 (12.1%)	0.9
Antihypertensives	2 (5.4%)	0 (0%)	0.2
Working situation			
Currently working	22 (61.1%)	25 (75.8%)	0.2
Not working[b]	7 (19.4%)	1 (3.0%)	0.06
Under education	7 (19.4%)	7 (21.2%)	1.0
School problems			
Problem reading in school	8 (22.9%)	3 (9.1%)	0.3
Problem writing in school	8 (22.9%)	1 (3.0%)	**0.042**
Received specialized education	9 (25.0%)	4 (12.1%)	0.2
Current living situation			0.5
Living with spouse	20 (55.5%)	22 (66.7%)	0.3
Living with parents	4 (11.1%)	1 (3.0%)	0.4
Living with other than parents	3 (8.3%)	3 (9.1%)	1.0
Living alone	7 (19.4%)	4 (12.1%)	0.5
Other living situation	2 (5.5%)	3 (9.1%)	0.7
Higher education			
None	5 (14.7%)	3 (9.1%)	0.7
Less than 3 years	4 (11.8%)	4 (12.1%)	1.0
Skilled craftsmanship	8 (23.5%)	4 (12.1%)	0.4
3–4 years of education	10 (29.4%)	11 (33.3%)	0.6
Longer education >4 years	2 (5.9%)	7 (21.2%)	0.07
Other	5 (14.7%)	4 (12.1%)	1.0
Smoking			
Never	19 (52.7%)	22 (66.6%)	0.2
Previous	13 (36.1%)	8 (24.2%)	0.4
Currently	4 (11.1%)	3 (9.1%)	1.0

Note: Data are presented as absolute numbers with percentages in parentheses.

*Statistical significance, presented in bold, was determined χ^2 test with a significance level of $p < 0.05$ to compare CAH with controls.

[a]Psychiatric medication is antidepressants, benzodiazepines, lithium or antipsychotics.

[b]Not working due to sick leave, leave of absence, early retirement, unemployed, sheltered employment. There were between 1 and 4 missing data in the questionnaires.

3.5.2 | Anxiety and depression

Although not reaching statistical significance, there was a tendency towards increased scores of anxiety, general negative effect, and depressive symptoms among males with CAH compared with male controls (Table 4, Figure 1).

3.5.3 | Personality

Females with CAH had lower scores of extraversion than female controls. The same applied to extraversions in CAH females and males combined compared with controls (43.5 vs. 51.7, $p = 0.005$), and also with regard to openness (47.6 vs. 52.6, $p = 0.04$) (Table 4, Figure 1).

3.5.4 | Cognitive complaints

Males with CAH exhibited a greater extent of cognitive complaints than male controls. In contrast, females with CAH did not exhibit any increase in cognitive complaints compared with female controls (Table 4).

3.5.5 | QoL

Females with CAH had significantly lower scores with regard to general health, physical limitations, and physical function than female controls, which also applied to CAH females and males combined. CAH males scored significantly lower than male controls regarding vitality. No differences were found regarding mental health and social function, neither for males and females separately, nor when combined (Table 4).

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TABLE 4 CAH individuals versus controls in terms of personality, social engagement, anxiety and depression.

	Female			Male			Combined
Participants	CAH	Control	*p* Value	CAH	Control	*p* Value	*p* value
N	26	24		11	9		
AQ Total	16.8 ± 6.3	14.1 ± 4.3	0.09	19.9 ± 6.5	14.9 ± 4.5	0.07	**0.012**
Social	3.1 ± 2.1	2.3 ± 1.4	0.1	3.7 ± 2.4	1.8 ± 1.2	**0.048**	**0.015**
Imagination	3.3 ± 2.1	2.7 ± 2.1	0.3	4.2 ± 2.4	2.7 ± 1.6	0.1	0.07
Attention switching	3.7 ± 2.2	2.9 ± 1.8	0.2	5.6 ± 2.3	3.3 ± 1.7	**0.025**	**0.017**
Attention to detail	5.0 ± 2.8	5.3 ± 2.4	0.7	3.9 ± 1.4	5.1 ± 2.8	0.2	0.3
Communication	2.3 ± 1.8	1.9 ± 1.6	0.4	2.9 ± 1.4	2.7 ± 1.9	0.8	0.3
Cognitive complaints							
Total cognitive complaints	30.9 ± 9	33.9 ± 10	0.3	37.1 ± 12	24.3 ± 12	**0.034**	0.6
Anxiety	1.8 ± 1.9	3.2 ± 3.4	0.09	2.9 ± 2.5	1.0 ± 1.3	0.06	0.5
General negative effect	5.2 ± 5.2	5.8 ± 6.4	0.7	6.9 ± 7.3	2.3 ± 3.1	0.1	0.6
Depression	3.1 ± 3.3	3.2 ± 3.5	0.9	4.7 ± 5.9	1.7 ± 2.2	0.2	0.4
NEO-PI-R							
Conscientiousness	50.4 ± 13.6	56.7 ± 10.9	0.08	55.5 ± 10.0	58.6 ± 12.4	0.6	0.08
Agreeableness	48.6 ± 12.2	47.3 ± 11.1	0.7	50.2 ± 11.7	53.8 ± 11.7	0.5	1.0
Openness	47.8 ± 10.2	52.1 ± 8.3	0.1	47.1 ± 14.7	54.1 ± 8.5	0.2	**0.043**
Neuroticism	48.3 ± 12.8	50.6 ± 10.8	0.5	51.7 ± 13.8	47.3 ± 9.9	0.4	0.9
Extraversion	45.3 ± 10.4	52.7 ± 12.6	**0.031**	39.2 ± 11.1	49.0 ± 13.0	0.09	**0.005**
Quality of life – SF36							
General health	0.67 ± 0.2	0.81 ± 0.1	**0.013**	0.69 ± 0.2	0.82 ± 0.2	0.2	**0.005**
Physical limitations	0.85 ± 0.2	0.99 ± 0.03	**0.006**	0.91 ± 0.2	0.95 ± 0.1	0.9	**0.014**
Physical function	0.90 ± 0.2	0.98 ± 0.04	**0.025**	0.95 ± 0.1	0.95 ± 0.1	0.9	**0.039**
Mental health	0.80 ± 0.1	0.81 ± 0.2	0.7	0.77 ± 0.2	0.88 ± 0.03	0.2	0.3
Vitality	0.58 ± 0.2	0.63 ± 0.2	0.5	0.59 ± 0.06	0.79 ± 0.2	**0.046**	0.2
Social function	0.89 ± 0.2	0.93 ± 0.1	0.3	0.91 ± 0.1	1.0 ± 0	0.1	0.2

Note: Mean ± SD, Student's *t* test was used for statistical assessment. $p < 0.05$ are bold. Combined *p* value: both male and female CAH individuals compared with all controls.

4 | DISCUSSION

In this observational study of individuals with CAH, we showed a divergent comorbidity profile of females compared with males with CAH. While females with CAH were overweight and showed some degree of insulin resistance, this was not the case for males with CAH. Males with CAH exhibited more autistic symptoms and cognitive complaints but almost comparable QoL profile and personality profile when compared with age-matched male controls. Females with CAH, on the other hand, reported lower QoL and lower level of extraversion, but had a more comparable autistic spectrum profile when compared with age-matched female controls. However, females and males with CAH combined demonstrated a decreased QoL and a less extroverted personality, faced physical limitations, and exhibited increased autistic traits. Concluding an increased rate of autistic traits in CAH patients should be done with caution due to sample sizes. Future studies should investigate this before more substantial conclusions can be drawn.

The distribution of CAH subtypes among the investigated CAH individuals resembled the previously described overall Danish CAH cohort.[5] Also, the demographic and anthropometric findings are consistent with previous research, showing reduced height in both females and males with CAH and increased BMI in females with CAH.[28] The decreased height in individuals with CAH may be due to excessive glucocorticoid treatment during childhood which stunts growth in childhood and adolescence and may increase BMI.[29] However, these effects may be less pronounced in future CAH individuals due to increased awareness of overtreatment during childhood and adolescence.

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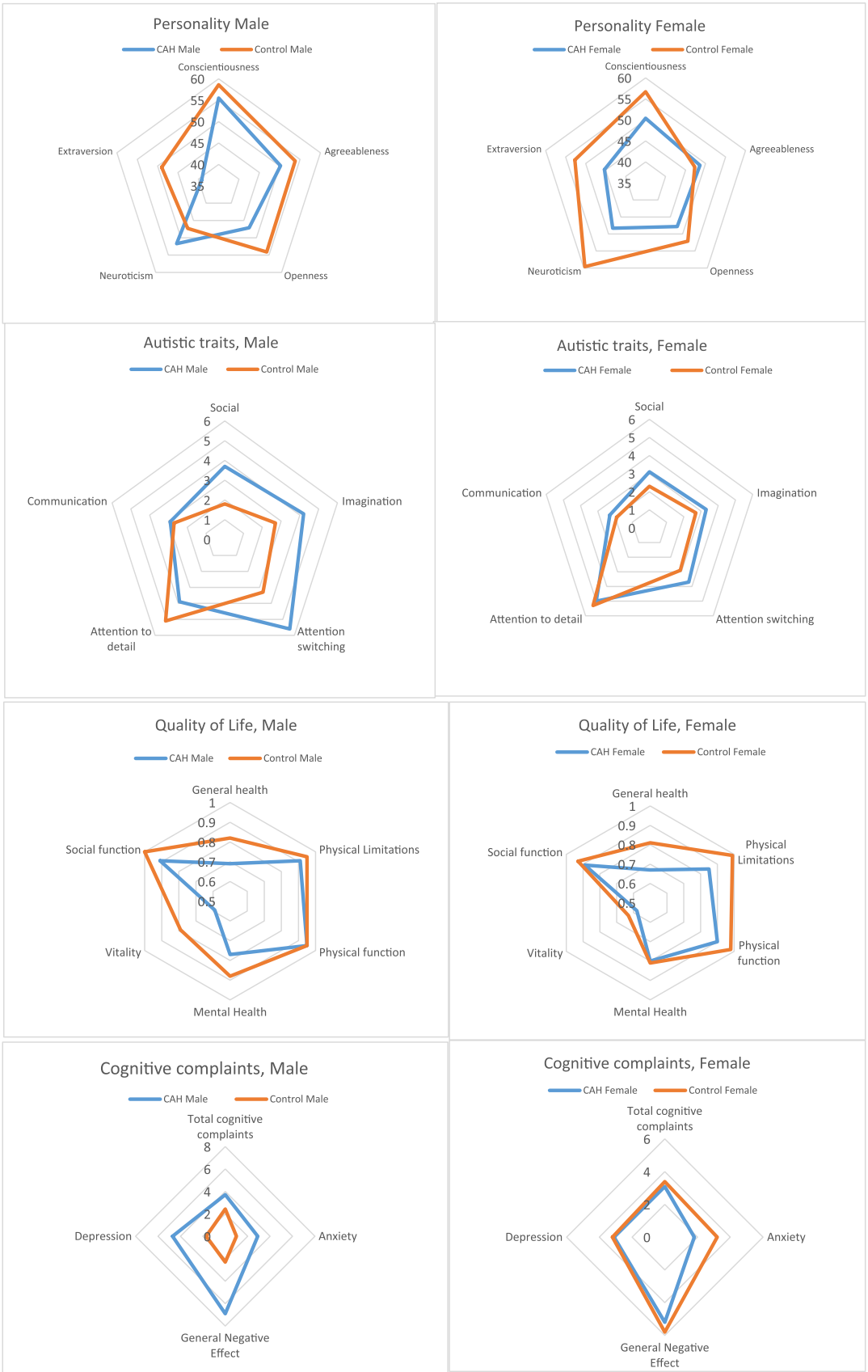

FIGURE 1 Radar plots of autistic traits (higher scores indicating more autistic traits), Personality, Quality of life (higher scores indicating better quality of life) and Cognitive complaints (higher scores indicating higher levels of cognitive complaints) in CAH males and females compared with controls.

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As expected, CAH was associated with higher levels of 17-OHP. Surprisingly, this was not related to the total daily cortisol dose and underlines the need for individualised treatment of CAH. Total daily cortisol dose was positively correlated with FSH, suggesting that some patients may have needed even higher doses of cortisol to normalize FSH, which may indicate slight undertreatment of some patients. However, levels of DHEAS, and in males with CAH also androstenedione, were found to be suppressed, which is an expected outcome of adequate or over-treatment. The daily cortisol dose was not correlated with sex, weight, or height, suggesting that other individual factors may determine the daily requirements, emphasizing the need for individualized dosing. Additionally, females with CAH were found to have higher levels of haemoglobin compared with controls, which is likely due to the stimulating effect of testosterone on the erythrocytosis.[30] Interestingly, we found no increase in testosterone level among females with CAH and no sex-specific correlation between testosterone and haemoglobin. In contrast, a UK study found a correlation between concentrations of testosterone and haemoglobin in two cohorts (n = 23 and n = 53) of women with CAH.[30] One possible explanation is that in the UK study levels of 17-OHP, testosterone and androstenedione were higher, indicating a less well-treated cohort although haemoglobin levels where similar.[30]

We found a strong negative correlation between DHEAS and HDL-levels, despite adjustment for relevant variables. This correlation has also previously been described,[29] however how DHEAS and HDL relates remains unexplained.

Females with CAH had higher levels of fasting plasma insulin and reduced insulin sensitivity compared with female controls. Although mean long-term blood glucose (HbA1c) levels were slightly higher in the female CAH group, this difference was not statistically significant. Additionally, the decrease in insulin sensitivity in CAH females was partially driven by the increased BMI. A previous study has reported increased HOMA-IR (a marker of insulin resistance) in individuals with CAH, which aligns with our findings.[6] A well-known cause of hyperinsulinemia and increased insulin resistance in CAH is overtreatment with corticosteroids, especially in virilized females. Hyperinsulinemia in individuals with CAH has previously been described as a reduction of insulin clearance rather than increased beta-cell function. The exact pathogenesis of insulin resistance in CAH remains unclear, but glucocorticoid overexposure may be a possible explanation.[31]

11-oxygenated C19 steroids, have been suggested to potentially serve as biomarkers of treatment efficacy in CAH.[32] We found that C19 steroids such as 11-OHA4, 11-KT, 11-OHT and 11-KA4, exhibited almost perfect correlations with A4 and 17-OHP in CAH individuals. Interestingly, in controls, the 11-oxygenated C19 steroids did not correlate with 17-OHP and androstenedione. However, they did show significant correlation with a variety of clinical traits such as BMI, blood pressure, alanine aminotransferase, alkaline phosphatase, haemoglobin, and echocardiographic indices such as VSD and AMS. These correlations were primarily driven by 11-OHA4. Our findings suggest that measuring 11-oxygenated C19 steroids in CAH individuals does not offer additional clinical information, but 11-oxygenated C19 steroids may have a greater impact in controls than previously assumed. However, previous conflicting results on this issue warrant further research.

In terms of autism spectrum symptoms, the present study shows that individuals with CAH had higher scores on the AQ-test and this difference was primarily driven by males with CAH. Males with CAH exhibited higher scores in social and attention switching, which is consistent with previous literature.[6] Interestingly, when comparing our findings on personality traits with those on autistic traits, we noted that individuals with CAH scored lower in traits such as openness and extraversion. These traits align with the elevated autistic scores, as they also relate to being less imaginative and more conservative in thinking. Seven individuals with CAH had high scores (> 26) on the AQ-test, suggesting the presence of autistic spectrum disorder. These findings provide further evidence of the relationship between CAH and autism, particularly in terms of social and attention switching behaviours.[22] CAH has previously been associated with impaired psychosocial outcomes.[33] Increased rates of autism have previously been theorized to arise from androgen excess in the amniotic fluid; however, this finding has been criticized. Kung et al. found no evidence supporting this theory.[34] This has led researchers to theorize that androgen excess in early childhood and adolescence may influence behaviour and possibly brain morphology. Indeed, some brain alterations have been observed using cerebral MRI in individuals with CAH. However, the connection between glucocorticoids, androgens, behaviour, and psychiatric disease remains an exploratory field.[35] In the present study we do not have detailed information concerning childhood treatment and thus their development, which would have been valuable information. All patients with classical salt-wasting CAH were diagnosed immediately after birth and treated with glucocorticoids, while patients with SV and NC CAH were only treated once they were diagnosed. This dichotomy with especially the classical salt-wasting CAH being treated and the simple virilizing CAH patients only being treated upon diagnosis, but likely relatively deficient in cortisol levels, could well impact brain development and thus the late outcome during adulthood. Studies have indicated that individuals with CAH are prone to experiencing higher levels of depression, and children diagnosed with CAH have experienced elevated levels of social anxiety.[36] Our study did not support that CAH females had increased levels of depressive symptoms compared with female controls. CAH males reported higher levels of anxiety and depressive symptoms compared with controls. These findings suggest that in terms of cognitive complaints, men with CAH may be more affected than females with CAH. While some studies have demonstrated normal psychometric intelligence in individuals with CAH, others have reported impaired executive functions and decreased IQ.[12,37] These differences may have an impact on the socioeconomic findings. CAH individuals reported challenges in the labour market, with a tendency towards higher rates of unemployment, although not significant. They reported challenges in school, with difficulty writing, which may display increased need for specialized education.

CAH individuals rated their general health lower than controls. Among females, physical function and physical limitations were lower, while males reported decreased vitality. No individual predictors for decreased general health were found other than having CAH or not.

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In general, this cohort was well treated and still showed decreased general health, increased autistic traits, and a less extroverted personality. One study on individuals with CAH suggested that the reported decrease in QoL may be attributed to having a chronic illness with its associated comorbidities and hospitalizations, the need for lifelong medication, sexual issues, and the fear of passing it on to their children.[20]

One limitation of this observational study is the sample size of 37 individuals with CAH and 33 controls, which limit the statistical power to detect smaller differences between individuals with CAH and controls. The risk of type 1 and 2 errors is high in studies with low number of participants and high numbers of clinical variables. We have interpreted data with caution and emphasize that results should be viewed with this in mind. Autistic scores should be interpreted with caution since scores may be inflated due to co-morbid anxiety. The study was conducted at a single tertiary centre, although recruitment was performed at two centres, generalization should be done with caution. Another limitation is the lack of follow-up to assess changes in the condition over time, which could be important in understanding the natural history of the CAH. Most of the genotype subgroups were too small to use for statistical assessment, one study has shown equally impaired health status among CAH subtypes which we use for justifying the combination of subtypes to increase statistical power.[38] Future studies should include subgroup, multicenter longitudinal studies to improve generalization.

One of the study's strengths is its comprehensive examination array, which adds credibility to the findings. All questionnaires used in the study demonstrated good internal consistency, as indicated by their Cronbach's alpha values, suggesting their reliability in measuring the intended constructs.

5 | CONCLUSION

Males with CAH have a higher level of autistic traits and females with CAH showed reduced QoL, although the cohort is generally well-treated. These reductions in QoL are primarily attributed to physical limitations. Our study highlights the critical importance of early diagnosis in facilitating the initiation of tailored, individualized treatment, aimed at minimizing complications. Future studies with more focus on QoL could be of great importance to increase patient care in CAH individuals as this impairment might improve with good clinical care, which future studies should be investigating this using longitudinal studies. Using 11-oxygenated C19-steroids as biomarkers did not offer incremental information in this study. Cardiovascular indices show slight alterations in individuals with CAH, with some indications of diastolic dysfunction which could indicate problems in the future when this population ages.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Some or all data sets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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REFERENCES

1. Moran C, Azziz R, Carmina E, et al. 21-Hydroxylase-deficient nonclassic adrenal hyperplasia is a progressive disorder: a multicenter study. *Am J Obstet Gynecol*. 2000;183(6):1468-1474. doi:10.1067/mob.2000.108020
2. El-Maouche D, Arlt W, Merke DP. Congenital adrenal hyperplasia. *Lancet*. 2017;390(10108):2194-2210. doi:10.1016/s0140-6736(17)31431-9
3. Nimkarn S, Lin-Su K, Berglind N, Wilson RC, New MI. Aldosterone-to-renin ratio as a marker for disease severity in 21-hydroxylase deficiency congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2007;92(1):137-142. doi:10.1210/jc.2006-0964
4. Reisch N, Willige M, Kohn D, et al. Frequency and causes of adrenal crises over lifetime in patients with 21-hydroxylase deficiency. *Eur J Endocrinol*. 2012;167(1):35-42. doi:10.1530/eje-12-0161
5. Berglund A, Ornstrup MJ, Lind-Holst M, et al. Epidemiology and diagnostic trends of congenital adrenal hyperplasia in Denmark: a retrospective, population-based study. *Lancet Reg Health - Europe*. 2023;28:100598. doi:10.1016/j.lanepe.2023.100598
6. Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, et al. Congenital adrenal hyperplasia—current insights in pathophysiology, diagnostics, and management. *Endocr Rev*. 2022;43(1):91-159. doi:10.1210/endrev/bnab016
7. Gidlöf S, Falhammar H, Thilén A, et al. One hundred years of congenital adrenal hyperplasia in Sweden: a retrospective, population-based cohort study. *Lancet Diabetes Endocrinol*. 2013;1(1):35-42. doi:10.1016/s2213-8587(13)70007-x
8. Hannah-Shmouni F, Morissette R, Sinaii N, et al. Revisiting the prevalence of nonclassic congenital adrenal hyperplasia in US Ashkenazi Jews and Caucasians. *Genet Med*. 2017;19(11):1276-1279. doi:10.1038/gim.2017.46
9. Pretorius E, Arlt W, Storbeck KH. A new dawn for androgens: novel lessons from 11-oxygenated C19 steroids. *Mol Cell Endocrinol*. 2017;441:76-85. doi:10.1016/j.mce.2016.08.014

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10. Barbot M, Mazzeo P, Lazzara M, Ceccato F, Scaroni C. Metabolic syndrome and cardiovascular morbidity in patients with congenital adrenal hyperplasia. *Front Endocrinol*. 2022;13:934675. doi:10.3389/fendo.2022.934675.
11. Improda N, Barbieri F, Ciccarelli GP, Capalbo D, Salerno M. Cardiovascular health in children and adolescents with congenital adrenal hyperplasia due to 21-hydroxilase deficiency. *Front Endocrinol*. 2019;10:212. doi:10.3389/fendo.2019.00212.
12. Karlsson L, Gezelius A, Nordenström A, Hirvikoski T, Lajic S. Cognitive impairment in adolescents and adults with congenital adrenal hyperplasia. *Clin Endocrinol*. 2017;87(6):651-659. doi:10.1111/cen.13441
13. Knickmeyer R, Baron-Cohen S, Fane BA, et al. Androgens and autistic traits: a study of individuals with congenital adrenal hyperplasia. *Horm Behav*. 2006;50(1):148-153. doi:10.1016/j.yhbeh.2006.02.006
14. Mathews GA, Fane BA, Conway GS, Brook CGD, Hines M. Personality and congenital adrenal hyperplasia: possible effects of prenatal androgen exposure. *Horm Behav*. 2009;55(2):285-291. doi:10.1016/j.yhbeh.2008.11.007
15. Pasterski V, Hindmarsh P, Geffner M, Brook C, Brain C, Hines M. Increased aggression and activity level in 3- to 11-year-old girls with congenital adrenal hyperplasia (CAH). *Horm Behav*. 2007;52(3):368-374. doi:10.1016/j.yhbeh.2007.05.015
16. Berenbaum SA, Resnick SM. Early androgen effects on aggression in children and adults with congenital adrenal hyperplasia. *Psychoneuroendocrinology*. 1997;22(7):505-515. doi:10.1016/s0306-4530(97)00049-8
17. Becker DE. Basic and clinical pharmacology of glucocorticosteroids. *Anesth Prog*. 2013;60(1):25-32. doi:10.2344/0003-3006-60.1.25
18. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412-419. doi:10.1007/bf00280883
19. Han TS, Krone N, Willis DS, et al. Quality of life in adults with congenital adrenal hyperplasia relates to glucocorticoid treatment, adiposity and insulin resistance: United Kingdom Congenital adrenal Hyperplasia Adult Study Executive (CaHASE). *Eur J Endocrinol*. 2013;168(6):887-893. doi:10.1530/eje-13-0128
20. Shafaay EA, Aldriweesh MA, Aljahdali GL, et al. The clinical characteristics and quality of life of 248 pediatric and adult patients with Congenital Adrenal Hyperplasia. *Front Endocrinol*. 2023;14:1122435. doi:10.3389/fendo.2023.1122435.
21. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *J Autism Dev Disord*. 2001;31(1):5-17. doi:10.1023/a:1005653411471
22. Broadbent J, Galic I, Stokes MA. Validation of autism spectrum quotient adult version in an Australian sample. *Autism Res Treat*. 2013;2013:984205. doi:10.1155/2013/984205
23. Gomez R, Stavropoulos V, Zarate D, Palikara O. Symptom Checklist-90-Revised: a structural examination in relation to family functioning. *PLoS One*. 2021;16(3):e0247902. doi:10.1371/journal.pone.0247902
24. Costa Paul T., Robert R. McCrae. The revised neo personality inventory (neo-pi-r). In *The SAGE handbook of personality theory and assessment: volume 2 – personality measurement and testing*. SAGE Publications Ltd; 2008:179-198. doi:10.4135/9781849200479
25. Goodman ZT, Timpano KR, Llabre MM, Bainter SA. Revisiting the factor structure and construct validity of the Cognitive Failures Questionnaire. *Psychol Assess*. 2022;34(7):671-683. doi:10.1037/pas0001127
26. Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. *Br J Clin Psychol*. 1982;21(1):1-16. doi:10.1111/j.2044-8260.1982.tb01421.x
27. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: scoping review. *SAGE Open Med*. 2016;4:2050312116671725. doi:10.1177/2050312116671725
28. Bonfig W, Bechtold S, Schmidt H, Knorr D, Schwarz HP. Reduced final height outcome in congenital adrenal hyperplasia under prednisone treatment: deceleration of growth velocity during puberty. *J Clin Endocrinol Metab*. 2007;92(5):1635-1639. doi:10.1210/jc.2006-2109
29. Qin Y, O. Santos H, Khani V, Tan SC, Zhi Y. Effects of dehydroepiandrosterone (DHEA) supplementation on the lipid profile: a systematic review and dose-response meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis*. 2020;30(9):1465-1475. doi:10.1016/j.numecd.2020.05.015
30. Karunasena N, Han TS, Mallappa A, et al. Androgens correlate with increased erythropoiesis in women with congenital adrenal hyperplasia. *Clin Endocrinol*. 2017;86(1):19-25. doi:10.1111/cen.13148
31. de Oliveira DM, Tura A, Vasques ACJ, et al. Insulin resistance in congenital adrenal hyperplasia is compensated for by reduced insulin clearance. *J Clin Endocrinol Metab*. 2021;106(4):1574-1585. doi:10.1210/clinem/dgab010
32. Kamrath C, Wettstaedt L, Boettcher C, Hartmann MF, Wudy SA. Androgen excess is due to elevated 11-oxygenated androgens in treated children with congenital adrenal hyperplasia. *J Steroid Biochem Mol Biol*. 2018;178:221-228. doi:10.1016/j.jsbmb.2017.12.016
33. Strandqvist A, Falhammar H, Lichtenstein P, et al. Suboptimal psychosocial outcomes in patients with congenital adrenal hyperplasia: epidemiological studies in a nonbiased national cohort in Sweden. *J Clin Endocrinol Metab*. 2014;99(4):1425-1432. doi:10.1210/jc.2013-3326
34. Kung KTF, Spencer D, Pasterski V, et al. No relationship between prenatal androgen exposure and autistic traits: convergent evidence from studies of children with congenital adrenal hyperplasia and of amniotic testosterone concentrations in typically developing children. *J Child Psychol Psychiatry*. 2016;57(12):1455-1462. doi:10.1111/jcpp.12602
35. Khalifeh N, Omary A, Cotter DL, Kim MS, Geffner ME, Herting MM. Congenital adrenal hyperplasia and brain health: a systematic review of structural, functional, and diffusion magnetic resonance imaging (MRI) investigations. *J Child Neurol*. 2022;37(8-9):758-783. doi:10.1177/08830738221100886
36. Engberg H, Butwicka A, Nordenström A, et al. Congenital adrenal hyperplasia and risk for psychiatric disorders in girls and women born between 1915 and 2010: a total population study. *Psychoneuroendocrinology*. 2015;60:195-205. doi:10.1016/j.psyneuen.2015.06.017
37. Johannsen TH, Ripa CPL, Reinisch JM, Schwartz M, Mortensen EL, Main KM. Impaired cognitive function in women with congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2006;91(4):1376-1381. doi:10.1210/jc.2005-1959
38. Wilson C. Adult CAH—does genotype correlate with phenotype? *Nat Rev Endocrinol*. 2013;9(4):187. doi:10.1038/nrendo.2013.32

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