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The impact of adherence and therapy regimens on quality of life in patients with congenital adrenal hyperplasia

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Abstract

Objective: Varying outcomes regarding the quality of life (QoL) have been reported in patients with congenital adrenal hyperplasia (CAH). To assess the impact of adherence rate to medical therapy regimens on QoL in patients with CAH.

Patients: Adolescents and adults aged 15–72 years with CAH due to 21-hydroxylase deficiency at Karolinska University Hospital, Stockholm, Sweden.

Measurements: QoL was assessed using the Addison QoL ($n = 72$) and RAND 36 questionnaires ($n = 75$). Adherence to therapy regimens was measured using the Adherence Starts with Knowledge questionnaire (ASK-12). Associations between QoL, type of glucocorticoid therapy prescribed and ASK-12 results were examined. Results were compared to reference RAND 36 data obtained from a representative sample from the general Swedish population.

Results: A good adherence rate to therapy regimens and a younger age were key factors for a better QoL in study participants with CAH. Younger patients on hydrocortisone and with good adherence had higher RAND 36 scores than older patients on prednisolone independently adherence. Participants with classic CAH (both the salt-wasting and simple virilizing form) reported higher QoL than those with nonclassic CAH. Patients with CAH, especially nonclassic, more frequently reported an impaired QoL than the general population, especially regarding limitations related to body pain, vitality and mental health.

Conclusion: A poor adherence rate to therapy regimens, rather than type of glucocorticoid was associated with impaired QoL in adolescents and adults with CAH.

KEYWORDS

adherence, adolescent, adults, congenital adrenal hyperplasia, quality of life, therapy

1 | INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a rare endocrine disorder of adrenal steroid biosynthesis and is characterized by impaired cortisol synthesis, hypoaldosteronism and hyperandrogenism.[1,2] Life-long oral glucocorticoid supplementation is essential for patients with classic CAH, including the salt-wasting (SW) and the simple virilizing (SV) forms.[1] As standard glucocorticoid supplementation cannot entirely mimic the normal circadian cortisol rhythm, supraphysiological doses are often needed to reduce excessive levels of androgen, which can lead to long-term adverse effects.[3] In nonclassic (NC) CAH, which is the milder form of the disorder, glucocorticoid supplementation is not vital but is often used to control the symptoms of excessive androgen levels.[4]

Impaired quality of life (QoL) and psychological morbidity have been more frequently observed in patients with adrenal insufficiency than in normal populations.[5] Studies investigating health-related outcomes including QoL in patients with CAH have shown conflicting results. Some have reported poor QoL, while others have reported better, similar, or only mildly impaired QoL in patients with CAH when compared with controls or the general population.[6–9]

Patients' nonadherence to medical therapy regimens is a prevalent and persistent healthcare problem for healthcare providers. External factors, such as the healthcare system, therapy characteristics, duration of the disease and internal factors including patients' attitudes and beliefs regarding medication can all affect adherence.[10–12] An earlier retrospective, matched cohort study found that patients with CAH had higher mortality and depression rates and lower treatment adherence rates than matched controls.[13]

To understand the impact of adherence and type of glucocorticoid regimen on physical, mental and emotional health and social functioning in patients with CAH, several factors need to be studied. The aim of the present study was to assess the impact of adherence rates and therapy regimens on QoL in patients with CAH.

2 | MATERIALS AND METHODS

2.1 | Subjects

The investigated cohort comprised 75 adolescents and adults aged 15–72 years with CAH. They were recruited from the Department of Paediatric Endocrinology at Astrid Lindgren Children's Hospital, Department of Endocrinology and the Department of Gynecology and Reproductive Medicine at Karolinska University Hospital, all in Stockholm, Sweden. A detailed description of the cohort has been previously published.[14]

In total, 54%, 23% and 23% of participants had the SW, SV and NC phenotypes, respectively. Seventy-seven percent had the classic form of CAH (SW and SV phenotypes). All had a 21-hydroxylase deficiency.

The subjects were divided into two age groups; adolescents and young adults ≤30 years of age (age group 1) and adults >30 years of age (age group 2), respectively. The cutoff of 30 years was used in accordance with several other CAH studies.[15–17]

The two types of glucocorticoids prescribed were prednisolone and hydrocortisone. In addition, the majority of participants were also prescribed mineralocorticoid replacement therapy. QoL was measured using self-reported questionnaires.[18,19]

The study was approved by the Regional Ethics Committee in Stockholm, Sweden. All participants provided written informed consent.

3 | QUESTIONNAIRES

3.1 | Measurements of quality of life

The Addison Quality of Life (AddiQoL) questionnaire has previously been used to assess QoL in patients suffering from adrenal insufficiency.[18] The questionnaire consists of 30 items divided into the subscales Fatigue, Symptoms, Emotions and Miscellaneous. AddiQoL, established by the European consortium EURADRENAL, has been translated into several European languages and tested in a multicenter study to ensure construct validity and reliability.[18] Each question is responded to by giving a score ranging from 1 to 4. A total score is obtained by adding together the scores of all the questions (total score range 30–120). Higher scores indicate a better QoL. AddiQoL consists of four subscales; *Fatigue* includes questions about general health and daily activities, *Emotion* assesses emotional health, *Symptoms* assesses physical symptoms and concerns about health and *Miscellaneous* includes questions about sleep and feelings when waking up. The item "I am satisfied with my sex life" was excluded from the total score due to a low response rate.

The 36-item Short-Form Health Survey (SF-36) is one of the most commonly used instruments to assess health-related quality of life. A version of the original instrument is available as RAND 36-Item Health Survey (RAND 36) and has not been specifically designed for a particular disease or treatment group.[19,20] RAND 36 is a validated multidimensional instrument that allows for self-reported scores of physical, mental and emotional wellbeing and contains 36 questions measuring both positive and negative health status.[19]

Eight subscales are included in RAND 36. The scale for *Physical functioning* (PF) measures work-related problems or difficulties performing other daily activities in the last 4 weeks. *Role function/Physical (RP)* includes questions regarding physical functioning and *Pain (BP)* addresses the amount of pain experienced and limitations caused by body pain. *General health (GH)* measures a subjective evaluation of general health status. The items included in the *Vitality (V)* subscale address feelings of energy and tiredness. The *Social functioning (SF)* subscale considers limitations to social activities. The *Role functioning/Emotional (RE)* subscale includes items on emotional functioning, while the subscale for *Mental health (MH)* includes questions about feelings of depression and nervousness. Finally, an item has been added regarding the experienced change in health; it asks respondents to compare general health now to 1 year ago and it is not included in one of the eight dimensions. Minor differences exist between the two

instruments RAND-36 and SF-36 in the scoring procedures for two of the eight subscales.[21] Reference data were obtained from a representative sample of the Swedish population ($n = 1378$), aged 15–75 years, that is commonly used as a control population.[22]

3.2 | Measurements of therapies

Therapies prescribing prednisolone, hydrocortisone, or no treatment were compared, after which type of glucocorticoids were compared. The hydrocortisone-equivalent dose was calculated based on the following formula; 1 mg of prednisolone = 4 mg hydrocortisone.[23] Thereafter, hydrocortisone-equivalent dose and number of doses per day were analyzed.

3.3 | Measurements of adherence

Adherence Starts with Knowledge (ASK-12) is a validated instrument that includes a 12-item scale with three adherence-related subscales; *Behaviour* (five items), *Health beliefs* (four items) and *Inconvenience/forgetfulness* (three items). Higher scores indicate lower adherence rates. A total score of ASK-12 < 22 was categorised as a good adherence rate and ≥22 was categorised as a poor adherence rate.[24,25]

3.4 | Statistical analysis

Results are presented as the mean ± SD or median (interquartile range [IQR]) according to the underlying distribution or group size. Comparisons between the two groups were made using the *t* test and one-sample *t* test when data were normally distributed, otherwise the Mann–Whitney rank-sum test was used and the median and IQR were reported. When continuous variables were compared in three groups, a one-way analysis of variance (normal distributions) was used. When a statistical significance was found, a posthoc analysis was performed using Scheffé's test, otherwise, the Kruskal–Wallis test was used. χ^2 test was used in frequency table calculations and Fisher's exact test was used when the expected frequency was small (<5). General linear models were performed to examine the associations between total QoL scores and phenotype/therapy regimen while controlling for potential covariates. Correlations between variables were assessed using linear regression analysis. All tests were two-sided and statistical significance was set at $p < .05$. Statistical analyses were performed using SPSS for Windows version 22 (SPSS).

4 | RESULTS

The cohort consisted of 75 patients with CAH aged 15–72 years answering QoL questionnaires; AddiQoL and RAND 36. Table 1 presents the clinical characteristics of the study population. Seventy-one participants answered both questionnaires—95% of the entire cohort.

All female patients with SW CAH had had genital surgery in the neonatal period ($n = 15$). Among women with SV CAH some had not undergone surgery. A comparison of QoL in relation to surgery is difficult as the frequency of genital surgery is related to the severity of CAH. The number of patients in this cohort was however small and did not allow for a statistical assessment concerning genital surgery and QoL.

Thirty-one (41%) of the adult participants were living with a partner while 20 (27%) were living alone, with significantly lower AddiQoL and RAND 36 scores compared with those living with a partner (data not shown).

4.1 | AddiQoL total score

The clinical scores of patients who completed the questionnaire AddiQoL which includes 29 items are presented in Table 2. The questionnaire was completed by 95% of the total cohort (a total of 71 patients, 56% male; form of CAH: 50% SW, 25% SV and 25% NC).

4.1.1 | Gender, phenotypes and age groups

A clear gender difference was found, with higher total scores in males than in females ($p = .01$). There was a tendency for NC participants to have lower AddiQoL scores than those with SW or SV CAH. The posthoc analysis revealed no significant difference between the different phenotypes of CAH. When SW and SV (both classic CAH) participants were compared with NC participants, higher total AddiQoL scores were found in those with classic CAH. When adjusted for gender, however, these differences were not statistically significant. When comparing participants ≤30-years-old with those who were >30 years old, significantly higher AddiQoL total scores were found in the younger group.

4.1.2 | Glucocorticoid therapy

Glucocorticoids were prescribed to 92% of participants. Forty-one (58%) were prescribed prednisolone treatment, 24 (34%) were prescribed hydrocortisone treatment and 6 (8%) were not prescribed any glucocorticoid treatment. No significant differences in AddiQoL total scores were found when these two glucocorticoid therapy options were compared. No associations between AddiQoL scores, equivalent dose of HC per day and number of doses per day were found.

4.2 | AddiQoL subscores

4.2.1 | Gender and phenotypes

We found gender differences in the subscales Emotions, Symptoms and Miscellaneous with higher scores found in male participants. There were no gender differences found in the fatigue subscales. Participants with

TABLE 1 Clinical characteristics of patients with congenital adrenal hyperplasia who answered quality of life questionnaires

	Total	SW	SV	NC	CF	Aged ≤30 years	SW	SV	NC	CF	Aged >30 years	SW	SV	NC	CF
Number, *n* (%)	75	41 (54)	17 (23)	17 (23)	58 (77)	34	23 (67)	6 (18)	5 (15)	29 (85)	41	18 (44)	11 (27)	12 (29)	29 (71)
Male/Female	44/31	26/15	14/3	4/13	40/18	23/11	15/8	6/0	2/3	21/8	21/20	11/7	8/3	2/10	19/10
Age (years), mean (SD)	35 (16.2)	31.4 (15.5)	40.3 (17.5)	38.3 (15.2)	33.9 (16.5)	20 (5.5)	19.6 (6.1)	20.4 (6.3)	20.6 (5.4)	19.8 (6)	47.4 (10.3)	46.4 (9.7)	51 (10.2)	45.7 (11.2)	48.2 (10)
BMI, missing 1, mean (SD)	25.4 (4.6)	25 (4.6)	26.7 (5.7)	25.1 (5.1)	25.5 (3.5)	23.8 (4.8)	24.3 (5.4)	21.5 (1.4)	24.4 (3.8)	23.8 (5)	26.7 (4.1)	25.8 (3.1)	29.8 (4.9)	25.4 (3.4)	27.2 (4.2)
Therapy															
Prednisolone, missing 1 SV, *n* (%)	42 (56)	23 (56)	10 (59)	9 (53)	33 (57)	8 (24)	6 (26)	1 (17)	1 (20)	7 (24)	34 (83)	17 (94)	9 (82)	8 (67)	26 (90)
HC-equivalent dose mg, mean (SD)	22.6 (8)	23.1 (6.1)	28.3 (9.7)	15.5 (5.3)	24.6 (7.5)	24.5 (5.6)	24.3 (5.9)	30	20	25.1 (5.8)	22.1 (8.5)	22.6 (6.3)	28.1 (10.3)	15 (5.3)	24.4 (8)
1 dose/day, *n* (%)	3 (7)	1 (4)		2 (22.2)	1 (3)						1 (3)	1 (6)		2 (25)	1 (4)
2 doses/day, *n* (%)	39 (93)	22 (96)	9 (90)	7 (77.8)	32 (97)	8 (100)	6 (100)	1 (100)	1 (100)	7 (100)	30 (88)	16 (94)	8 (89)	6 (75)	24 (96)
Hydrocortisone (HC), *n* (%)	27 (36)	18 (44)	7 (41)	2 (12)	25 (43)	24 (70)	17 (74)	5 (83)	2 (40)	22 (76)	3 (7)	1 (6)	2 (18)		3 (10)
HC-equivalent dose (mg), mean (SD)	23.4 (7.9)	21.8 (6.3)	30.1 (7.1)	13.7 (7.4)	24.1 (7.5)	22.1 (7.3)	21.3 (6.1)	28.2 (7.6)	13.8 (7.4)	22.9 (6.9)	33.3 (5.8)	30	35 (7.1)		33.3 (5.8)
2 doses/day, *n* (%)	1(4)		1 (14.3)		1 (4)						1 (33.3)		1 (50)		1 (33.3)
3 doses/day, *n* (%)	17 (63)	12 (66.7)	3 (42.9)	2 (100)	15 (60)	16 (66.7)	11 (64.7)	3 (60)	2 (100)	14 (63.6)	1 (33.3)	1 (100)			1 (33.3)
4 doses/day, *n* (%)	9 (33)	6 (33.3)	3 (42.9)		9 (36)	8 (33.3)	6 (35.3)	2 (40)		8 (36.4)	1 (33.3)		1 (50)		1 (33.3)
No therapy, *n* (%)	6 (8)			6 (35)		2 (6)			2 (40)		4 (10)			4 (33)	

Abbreviations: CF, classic form of CAH; HC, hydrocortisone; SV, simple virilizing; SW, salt-wasting.

TABLE 2 AddiQoL scores in patients with congenital adrenal hyperplasia divided into gender, age groups, phenotypes and glucocorticoid therapy and no therapy

	Total	*p* (M/F)	*p* (age group)	SW	SV	NC	*p**SW/SV/NC	*p***SW/SV/NC	*p* CF/NC	*p*** CF/NC	*p**** CF/NC	Prednisolone	Hydrocortisone	*p* P/H	No therapy	*p** P/H/NT
Number of answers, *n* (M/F)	71 (40/31)			35 (22/13)	18 (14/4)	18 (4/14)						41 (20/21)	24 (17/7)		6 (3/3)	
Age (years), mean (SD)	36.8 (16.5)															
Total score, mean (SD)	86.4 (12.9)	**.01**		88.6 (12.2)	87.7 (11.9)	80.7 (13.9)	.09	.3	**.03**	.1	**.03**	85.1 (13)	88.6 (11.1)	.1	86 (19.1)	.5
Male, median (IQR)	90.5 (80–102)			91 (87–111)	89 (78.3–110.5)	89 (83–108.8)	.8		.9			88.5 (80–102)	91 (72–102)	.2	91 (92–96[a])	.7
Female, median (IQR)	85 (75–93)			89 (78.3–95.8)	85.5 (84–91[a])	84 (71–92.3)	.16		.06			84 (76–93)	89 (74–92[a])	.7	84 (53–90[a])	.5
Age group 1 ≤ 30 years																
Number of answers, *n* (M/F)	28 (19/9)			17 (11/6)	6 (6/0)	5 (2/3)						6 (3/3)	20 (14/6)		2 (2/0)	
Total score, mean (SD)	90.4 (11.2)	.2	**.03**	89.4 (11.2)	99 (9.4)	83.8 (8)	.06	.1	.1	.2		88.7 (18.4)	91.1 (9.3)	.7	89 (2.8)	.9
Age group 2 > 30 years																
Number of answers, *n* (M/F)	43 (21/22)			18 (11/7)	12 (8/4)	13 (2/11)						35 (17/18)	4 (3/1)		4 (2/2)	
Total score, mean (SD)	83.7 (13.3)	.07		87.8 (13.5)	82.1 (8.6)	79.5 (15.8)	.2	.4	.2	.5		84.4 (12.1)	76.3 (12.1)	.2	84.5 (24.49)	.5
AddiQoL subscore																
Fatique, median (IQR)	24 (20–26)	.3		25 (20–26)	24.5 (20.5–26)	23 (19.5–25.3)	.3		.2			24 (19.5–26)	25 (22.3–26)	.3	26 (17.8–27.5)	.5
Male, median (IQR)	25 (20.3–26.8)			25 (20.8–27)	24.5 (18.8–26.3)	23 (20.3–28)	.8		.9			24 (19.5–26.8)	25 (21.5–26.5)	.5	25 (20–25[a])	.8
Female, median (IQR)	24 (20–26)			25 (19.5–26)	24.5 (21.8–25.8)	23 (18–25.3)	.5		.2			24 (19.5–25.5)	23 (22–26)	.8	27 (11–27[a])	.8
Emotions, median (IQR)	24 (21–26)	**.005**		24 (22–27)	24.5 (22.8–26.3)	22 (20.8–24.3)	.07		**.02**			23 (21–26)	24 (23–27)	.2	23 (19.5–26.8)	.5
Male, median (IQR)	24.5 (22–27)			24.5 (22.8–27.5)	24.5 (21.8–27)	24 (20.5–28.3)	.8		.7			24.5 (21.3–26.8)	24 (24–27)	.6	26 (22–26[a])	.8
Female, median (IQR)	23 (21–25)			23 (21–25.5)	24 (23–25.8)	21.5 (20.8–23.3)	.2		.1			23 (21–25)	23 (22–25)	.5	21 (15–21[a])	.5

TABLE 2 (Continued)

	Total	*p* (M/F)	*p* (age group)	SW	SV	NC	p^{*}SW/SV/NC	p^{**}SW/SV/NC	*p* CF/NC	p^{**} CF/NC	p^{***} CF/NC	Prednisolone	Hydrocortisone	*p* P/H	No therapy	p^{*} P/H/NT
Symptoms, median (IQR)	27 (25–31)	**.018**		28 (27–32)	27.5 (25.8–30.5)	27 (22–31)	.3		.1			27 (25–30)	29 (27–31.8)	.1	29.5 (22.3–32.5)	.6
Male, median (IQR)	28 (27–32)			28 (26.8–33)	28.5 (25.8–32)	29.5 (27–33.5)	.9		.7			27 (26.3–33.5)	29 (26.5–32)	.7	32 (27–32[a])	.7
Female, median (IQR)	27 (24–29)			27 (27–29.5)	26.5 (25.3–27.8)	25 (21.8–29.5)	.4		.2			27 (23–28.5)	28 (27–29)	.1	24 (17–24[a])	.3
Miscellaneous, median (IQR)	12 (10–13)	**.01**		12 (11–14)	12 (10–13)	10 (8–12.3)	**.023**		**.001**			12 (10–12.5)	12 (11–13)	.2	13 (8.15.3)	.4
Male, median (IQR)	12 (11–13.8)			12 (11–14)	12 (10–13)	13 (10.8–15.3)	.4		.5			12 (11–13.8)	12 (11–13.5)	.5	13 (13[a])	.2
Female, median (IQR)	11 (8–12)			12 (11.5–12.5)	12.5 (9.8–13)	9.5 (8–11)	**.023**		**.006**			11 (8.5–12)	12 (11–12)	.4	8 (8[a])	.7

Note: Values in bold indicate statistically significant results.

Abbreviations: AddiQoL, Addison Quality of Life; CF, classic form of CAH; F, female; GLM, generalized linear model; H, hydrocortisone; IQR, interquartile range; M, male; NC, nonclassic; NT, no therapy; P, prednisolone; SD, standard deviation; SV, simple virilizing; SW, salt-wasting.

[a]50 percentile IQR.

p, independent *t* test/Mann–Whitney *U* test.

$^{*}p$, analysis of variance/Kruskal–Wallis *U* test; $^{**}p$, GLM adjusted for gender; $^{***}p$, GLM adjusted for age.

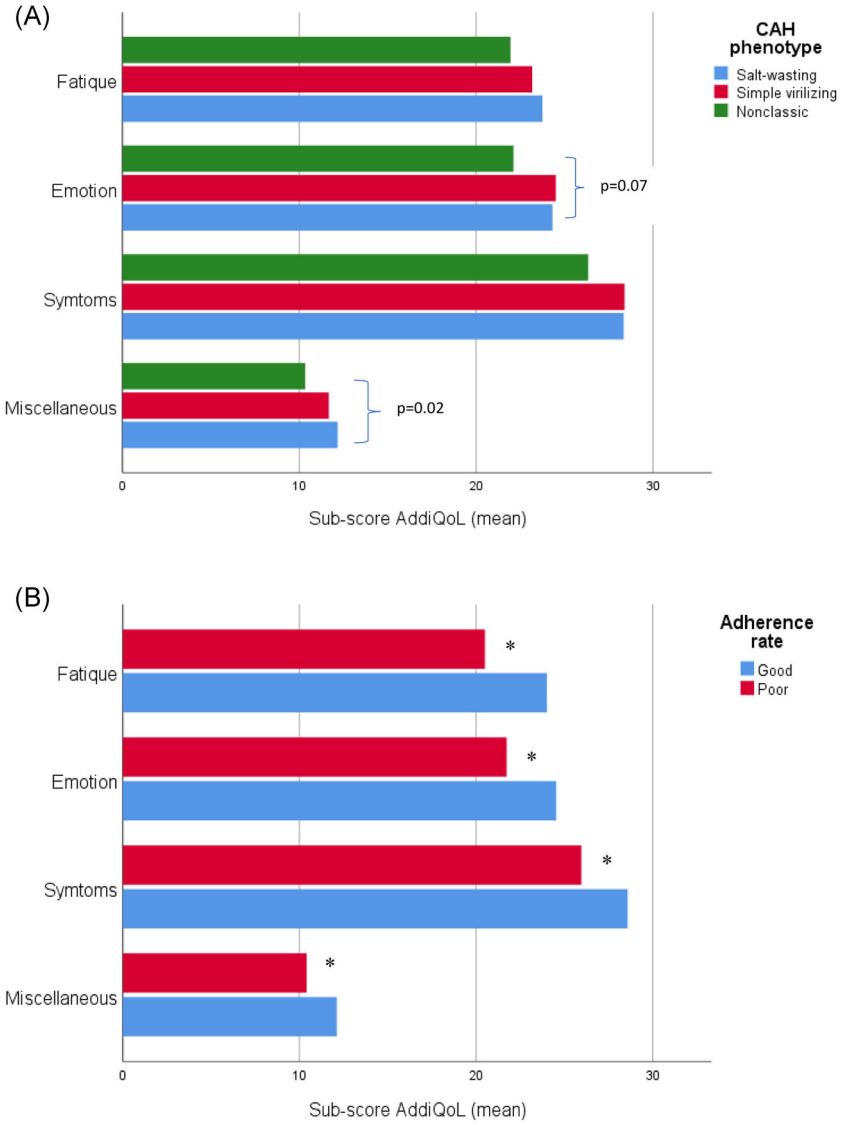

FIGURE 1 (A) Addison Quality of Life (AddiQoL) subscales divided into phenotypes. (B) AddiQoL subscales divided into poor and good adherence rates. *$p < .01$

the SW form of CAH reported higher scores on the Miscellaneous subscale as well as a tendency towards higher scores on the Emotions subscale than those with the NC form of CAH (Figure 1A). When comparing classic CAH participants with NC CAH participants, higher Emotions and Miscellaneous scores were found in those with the classic phenotype.

4.2.2 | Therapy adherence rates and QoL

Sixty-seven participants, that is, 89% of the entire cohort, completed both the ASK-12 and the AddiQoL questionnaires (Table 3). The total scores of AddiQoL were significantly lower in participants with poor adherence rates than in participants with good adherence rates (78.6 vs. 89.2, $p = .001$) (Figure 1B).

No differences were found when checking for gender, age group, phenotype, or glucocorticoid therapy.

No other scores differed for the adherence-related subscales for behavior, health beliefs and inconvenience/forgetfulness (data not shown).

Fifty-seven (79%) of participants answered the question regarding sexual issues. When including this item, similar gender differences, with slightly higher scores in the males, were found, but there was no difference between the phenotype groups (data not shown).

Linear regression analysis showed that a good adherence rate in combination with a younger age affected the total sum of AddiQoL by increasing scores. No such association was found for gender or type of glucocorticoid therapy (data not shown).

4.3 | RAND 36 total score

Table 4 presents the clinical scores of patients who completed the questionnaire RAND 36, which was completed by 75 participants, that is,

TABLE 3 AddiQoL and RAND 36 scores in patients with congenital adrenal hyperplasia divided into good and poor adherence rate, gender, phenotypes, glucocorticoid therapies and age groups

AddiQoL							Rand 36					
Adherence rate	**All**	***p***	**Good**	**Poor**	***p*[a]**	***p*[b]**	**All**	***p***	**Good**	**Poor**	***p*[a]**	***p*[b]**
Number of answers (*n*)	67		45	22			71		50	21		
Total score, mean (SD)	85.7 (12.9)		89.2 (10.9)	78.6 (13.5)	**.001**		613 (172.3)		647.7 (152)	528.7 (192.2)	**.007**	
Gender (male/female)	38/29		26/19	12/10			42/29		30/20	12/9		
Total score, male, mean (SD)	88.8 (12.2)	**.01**	91.7 (11.5)	82.7 (13.5)	**.031**	.5*	638.7 (158)	.1	660 (151.7)	568.7 (168.1)	.09	.8*
Total score, female, mean (SD)	81.7 (12.5)		85.8 (9.2)	73.7 (14.6)	**.01**		576.6 (187.3)		629.4 (154.3)	475.2 (218.8)	**.038**	
Phenotype (SW/SV/NC)	34/18/15		25/13/7	9/5/8			40/17/14		31/12/7	9/5/7		
Total score, SW, mean (SD)	88.6 (12.2)	0.1	90.9 (11.5)	80.2 (12.7)	**.02**	.2***	634.1 (173.2)	.1	659.9 (158.4)	545.3 (201.8)	.08	.1**
Total score, SV, mean (SD)	87.7 (11.9)		88.4 (11.6)	86 (13.9)	.7		632.2 (151.7)		637.8 (164.4)	619 (131.9)	.8	
Total score, NC, mean (SD)	80.7 (13.9)		84.9 (6.2)	72.1 (14.8)	**.005**		526.4 (178.2)		610.7 (104.5)	442.7 (203.4)	.07	
Glucocorticoid therapy												
Prednisolone/hydrocortisone	39/24		26/18	13/6			40/27		27/22	13/5		
Total score, Prednisolone, SW, mean (SD)	88.6 (11)	.3	87.7 (12.2)	77.9 (12.2)	**.02**	.5***	588.8 (178.9)	.1	620 (164.8)	523.9 (195.9)	.1	.3***
Total score, Hydrocortisone, mean (SD)	85.1 (13)		91.1 (9)	81.2 (14.1)	**.05**		662.7 (140.1)		677.2 (133.7)	599 (165.9)	.2	
Age groups												
Aged ≤ 30 years/Aged > 30 years	28/39		18/27	10/12			34/37		24/26	10/11		
Total score, Aged ≤ 30 years, mean (SD)	90.4 (11.2)	**.03**	93.8 (9.5)	84.3 (11.7)	**.03**	.7****	661.2 (120)	**.02**	689.8 (98.6)	592.7 (143.2)	.07	.9****
Total score, Aged > 30 years, mean (SD)	83.7 (13.3)		86.2 (10.8)	73.8 (13.4)	**.004**		573 (198)		608.8 (181.8)	470.5 (218.2)	**.05**	

Note: Values in bold indicate statistically significant results.

Abbreviations: AddiQoL, Addison Quality of Life; IQR, interquartile range; NC, nonclassic; SD, standard deviation; SW, salt-wasting; SV, simple virilizing.

[a]*p*, independent *t* test comparing adherence.

[b]*p*, χ^2 test.

**p*, χ^2 test, Gender/adherence; ***p*, χ^2 test, Phenotype/adherence; ****p*, χ^2 test, Therapy/adherence; *****p*, χ^2 test, Age group/adherence.

TABLE 4 RAND 36 scores in patients with congenital adrenal hyperplasia divided into gender, age groups, phenotypes, glucocorticoid therapy or no therapy

	Total	*p* (M/F)	*p* (age group)	SW	SV	NC	*p** SW/SV/NC	*p* CF/NC	*p*** CF/NC	*p**** CF/NC	Prednisolone	Hydrocortisone	*p* P/H	*p**** P/H	No therapy	*p** P/H/NT
Number of answers, *n* (M/F)	75 (44/31)			41 (26/15)	17 (14/3)	17 (4/13)					42 (20/22)	27 (21/6)			6 (3/3)	
Total score, mean (SD)	613 (172.3)	.1		637.5 (172.4)	632.2 (151.6)	534.8 (177.5)	.1	**.03**	**.06**	**.05**	595.2 (177.2)	662.7 (140.1)	.07	.7	514.3 (227.8)	.09
Male, median (IQR)	700 (569–750)			717 (603–756)	667 (498–740)	605.5 (467–699)	.27	.2			667 (549–737)	729 (625–756)	.2		668 (441–668[a])	
Female, median (IQR)	664 (480–717)			709 (480–745)	699 (619–699[a])	519 (376–680)	.18	.06			660.5 (464–709)	686.5 (620–727)	.3		334 (188–334[a])	
Age group, 1 ≤ 30 years																
Number of answers, *n* (M/F)	34 (23/11)			23 (15/8)	6 (6/0)	5 (2/3)					8 (3/5)	24 (18/6)			2 (2/0)	
Total score, mean (SD)	661.2 (120)	.3	**.02**	669.3 (114.9)	734.3 (53.1)	536.5 (121.4)	**.016**	**.01**	**.02**		615 (143)	686 (104)	.1		555 (161)	.2
Age group 2 > 30 years																
Number of answers, *n* (M/F)	41 (21/20)			18 (11/7)	11 (8/3)	12 (2/10)					34 (17/17)	3 (3/0)			4 (1/3)	
Total score, mean (SD)	573.1 (198.6)	.4		596.9 (223.1)	576.5 (160.5)	534.2 (201.1)	.7	.4	.6		591 (186)	480 (271)	.3		494 (276)	.5
Physical functioning,median (IQR)	95 (85–100)	.7	**.01**	100 (85–100)	95 (84–100)	95 (85–100)	.9	.6			95 (85–100)	100 (95–100)	**.04**		92.5 (65–100)	.13
Male, median (IQR)	95 (85–100)			95 (83–100)	95 (76–100)	100 (96–100)	.3	.1			92.5 (76–99)	100 (93–100)	.06		100 (100)	**.034**
Female, median (IQR)	100 (85–100)			100 (95–100)	97 (88–100)	90 (80–100)	.2	.08			100 (85–100)	100 (99–100)	.09		78 (35–75[a])	**.016**
Social functioning, median (IQR)	100 (75–100)	.1	**.02**	100 (75–100)	100 (69–100)	75 (63–100)	.3	.1			100 (63–100)	100 (88–100)	**.03**		81.5 (54–100)	.09
Male, median (IQR)	100 (75–100)			100 (85–100)	100 (63–100)	87.5 (66–100)	.9	.6			100 (66–100)	100 (88–100)	.5		100 (63–100[a])	.8
Female, median (IQR)	88 (63–100)			88 (63–100)	100 (75–100[a])	75 (63–100)	.5	.4			75 (63–100)	100 (64–100)	**.04**		63 (25–63[a])	.1
Role function, median (IQR)	100 (54–100)	.8	.3	100 (59–100)	100 (94–100)	100 (25–100)	.5	.5			100 (25–100)	100 (100)	.2		62.5 (19–100)	.2
Male, median (IQR)	100 (75–100)			100 (69–100)	100 (69–100)	100 (44–100)	.8	.8			92.5 (38–100)	100 (75–100)	.6		100 (25–100[a])	.9
Female, median (IQR)	100 (31–100)			100 (50–100)	100 (100)	100 (13–100)	.09	.3			95 (25–100)	100 (100)	.1		75 (0–25[a])	.1
Role emotional, median (IQR)	100 (33–100)	.2	.8	100 (67–100)	100 (92–100)	100 (0–100)	.2	.07			100 (33–100)	100 (67–100)	.8		50 (0–100)	.4

TABLE 4 (Continued)

	Total	*p* (M/F)	*p* (age group)	SW	SV	NC	*p** SW/SV/NC	*p* CF/NC	*p*** CF/NC	*p**** CF/NC	Prednisolone	Hydrocortisone	*p* P/H	*p**** P/H	No therapy	*p** P/H/NT
Male, median (IQR)	100 (75–100)			100 (100)	100 (59–100)	66.5 (8–100)	.4	.2			100 (75.2–100)	100 (83.5–100)	.8		100 (0–100[a])	.9
Female, median (IQR)	100 (33–100)			100 (33–100)	100 (100)	100 (0–100)	.2	.3			100 (33–100)	83.5 (50.3–100)	.7		0 (0[a])	.3
Mental health, median (IQR)	80 (64–92)	**.007**	.2	88 (70–92)	84 (64–88)	56 (52–72)	**.003**	**.001**			82 (56–92)	84 (68–92)	.5		66 (47–70)	.1
Male, median (IQR)	84 (68–92)			88 (75–96)	84 (65–88)	66 (55–68)	.3	**.02**			86 (68–96)	84 (76–92)	.9		68 (64–68[a])	.2
Female, median (IQR)	64 (52–88)			80 (52–92)	64 (64[a])	56 (38–80)	.3	.1			68 (50–89)	66 (61–83)	.9		56 (20–56[a])	.5
Vitality, median (IQR)	65 (45–80)	.09	.08	75 (55–80)	65 (42.5–70)	45 (35–62.5)	**.006**	**.005**			62.5 (40–75)	70 (60–80)	.1		47.5 (13.8–82.5)	.2
Male, median (IQR)	67.5 (46.3–80)			72.5 (60–81.3)	65 (43.8–71.3)	45 (22.5–71.3)	.2	.1			65 (45–78.8)	70 (60–80)	.3		45 (15–45[a])	.4
Female, median (IQR)	55 (40–75)			75 (40–80)	55 (40–55[a])	45 (35–62.5)	.1	.08			55 (40–75)	67.5 (38.8–78.8)	.5		50 (10–50[a])	.8
Body Pain, median (IQR)	100 (78–100)	.1	**.01**	100 (85–100)	90 (69–100)	78 (63–95)	**.016**	**.01**			95 (69.5–100)	100 (80–100)	.2		75 (49.5–100)	.3
Male, median (IQR)	100 (78.5–100)			100 (87.5–100)	95 (69.5–100)	79 (72–95)	.2	.2			100 (72–100)	100 (80–100)	.9		80 (70-80[a])	.9
Female, median (IQR)	90 (68–100)			100 (78–100)	90 (68–90[a])	78 (56.5–90)	.1	**.05**			90 (68–100)	100 (76–100)	.2		55 (33–55[a])	.2
General health, median (IQR)	75 (50–90)	.2	**.015**	85 (52.5–95)	80 (47.5–87.5)	60 (47.5–72.5)	.08	**.04**			65 (45–85)	85 (60–95)	**.02**		77.5 (43.8–87.5)	.08
Male, median (IQR)	82.5 (55–93.8)			85 (58.8–95)	72.5 (45–88.8)	77.5 (66.3–85)	.5	.8			67.5 (46.3–88.8)	85 (62.5–97.5)	.1		85 (70–85[a])	.2
Female, median (IQR)	65 (45–85)			80 (45–95)	85 (55–85[a])	55 (45–65)	.1	**.05**			60 (45–85)	77.5 (60–85)	.2		50 (25–50[a])	.5

Note: Values in bold indicate statistically significant results.

Abbreviations: CF, classic form of CAH; F, female; H, hydrocortisone; GLM, generalized linear model; IQR, interquartile range; M, male; NC, nonclassic; NT, no therapy; P, prednisolone; SD, standard deviation; SV, simple virilizing; SW, salt-wasting.

[a]50 percentile IQR.

p—independent test/Mann–Whitney *U* test.

**p*—analysis of variance/Kruskal–Wallis *U* test; ***p*—GLM adjusted for gender; ****p*—GLM adjusted for age.

the entire cohort (59% male; form of CAH: 54% SW, 23% SV and 23% NC).

4.3.1 | Gender, phenotype and age group

There was a slight gender difference in the RAND 36 total scores with higher scores found in males. No difference in total scores was found when SW, S and NC CAH were compared. However, participants with classic CAH reported higher RAND 36 total scores than those with the NC form of CAH once adjusted for gender or age.

A difference between age groups was found with higher scores seen in participants ≤30 years old ($p = .02$). In the younger group, which included adolescents and young adults, participants with classic CAH had significantly higher total scores than those with NC CAH ($p = .016$). The posthoc analysis confirmed that there were differences between the phenotypes (data not shown).

4.3.2 | Glucocorticoid therapy

Glucocorticoid therapy was prescribed to 92% of participants. Forty-two (56%) were prescribed prednisolone treatment and 27 (36%) were prescribed hydrocortisone treatment, while 6 (8%) were not prescribed any glucocorticoid treatment. When we analyzed the entire study group, slightly higher scores were seen in participants treated with hydrocortisone than in those treated with prednisolone. However, no such differences were found when adjusted for age or comparing the age groups separately. We found no associations between RAND 36 score, hydrocortisone-equivalent dose of glucocorticoid and number of doses per day when adjusted for age.

4.4 | RAND 36 subscores

4.4.1 | Gender and phenotypes

Significantly lower mental health scores were found in female participants than in males. There were no differences in physical functioning, social functioning, role function, role emotional function, body pain, or general health scores with regard to gender. When comparing phenotypes, higher scores were found in mental health, vitality and body pain in participants with the SW form of CAH.

Participants with the classic form of CAH demonstrated higher scores in mental health, vitality, body pain and general health than NC participants.

4.4.2 | Glucocorticoid therapy

When we analyzed the entire study group and comparing glucocorticoid therapy regimens, significantly higher physical functioning, social functioning and general health scores were found in participants who were prescribed hydrocortisone treatment. When assessing males and females separately, we found higher physical functioning scores in males and females receiving glucocorticoid treatment than those who were not. No other differences in role function, role emotional function, or body pain were found.

4.4.3 | Adherence rate and QoL

Seventy-five participants, that is, the entire cohort completed both the ASK-12 and the RAND 36 questionnaires (Table 3). The total scores for RAND 36 were significantly lower in participants with poor adherence rates than in those with good adherence rates ($p = .007$), with no difference was found between genders.

General linear regression analysis showed that younger patients on hydrocortisone and with good adherence had higher RAND 36 scores than older patients on prednisolone independently adherence ($p = .03$). No other differences were found when adherence was compared to gender, phenotype and therapy.

4.4.4 | RAND 36 and the normal population

Overall, study participants with CAH showed an impaired health profile when compared to the general Swedish population ($p < .05$), in particular in regard to limitations related to vitality, role emotional functioning and mental health in patients with NC CAH (Figure 2).

5 | DISCUSSION

Adherence to medical therapy regimens is a central issue due to the significant key role it plays in achieving satisfactory results when treating patients with CAH.[13] This study shows that adherence rates were associated with QoL in adolescents and adults with CAH. This has not been highlighted as a key factor of QoL in patients with CAH before.[9,13,26]

5.1 | Adherence rate and QoL

An important clinical question to consider when treating patients with CAH is how much adherence is enough to obtain the full treatment benefits of cortisol.[27] It is well known today that patients living with a chronic disorder commonly have a medication adherence of around 50%–70%[12,14] and nonadherence has been shown to contribute to poor health outcomes including impaired QoL.[11] This is in line with our results with a poor adherence rate to therapy regimens as a key factor for impaired QoL in adolescents and adults with CAH.

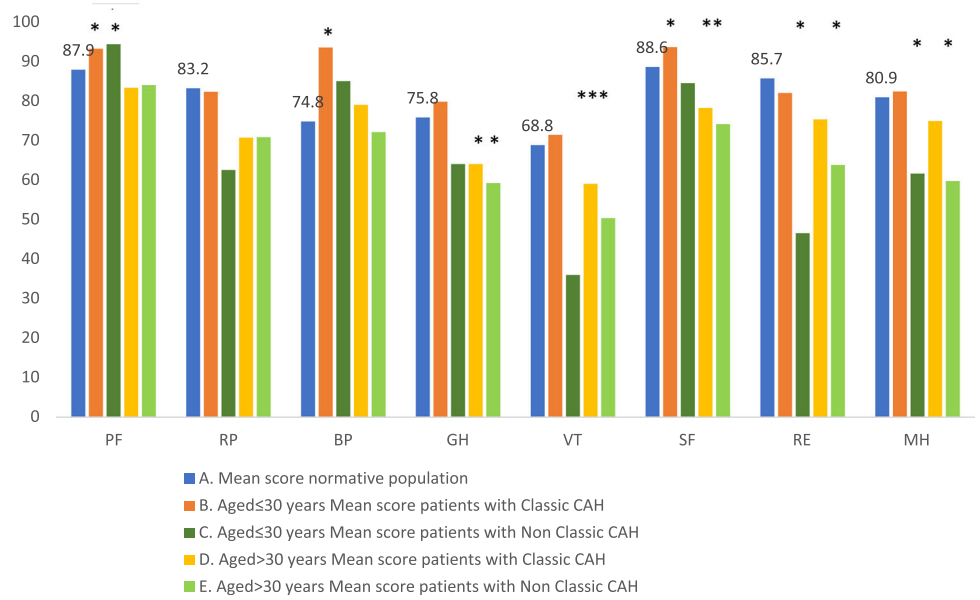

FIGURE 2 RAND SF-36 domain scores in patients divided into the severity of congenital adrenal hyperplasia and age groups compared with general Swedish population SF-36 data BP, body pain; GH, general health; MH, mental health; PF, physical functioning; RE, role, functioning/emotional; RP, role functioning/physical; SF, social functioning; VT, vitality. PF: $p < .05$ A versus B; A versus C; BP: $p < .05$ A versus B; GH: $p < .05$ A versus D; A versus E. VT: $p < .05$ A versus C; A versus D; A versus E; SF: $p < .05$ A versus B; A versus D; A versus E; RE: $p < .05$ A versus C; A versus E; MH: $p < .05$ A versus C; A versus E

5.2 | Adherence rates, therapies and QoL

The most effective form of glucocorticoid therapy in adolescents and adults with CAH is still being discussed.[28,29] Hydrocortisone has a short plasma half-life, which means that multiple doses are required throughout the day to achieve sufficient cortisol levels.[30] Prednisolone may be beneficial in patients with low adherence as it only requires one or two doses daily, due to its longer plasma half-life.[31] Therapy factors such as doses per day and long-acting effects have been named as possible reasons for poor adherence rates. However, our results show no difference in adherence rates between patients on prednisolone and patients on hydrocortisone, which is in line with some previous studies but not all.[5,16,32] One explanation for this might be that the general care of patients is of importance and this may differ between medical treatment units, while patients participating in our study were recruited from a single university hospital. Regular practical CAH training sessions with the aim of improving patients' understanding of the benefits of medication as well as increasing their knowledge of the high-risk nature of their illness are possible factors that have contributed to our results.[14,33]

Fluctuating cortisol and adrenal androgen levels may have an impact on QoL and several studies have shown different results regarding treatment regimens.[28,29] Additionally, patients with impaired QoL, poor disease control and low adherence rates are sometimes prescribed a more potent glucocorticoid with a longer half-life, which makes it difficult to understand the relationship between cause and effect.[8] However, AddiQoL scores did not differ between therapy regimens in this study, which is consistent with a recently published Cochrane review[28] that concluded that uncertainty remains regarding the most effective form of glucocorticoid replacement therapy in both child and adult CAH patients when it comes to QoL and the prevention of different specific disease complications.[28] Our results from the non-disease-specific QoL questionnaire RAND 36 showed higher scores in three of the subscales in participants treated with hydrocortisone, which is in line with some studies showing that hydrocortisone treatment has a lower negative impact on QoL than other glucocorticoid regimens.[7,8] However, we found no such difference in those aged over 30 years, which may be explained by health-related issues and long-term side effects of glucocorticoid treatment.[1,28]

5.3 | Gender and QoL

Male participants in our study showed higher or slightly higher QoL scores than females in both the AddiQoL and RAND 36 questionnaires. Conflicting results of self-reported QoL data have frequently been reported for males and females with CAH. It is possible that the impact of androgen exposure affects men, women, boys and girls differently. Girls with SW and SV CAH are born with varying degrees of prenatal virilization and additionally, the increasing androgen exposure due to lack of treatment or undertreatment may negatively affect QoL.[6,34] However, in children, QoL scores have not been reported to differ by gender.[8] A recently published study on males with CAH reported their QoL scores to be comparable with normative populations and higher than patients with another chronic illness.[17]

5.4 | Phenotype and QoL

When comparing the phenotype groups of CAH once adjusted for gender, we found a difference in the RAND 36 total scores, with better scores found in participants with the classic form of CAH. This may seem counter-intuitive at first but it is in accordance with previous studies where patients with NC CAH have reported worse QoL than those with classic CAH, despite NC CAH being considered a milder form of the disorder. The reason for this has been hypothesized to be due to the later diagnosis of patients with NC CAH.[5,7] They may suffer symptoms of androgen exposure before receiving a diagnosis and they may experience being diagnosed as more negative and difficult to adjust to than those with classic CAH who are typically diagnosed in the neonatal period. Our findings in this respect may be similar to the reported differences in QoL among those having a congenital versus an acquired disease.[5]

5.5 | Age groups and QoL

Long-term health problems in adults with CAH include bone, cardiovascular and metabolic health, fertility issues in both females and males along with pregnancy management and psychosexual issues, all of which have been extensively studied.[35] The Addison's disease-specific AddiQoL questionnaire has previously shown, in a large cross-sectional study on Addison's disease, that HRQoL scores are lower in older age groups.[18] This is in line with our results in the present study with the younger age group scoring higher for QoL than the older age group. Six participants in the older age group were born after 1986, the year that the neonatal screening programme was introduced in Sweden, which may have had a positive effect on QoL. The introduction of the programme has resulted in improvements being seen in several health outcomes.[36,37]

5.6 | Strength and limitations

The limited sample size is the major limitation of the present study, especially the number of answers in the hydrocortisone-treated older age group and prednisolone-treated younger age group, making it problematic to draw any conclusions. The influence of younger age may be more important, as the younger patients have fewer side effects and long-term health issues. Some of our results comparing glucocorticoid treatments could be explained by a lack of power or sensitivity. Another weakness was that the question on sexual issues included in the AddiQol questionnaire was excluded due to its low response rate. Moreover, we used glucocorticoid treatments that were being used at the time of the study in our calculations on therapy effects, but therapy regimens may have changed over the participants' lives, especially in those aged over 30 years. Despite this, current medication is more likely to affect the parameters measured in QoL questionnaires than previously prescribed therapy regimens. A strength of this study, on the contrary, is that we have used two different QoL questionnaires; AddiQoL with its disease-specific items and RAND 36, which is not specific to any disease or treatment group.

6 | CONCLUSION

A good adherence rate to therapy regimens in combination with a younger age was associated with higher QoL in CAH patients. No differences were found when adherence rates with regard to gender, phenotypes, or therapies were compared. A gender difference, however, was found with higher AddiQoL total scores seen in males.

Patients with more severe phenotypes of CAH (SW and SV) reported higher QoL than participants with the NC form of CAH. Younger patients on hydrocortisone and with good adherence had a better QoL than older patients on prednisolone.

Patients with CAH showed an impaired QoL when compared to the general Swedish population, especially nonclassic patients with regard to limitations related to body pain, vitality and mental health.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Kerstin Ekbom conceived the study, applied for research funding, performed the study, conducted statistical analyses, interpreted the results and wrote the paper. Anna Strandqvist, Svetlana Lajic and AL oversaw the study and critically revised the paper. Henrik Falhammar, Anna Nordenström conceived the study, interpreted the results, oversaw the study and critically revised the paper.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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