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Original Research

Blood pressure and its associations in 554 children and young people with congenital adrenal hyperplasia

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Abstract

Background: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) affects approximately 1 in 15 000 individuals. We leveraged the power of multicentre registry data to assess the trend and predictors of blood pressure (BP) within children and young persons with 21OHD to inform monitoring strategies.

Method: Data from the International CAH Registry in patients younger than 20 years was compared to normative values. Values of BP were modeled to create reference curves, multiple change point analysis applied to quantify the difference with normative data. Covariate adjustment was informed by a directed acyclic graph, prior to joint outcome regression modeling to accurately assess predictors of BP.

Results: A total of 6436 visits within 554 patients (52.5% females) showed BP-Standard deviation scores (SDS) were higher at younger ages. Patients under five years had systolic BP-SDS of 1.6 (Q1:0.6-Q3:2.7) decreasing to 1.0 (Q1:0.2-Q3:1.8) over 5 years, equating to 31.0% over the 95th centile decreasing to 15.0%. Higher doses of fludrocortisone were associated with a small increase in systolic BP equivalent to 1.2 mmHg with every 100 µg extra fludrocortisone. Renin of 100µU/mL was associated with 4.6 mmHg lower systolic BP than a renin of 1µU/mL, higher 17OH-progesterone and androstenedione also predicted lower systolic and diastolic BP ($P < .05$).

Conclusion: Higher BP in children with 21OHD is common and particularly pronounced at a younger age, but may not be attributable to excessive mineralocorticoid replacement. There is a need to improve our understanding of the determinants of this raised BP as well as its long-term effects.

Keywords: blood pressure, congenital adrenal hyperplasia, glucocorticoids, statistical modeling, Bayesian analysis

Significance

We used advanced regression modelling to study a large group of children with congenital adrenal hyperplasia. We showed that increased levels of renin, androstenedione and 17OHP were associated with lower blood pressure (BP), although BP was higher than normative values, with a larger differential at younger ages. Although increased doses of mineralocorticoid resulted in a higher BP, the effect size was marginal at 1 mmHg per 100 µg of Fludrocortisone. Further long-term research into cardiovascular outcomes in patients with CAH will help us understand whether increased BP at young ages has any adverse clinical outcomes.

Introduction

Congenital adrenal hyperplasia (CAH) is the most common form of inherited adrenal insufficiency, affecting between 1 in 10 000 to 1 in 15 000 people. It is caused in over 90% of cases by deficiency of the enzyme 21-hydroxylase which converts 17OH-progesterone (17OHP) to 11-deoxycortisol, the main substrate used in the production of cortisol. Patients with classic 21-hydroxylase deficiency (21OHD) need lifelong treatment with glucocorticoid replacement, most commonly hydrocortisone in childhood.[1,2] The majority of patients are also at risk of salt wasting due to aldosterone deficiency caused by the lack of conversion of progesterone to deoxycorticosterone. This mineralocorticoid deficiency is treated with fludrocortisone. Salt replacement is also recommended at young ages, although use is variable.[1,3,4]

Blood pressure (BP) in children with 21OHD is contentious,[5] small studies in under 24 patients reporting normal BP,[6,7] but studies investigating 24 h ambulatory readings in 38 or fewer patients finding elevated BP.[8-10] Others, including analysis of registry data from 716 children in 2 countries, report that high BP readings are a transient problem in early childhood that resolves.[3,11] This previous registry study was unable to assess biomarkers of disease control in relation to BP.[3]

High doses of fludrocortisone in 21OHD to prevent salt loss can cause hypertension, as can high doses of glucocorticoids.[3,12,13] However, the optimum dose of fludrocortisone has

not been studied, and the extent to which hypertension in children with 21OHD correlates with long-term adverse outcomes or co-morbidities is unknown.[1,5,14] As cardiovascular diseases remain the leading cause of global mortality,[15] there is a pressing need to understand how hormone replacement and biomarkers of disease control impacts on BP in patients with 21OHD, to inform appropriate prevention and monitoring strategies.

The International CAH Registry provides rich longitudinal data from CAH patients with 21OHD.[16] We set out to use advanced statistical modeling to assess the trend in BP throughout childhood and compare this to normative data from the National Heart, Lung, and Blood Institute (NHLBI),[17] and assess the impact of different aspects of patient treatment on BP in children with 21OHD.

Methods

This retrospective cohort study included children with a diagnosis of 21OHD with consent for data sharing with the I-CAH Registry, and was conducted according to the Declaration of Helsinki. The I-CAH Registry is an international database of pseudonymized information on patients with CAH and is approved by the National Research Ethics Service in the United Kingdom as a research database of information collected as part of routine clinical care (Research ethics committee reference: 19/WS/0131). No patients were excluded. Data were extracted on 21/12/2021 and analysis was restricted to visits of patients under the age of 20 years. We carried out data pre-processing and clarification by longitudinal visualization of variables with liaison with contributing centers to correct data entry errors.

Missing data

Missing data were assessed using a hierarchical hybrid approach of spline interpolation between longitudinal points for height and weight, last observation carried forward or next observation carried backward for dosing, and joint modeling multilevel multiple imputation for biomarkers and BP values. Analysis was conducted in ten imputation sets and estimates combined with Rubin's rules.[18] A sensitivity analysis assessing the impact of missing data was performed by repeating all analyses with cases with complete data only (methods 1[19]).

Statistical analysis

Summary and reference values

Statistical analysis was carried out in *R, a language and environment for statistical computing* (R Foundation for Statistical Computing, Vienna, Austria; packages in Table S1[19]). Summary statistics were calculated using the median and interquartile range of continuous variables. Standard deviation scores (SDS) were derived by comparing to World Health Organization (WHO) reference standards for growth,[20] and NHLBI normative data over 1 year of age for BP.[17,21] Absolute BP values were modeled with a Lambda-Mu-Sigma (LMS) approach to create smoothing reference curves. We subtracted the NHLBI median BP for age from the I-CAH registry median BP for age, and conducted multiple change point analysis to assess the age at which BP in those with CAH plateaued above normative values.

Dosing and biomarkers

Glucocorticoid dose, fludrocortisone dose, and salt replacement were summed as total daily doses. Glucocorticoids were converted to hydrocortisone equivalent by using British National formulary specified conversion ratios (Table S2,[19] hydrocortisone(mg)=prednisolone(mg)×4).[22] Biomarkers assessed included 17OHP, androstenedione, and renin. There was no standardized protocol for positioning of patients during blood tests or for timing of biomarker measurement in relation to dose or time of day. Lower and upper limits of detection and units of biomarkers were standardized across centers, and plasma renin activity (PRA) converted to renin (Table S3,[19] PRA(nmol/L/hr)×0.158 = renin(μIU/mL)).[23] Biomarkers were ln transformed prior to multivariable modeling to better approximate normality.

Covariate adjustment

A directed acyclic graph was developed with domain experts (Figure S1[19]) to ensure appropriate covariate adjustment sets to estimate the effect of each variable of interest on BP. The aim was to adjust for confounders that affect both the exposure and outcome of interest. If the effect of an exposure is mediated through a variable, that variable should not be adjusted for to avoid collider bias.[24]

Regression modeling

To estimate predictors of BP, we applied multilevel joint modeling regression, simultaneously assessing both systolic and diastolic BP as our outcome variables. We used the directed acyclic graph to select appropriate covariate adjustment sets for each target of estimation. We used both a treatment center level and patient level random intercept with a random slope applied for age to account for multiple measures and varying trajectories within patients.

Results

Patient biometrics and biomarkers

This retrospective observational study included 554 patients (52.5% female, 46.4% male, 1.1% not assigned) from 35 centers across 18 countries (Table 1, imputed statistics Table S4[19]). There was a total of 6436 visits with a median of 9 visits per patient (Quartile 1 [Q1]:6 to Quartile 3 [Q3]:16), visits spanning a median of 3.2 years (Q1:2.5 to Q3:7.3) within patients. Median age at visit was 3.0 years (Q1:1.0 to Q3:7.7), a greater proportion of visits at younger ages reflecting more frequent assessment of younger patients and attrition from registry data entry (Figure S2[19]).

Renin was measured in 32.9% of visits with median value of 4.5μIU/mL (Q1:0.4 to Q3:61.8), androstenedione in 39.2% of visits with median of 0.7 nmol/L (Q1:0.05 to Q3:3.5) and 17OHP in 42.5% of visits with median of 21.2 nmol/L (Q1:2.7 to Q3:115.0). Less than 50% of biomarkers had precise time of measurement documented (Table S5, Figure S3[19]). Glucocorticoid treatment consisted of hydrocortisone in 69% cases (alternative preparations Table S6[19]), at a median dose of 14.3 mg/m^2 (Q1:9.9 to Q3:15.6) hydrocortisone equivalent; fludrocortisone and salt supplements were prescribed in 84% and 14% cases, respectively. Median height SDS at visit was −0.3 (Q1:−1.3 to Q3:0.6), with median BMI SDS of 0.5 (Q1:−0.3 to Q3:1.3) (Figure 1[19]).

Blood pressure

The BP-SDS was higher at younger ages, patients under five having median systolic SDS 1.6 (Q1:0.6 to Q3:2.7), those

Table 1. Summary statistics.

Sex assigned at birth	Male	Female	Not assigned	Total sample
Number of countries	17	17	4	18
Number of centers	31	31	4	35
Number of patients	257	291	6	554
Number of visits	3018	3361	57	6436
Number of visits per patient	9	9	8	9
Median (Q1 to Q3)	(7 to 16)	(5 to 16)	(2 to 11)	(6 to 16)
Number of years visits spanned within patients	3.2	3.2	2.1	3.2
Median (Q1 to Q3)	(2.7 to 6.9)	(2.1 to 8.0)	(0.2 to 3.1)	(2.5 to 7.3)
Age of patients at youngest visit (years)	0.13	0.21	0.08	0.16
Median (Q1 to Q3)	(0.04 to 0.99)	(0.04 to 3.03)	(0.03 to 0.26)	(0.04 to 2.17)
Age of patients at most recent visit (years)	5.70	6.01	2.25	5.81
Median (Q1 to Q3)	(3.09 to 11.47)	(3.07 to 14.35)	(0.46 to 3.17)	(3.07 to 12.87)
Systolic BP at visit (mmHg)	107 ($n = 1556$)	105 ($n = 1652$)	99 ($n = 21$)	106 ($n = 3229$)
Median, (n) [Q1 to Q3][a]	[97 to 118]	[96 to 116]	[85 to 107]	[97 to 117]
Systolic BP SDS at visit[a]	1.5 ($n = 1492$)	1.1 ($n = 1564$)	—	1.3 ($n = 3056$)
Median (n) [Q1 to Q3]	[0.5 to 2.4]	[0.3 to 2.1]		[0.4 to 2.2]
Diastolic BP at visit (mmHg)	64 ($n = 1542$)	64 ($n = 1645$)	60 ($n = 20$)	64 ($n = 3207$)
Median, (n) [Q1 to Q3][a]	[57 to 71]	[57 to 70]	[50 to 71.25]	[57 to 70]
Diastolic BP SDS at visit[a]	1.1 ($n = 1478$)	0.9 ($n = 1559$)	—	1.0 ($n = 3037$)
Median (n) [Q1 to Q3]	[0.4 to 2]	[0.3 to 1.6]		[0.3 to 1.8]
Visits prescribed hydrocortisone[b]	2200 (72.9%)	2214 (65.9%)	35 (61.4%)	4449 (69.1%)
n (%) [missing n, % missing][a]	[610, 20.2%]	[648, 19.3%]	[22, 38.6%]	[1280, 19.9%]
Total Hydrocortisone equivalent at visit per BSA (mg/m^2)[a,c]	14.1 ($n = 2237$)	14.5 ($n = 2438$)	18.4 ($n = 25$)	14.3 ($n = 4700$)
Median (n) [Q1 to Q3]	[9.8 to 15.5]	[9.9 to 15.7]	[13.5 to 20.3]	[9.9 to 15.6]
Visits prescribed fludrocortisone	2577 (85.4%) [180,	2754 (81.9%) [140,	51 (89.5%)	5382 (83.6%) [326,
n (%) [missing n, % missing][a]	6.0%]	4.2%]	[6, 10.5%]	5.1%]
Total Fludrocortisone at visit per body surface area (when prescribed) (µg/m^2)[a]	318 ($n = 2442$)	292 ($n = 2527$)	555 ($n = 38$)	307 ($n = 5007$)
Median (n) [Q1 to Q3]	[103 to 396]	[99 to 321]	[207 to 484]	[102 to 356]
Visits prescribed salt	400 (13.3%)	486 (14.5%)	35 (61.4%)	921 (14.3%)
n (%), [missing n, % missing][a]	[290, 9.6%]	[204, 6.1%]	[5, 8.8%]	[499, 7.8%]
Renin (µIU/mL)	5.0 ($n = 1059$)	4.0 ($n = 1041$)	0.4 (n = 16)	4.5 ($n = 2116$)
Median (n) [Q1 to Q3][a]	[0.3 to 69.1]	[0.4 to 54.0]	[0.1 to 3.2]	[0.4 to 61.8]
17OH-Progesterone (nmol/L)	18.2 ($n = 1380$)	26.9 ($n = 1325$)	12.1 ($n = 31$)	21.18 ($n = 2736$)
Median (n) [Q1 to Q3]	[2.0 to 100.0]	[3.0 to 140.0]	[4.0 to 62.8]	[2.72 to 115.0]
Androstenedione (nmol/L)	0.1 ($n = 1285$)	1.0 ($n = 1211$)	0.1 ($n = 29$)	0.7 ($n = 2525$)
Median (n) [Q1 to Q3]	[0.1 to 3.0]	[0.1 to 6.0]	[0.1 to 1.0]	[0.1 to 3.5]

[a]Summary statistics of imputed values in Table S4[19].
[b]Remaining visits patients prescribed either cortisone acetate ($n = 352$), dexamethasone (134), prednisone (37), prednisolone (105), methylprednisolone (1), mixed dosing (59), or no glucocorticoid (86) (Table S6[19]).
[c]Hydrocortisone equivalent calculated by multiplying preparations by the following factors: prednisolone/prednisone x4; dexamethasone x80; cortisone acetate x0.8; methylprednisolone ×5 (Table S2 for full frequency tables of preparations[19])
Abbreviations: n , number; BSA, Body surface area; Q1 , quartile 1; Q3 , quartile 3; SDS, standard deviation score.

over 5 having median systolic SDS of 1.0 (Q1:0.2 to Q3:1.8). This equated to 31.0% over the 95th centile for age and sex under 5 years, decreasing to 15.0% in those over 5. For diastolic, median BP-SDS decreased from 1.6 (Q1:0.8 to Q3:2.5) to 0.6 (Q1:0.1 to Q3:1.2), proportions over 95th centile decreasing from 27.5% to 3.3%.

In absolute terms, modeled median systolic BP was 23 mmHg higher at age 1 decreasing to 7 mmHg higher at age 10 in males. Equivalent readings in females were 18 mmHg higher decreasing to 9 mmHg higher, diastolic BP showing a similar trajectory (Figure 2, Table 2).

Blood pressure changepoint analysis in comparison to normative values

Multiple change point analysis estimated the difference of median BP in patients above normative data stopped decreasing in males at age 11.5 years for systolic and 5.9 years for diastolic. In females, this occurred later at age 13.1 years for systolic and 7.0 years for diastolic. Following the change points, the median BP in male patients was 9.2 mmHg above normative for systolic, 7.3 mmHg above for diastolic and in females 6.4 mmHg above for systolic and 5.6 mmHg above for diastolic (Table S7, Figure S4[19]).

Predictors of blood pressure in boys and girls

The directed acyclic graph (Figure S1[19]) highlighted renin, androstenedione and 17OHP as mediators of the effect of drug doses on BP. To estimate the total effect of medications on BP, the independent variables were restricted to the covariates of age, sex, height, weight (Figure 3), and other drug doses. To estimate the extent to which each biomarker predicted BP, ancestor variables of drug doses were avoided, and covariates age, sex, height, and weight controlled for (Table 3, full models Table S8[19]).

Higher renin, higher 17OHP and higher androstenedione all predicted lower BP. This translated to patients with a renin of 100µU/mL having systolic BP 4.6 mmHg lower and diastolic BP 2.3 mmHg lower than patients with a renin of 1µU/mL. Patients with a 17OHP of 100 nmol/L had systolic BP 2.9 mmHg lower and diastolic BP 2.3 mmHg lower than patients with a 17OHP of 1 nmol/L. Patients with androstenedione of 10 nmol/L had systolic BP 1.7 mmHg lower

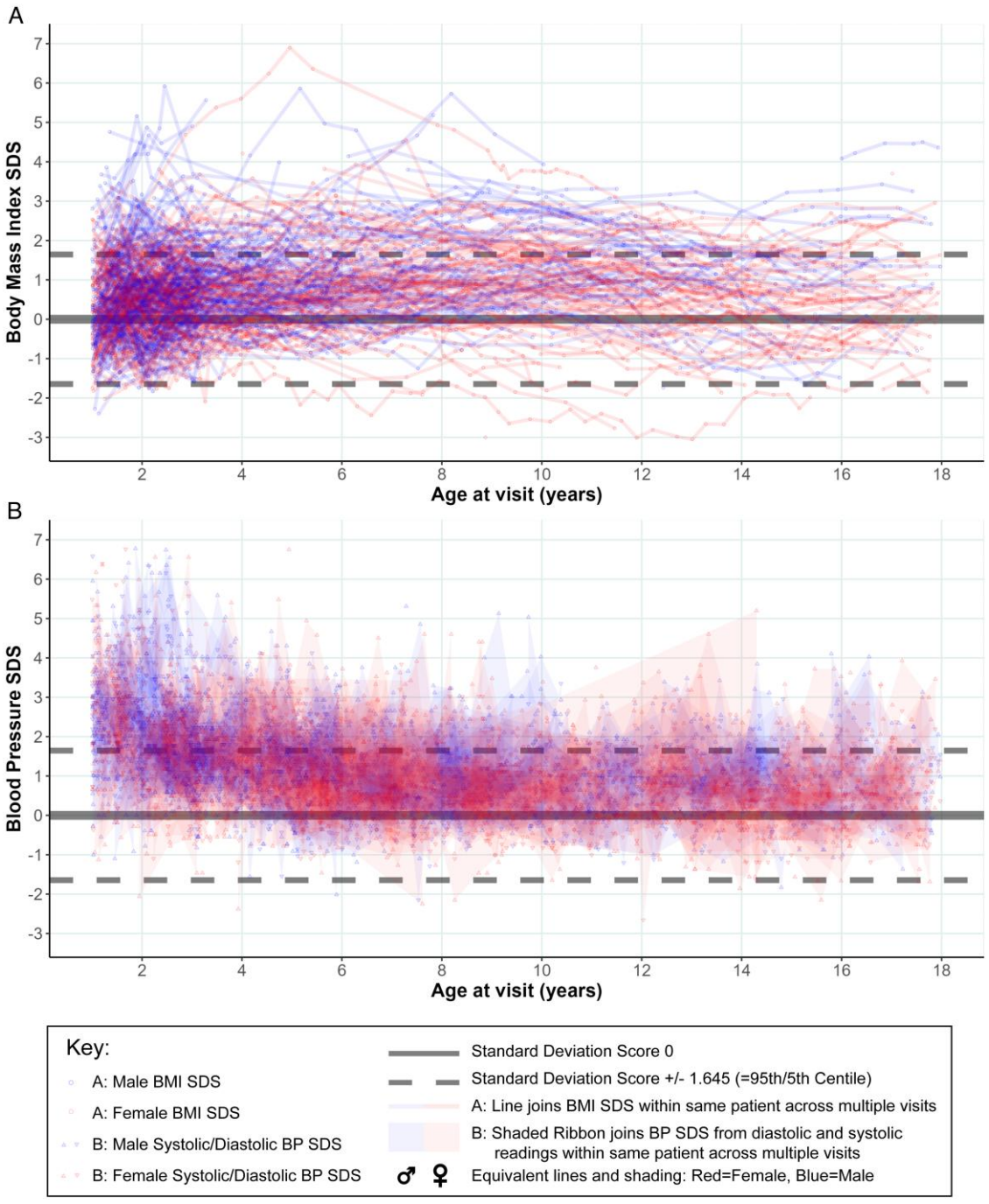

Figure 1. Variation of BMI-SDS (A) and BP-SDS (B) on age. BMI, body mass index; BP, blood pressure; SDS, standard deviation score.

and diastolic BP 1.4 mmHg lower than patients with an androstenedione of 1 nmol/L.

Higher doses of fludrocortisone were associated with higher systolic and diastolic BP, but dose of glucocorticoid and salt did not have any consistent significant effect. However, while statistically significant, the effect of fludrocortisone on BP was clinically small, with the equivalent of 100 µg of extra fludrocortisone being associated with an increase in systolic BP of 1.2 mmHg and diastolic BP of 0.8 mmHg.

Sensitivity analyses

Bayesian joint models run without imputed data did not show any significant difference in the size or direction of the estimates of interest. Models estimated using SDS for biometrics and BP as well as doses per body surface area also showed no significant difference (Table S8[19]).

Discussion

We reviewed data from over 6000 clinic visits of over 550 patients with CAH under 20 years of age and found that the BP was higher than normative values. This increase was greater at younger ages, and similar in boys and girls. Joint outcome regression modeling showed only a small average increase in BP due to mineralocorticoid replacement, and no significant effect on BP from glucocorticoid

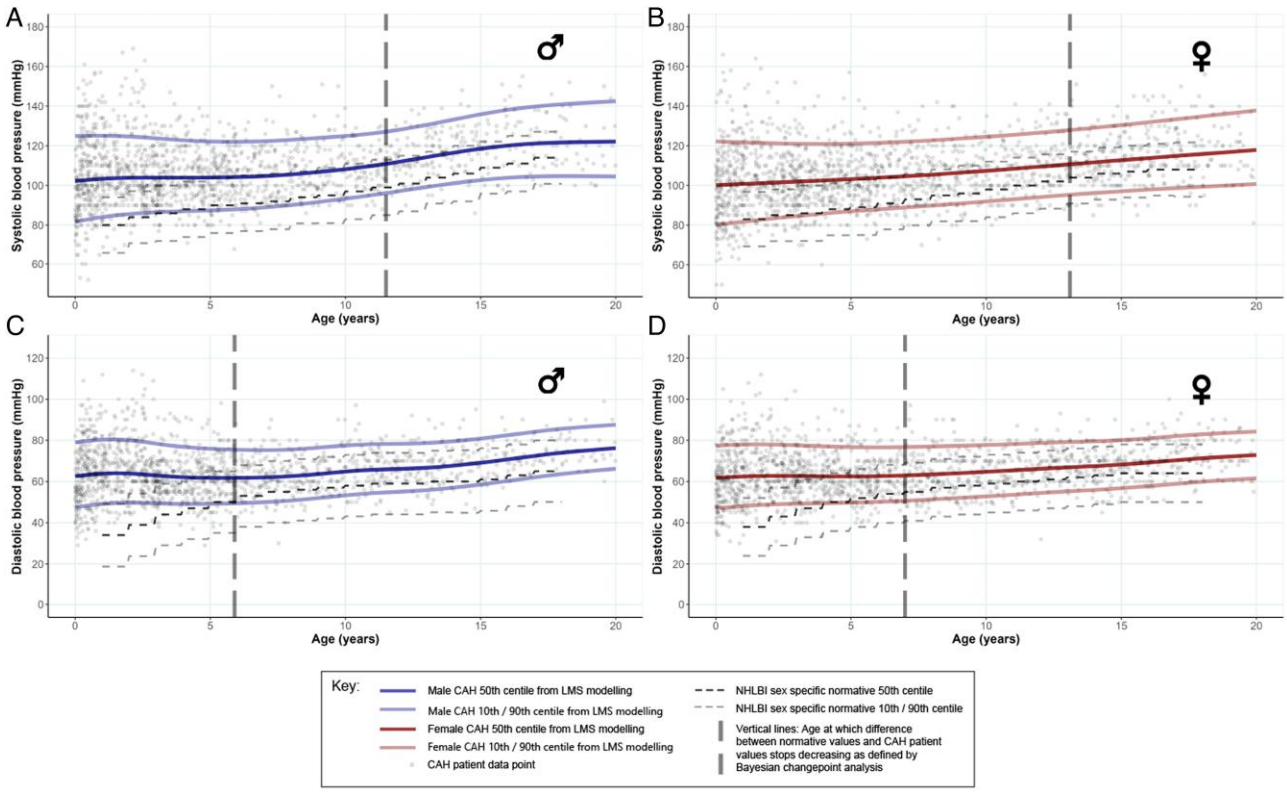

Figure 2. LMS modeling of blood pressure. (A) Male systolic BP modeling; (B) Female systolic BP modeling; (C) Male diastolic BP modeling; (D) Female diastolic BP modeling. BP, blood pressure; LMS, Lambda, Mu, Sigma; CAH, congenital adrenal hyperplasia; NHLBI, National Heart, Lung and Blood Institute.[17] CAH LMS patient centiles fit individually to each of 10 imputed datasets, with centile estimates combined using Rubin's rules.

or salt replacement. Higher levels of renin, 17OHP and androstenedione all predicted lower BP when controlling for age, sex, height, and weight.

Higher BP in children with CAH has previously been attributed to inappropriately high mineralocorticoid replacement. We saw a low regression coefficient when modeling predictors of BP consistent with an extra 100 µg of fludrocortisone causing approximately 1 mmHg increase in systolic and diastolic BP. This corroborates the findings of other studies showing higher BP at larger doses of fludrocortisone in childhood.[11,25] However, our much larger cohort in combination with robust modeling appropriately adjusting for known confounders allowed us to estimate a reliable effect size. This effect size was low, and can reassure clinicians that appropriate mineralocorticoid replacement is not likely to drive a patient into clinically significant hypertension. This low effect size also explains how smaller studies have failed to show any significant difference in BP with fludrocortisone dose.[26,27]

The lack of effect of daily hydrocortisone equivalent dose on BP in this study is further evidence that there is a variable dose requirement between patients with CAH, even when accounting appropriately for their age, sex, height and weight. The difference in regression coefficients between glucocorticoid and mineralocorticoid doses highlights that these doses should not be combined during analysis, but considered individually as they have separate pharmacological affects.[28]

The negative correlation between renin and BP that we have shown highlights that this marker does have value when monitoring patients with CAH.[1,2,11] Our large sample, careful transformation and handling of covariates has likely contributed to this finding where previous work has shown no association.[29] Nonetheless, a model explaining only 1/3 of the variability in BP indicates why this marker is sometimes challenging to interpret in isolation within an individual patient, in part due to its variation with postural position.[30,31] Renin measurement should thus be standardized, with results interpreted alongside clinical measurements of BP and electrolytes and considered against potential novel biomarkers within future studies to understand optimum mineralocorticoid replacement in CAH.

Higher 17OHP and androstenedione have been shown to be associated with lower BP in CAH in other studies.[7,32] In vitro, 17OHP has been shown to bind to the mineralocorticoid receptor and antagonize the effect of aldosterone,[33] consistent with our results that higher levels of 17OHP are associated with lower BP. Our sensitivity analysis suggested that higher levels of 17OHP taken later in the day predicted a lower BP consistent with such readings being reflective of poorer disease control than similar levels before 9am,[19] although this was limited by the reduced amount of data with precise time of measurement available. The large regression coefficients of patient weight within our model, consistent with the undisputed knowledge that heavier children are more likely to have higher BP,[34] show the importance of adjusting appropriately for covariates and the value of guiding this analysis by the use of domain expertise mapped within a directed acyclic graph. However, the association of higher 17OHP and androstenedione levels with lower BP might also reflect reduced adherence to replacement therapy in respective individuals.

Salt was prescribed in less than 15% of visits and largely concentrated in those under 5 years, which may have contributed to its lack of a statistically significant effect on BP.

Table 2. Blood pressure by sex and age.

Age (Years)	Male systolic	Male diastolic	Female systolic	Female diastolic
		Median (mmHg) (10th-90th centile) [Difference of median of CAH patients above normative values (mmHg)]		
1	103.3 (84.0 to 125.1) [23.3]	63.8 (49.1 to 80.3) [29.8]	100.8 (81.7 to 121.7) [17.8]	62.4 (48.1 to 77.9) [24.4]
2	103.8 (85.6 to 124.7) [19.8]	63.9 (49.7 to 80.0) [24.9]	101.4 (83.2 to 121.3) [16.4]	62.7 (48.8 to 78.0) [19.7]
3	103.9 (86.5 to 123.8) [17.9]	63.0 (49.4 to 78.4) [19.0]	101.9 (84.6 to 121.0) [15.9]	62.6 (49.2 to 77.6) [15.6]
4	103.9 (87.0 to 122.8) [15.9]	62.1 (49.1 to 76.8) [15.1]	102.5 (85.8 to 120.9) [14.5]	62.5 (49.5 to 77.1) [12.5]
5	104.0 (87.4 to 122.2) [14.0]	61.8 (49.2 to 75.9) [11.8]	103.2 (86.9 to 121.1) [14.2]	62.4 (49.8 to 76.7) [10.4]
6	104.2 (88.0 to 122.1) [13.2]	61.8 (49.5 to 75.4) [8.8] ***Plateau in difference after 6 years***	103.9 (87.9 to 121.5) [12.9]	62.6 (50.2 to 76.6) [8.6]
7	104.7 (88.9 to 122.3) [12.7]	62.0 (50.0 to 75.2) [7.0]	104.6 (88.9 to 122.0) [11.6]	62.9 (50.7 to 76.7) [7.9] ***Plateau in difference after 7 years***
8	105.6 (90.2 to 123.0) [11.6]	62.6 (50.8 to 75.5) [6.6]	105.5 (89.9 to 122.8) [10.5]	63.5 (51.3 to 77.0) [6.5]
9	106.8 (91.7 to 124.0) [11.8]	63.6 (52.0 to 76.4) [6.6]	106.4 (90.9 to 123.6) [10.4]	64.1 (52.0 to 77.3) [6.1]
10	105.6 (90.2 to 123.0) [11.6] ***Plateau in difference after 11 years***	64.8 (53.3 to 77.5) [6.8]	105.5 (89.9 to 122.8) [10.5]	63.5 (51.3 to 77.0) [6.5]
12	112.0 (97.2 to 128.1) [11.0]	66.1 (55.1 to 78.3) [7.1]	109.5 (94.1 to 126.6) [7.5] ***Plateau in difference after 13 years***	66.2 (54.4 to 78.7) [5.2]
14	116.5 (101.1 to 133.2) [10.5]	67.7 (57.0 to 79.5) [7.7]	111.7 (96.2 to 129.1) [5.7]	67.5 (55.9 to 79.5) [4.5]
16	120.1 (103.9 to 138.1) [9.1]	70.7 (60.2 to 82.4) [7.7]	113.8 (97.9 to 131.9) [5.8]	69.2 (57.8 to 81.0) [5.2]
18	121.7 (104.7 to 140.9) [7.7]	74.0 (63.6 to 85.6) [9.0]	115.9 (99.4 to 134.8) [7.9]	71.3 (59.9 to 82.9) [7.3]

Blood pressure median and centiles derived from Lambda, Mu, Sigma modeling across all data within sex. Normative BP data was derived from the National Heart, Lung, and Blood Institute guidelines.[17] Plateau in difference calculated by Bayesian multiple change point analysis (Table S7[19]).

However, our sensitivity analysis restricting analysis to patients under five showed similar results, and is consistent with another I-CAH study that showed no difference in BP between CAH patients on salt and those without,[25] although the patients in that study not on salt were taking higher doses of mineralocorticoid replacement. Overall, appropriate salt replacement in CAH should not be considered to have the same effects of excess dietary salt in adulthood.

The limitations of this study are highlighted by the large proportion of missing data for BP and biomarkers that is typical for large, real-world data sets. Robust multiple imputation techniques that have shown results similar to those produced by complete case analysis is reassuring. However, measurements of both BP and biomarkers vary significantly between centers, and therefore put the findings at risk of regression dilution bias. This center effect has been controlled for appropriately as a center level random effect in the modeling, but may still have some residual effect on the estimates presented. Our modeling assumes linearity in relationships that are likely non-linear, and the effect

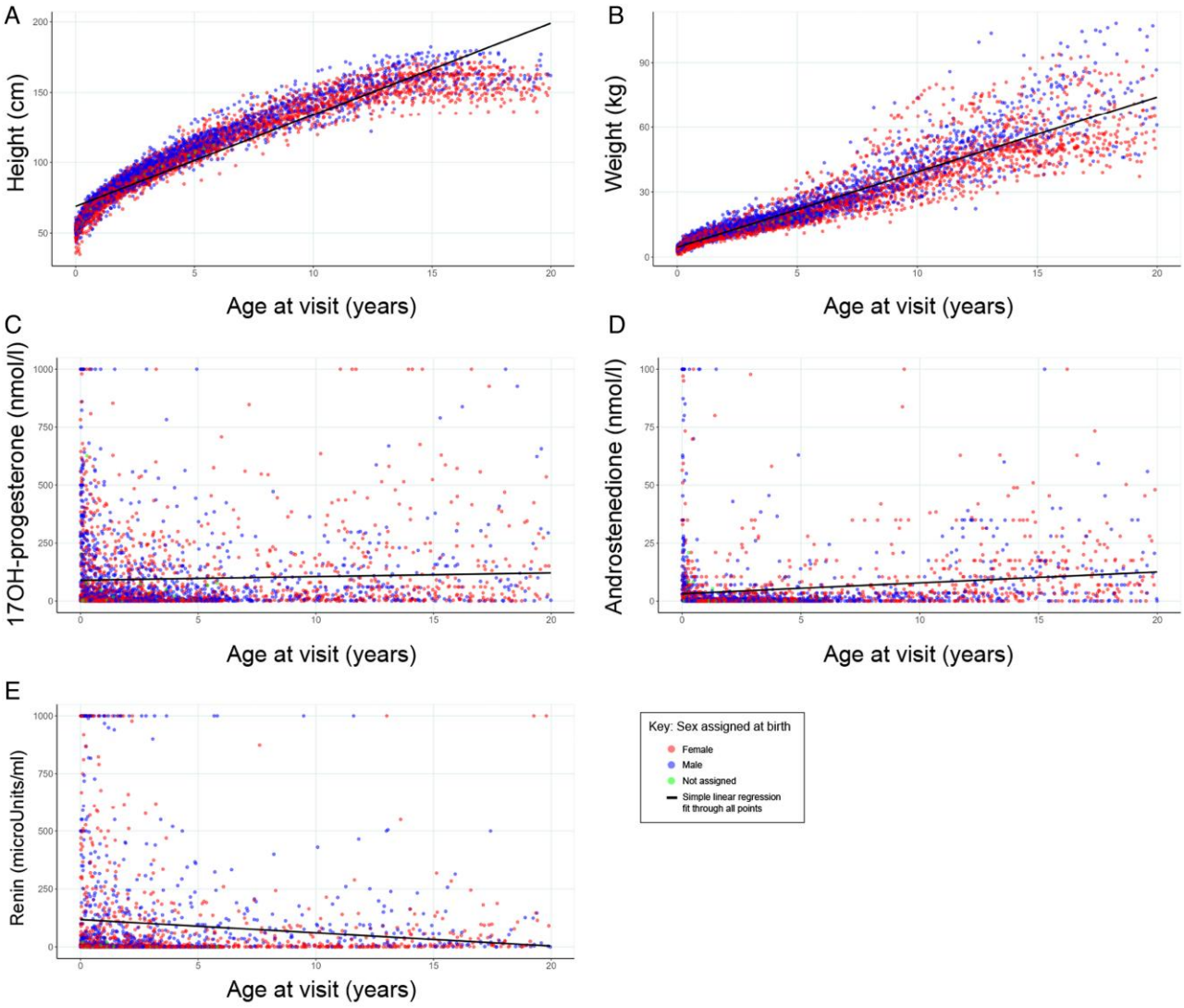

Figure 3. Variation of height, weight, and biomarkers on age. (A) Height on age; (B) Weight on age; (C) 17-OH Progesterone on age; (D) Androstenedione on age; (E) Renin on age. Simple linear regression line plotted through all points to show trend of data with increasing age.

sizes we report should not be extrapolated beyond the characteristics of the stable population from which we have estimated them.

Accurate measurement of BP in children in an outpatient setting is challenging, with this study limited by a lack of standardization in measurement between centers. We have not investigated a similar healthy control group, but relied upon normative data from other cohorts where stricter protocols around measurement are likely to have meant more accurate readings. Patients may be upset undergoing blood tests at the same visit and thus have artificially raised BP due to duress. However, such duress also risks artificially raising steroid biomarkers, yet we found higher steroid biomarkers associated with lower BP. Unfortunately, we have been unable to assess compliance in this study, an unmeasured covariate that may be associated with other known covariates such as weight. However, CAH is a rare disease, and this data from over 6000 clinic visits is only possible thanks to collaboration across continents facilitated by an international registry. With variable numbers of visits within patients our multilevel joint modeling design with careful covariate adjustment and appropriate support from professional statisticians has facilitated valuable insights from a complex dataset.

The higher BP-SDS shown in CAH patients in this study, and the relatively higher BP at younger ages warrants further investigation. Studies have shown vascular remodeling related to higher BP in the aorta and carotids in young patients, and an increase in prevalence of left ventricular diastolic dysfunction evident in even small cohorts of young patients.[5,9,35] However, the impact of different treatment strategies on these outcomes is unknown. Further engagement with long term disease registries and linking of datasets between children and adult services will help establish how best to respond to raised BP in patients with CAH. Independent patient data meta-analysis would help to assess whether other metrics of cardiovascular health measured in smaller studies should be regularly monitored to improve patient outcomes and quality of life.

Table 3. Predictors of blood pressure.

Target of estimation	Appropriate covariate adjustment set[a]	Estimate of effect on systolic BP (95% CI)	Estimate of effect on diastolic BP (95% CI)	R^2 systolic model (95% CI)	R^2 diastolic model (95% CI)
Effect of daily hydrocortisone equivalent dose (mg) on BP	*Age*, *Sex*, *Height*, *Weight*, *Other medication dosing*	0.052 (−0.057 to 0.162)	0.031 (−0.045 to 0.107)	0.27 (0.14 to 0.40)	0.17 (0.06 to 0.28)
Effect of daily fludrocortisone dose (µg) on BP		0.012[b] (0.005 to 0.020)	0.008[b] (0.003 to 0.014)		
Effect of Daily salt dose (g) on BP		−0.69 (−2.14 to 0.77)	−0.56 (−1.54 to 0.42)		
Extent ln Renin (ln (µU/mL)) predicts BP	*Age*, *Sex*, *Height*, *Weight*	−1.00[b] (−1.47 to −0.53)	−0.71[b] (−1.13 to −0.29)	0.32 (0.19 to 0.45)	0.21 (0.09 to 0.32)
Extent ln 17OHP (ln (nmol/L)) predicts BP		−0.64[b] (−1.00 to −0.27)	−0.50[b] (−0.78 to −0.22)	0.31 (0.17 to 0.45)	0.20 (0.07 to 0.32)
Extent ln androstenedione (ln (nmol/L)) predicts BP		−0.73[b] (−1.18 to −0.28)	−0.61[b] (−0.96 to −0.25)	0.31 (0.17 to 0.45)	0.20 (0.08 to 0.32)

Interpretation of statistically significant coefficients at clinically meaningful values (reverse ln transformed where appropriate):
100 µg of extra fludrocortisone was associated with an increase in systolic BP of 1.2 mmHg and diastolic BP of 0.8mmHg
Patients with a renin of 100µU/mL having systolic BP 4.6 mmHg lower and diastolic BP 3.3 mmHg lower than patients with a renin of 1µU/mL
Patients with a 17OHP of 100 nmol/L had systolic BP 2.9 mmHg lower and diastolic BP 2.3 mmHg lower than patients with a 17OHP of 1 nmol/L
Patients with an androstenedione of 10 nmol/L had systolic BP 1.7 mmHg lower and diastolic BP 1.4 mmHg lower than patients with an androstenedione of 1 nmol/L

[a]Appropriate adjustment sets were applied informed by the directed acyclic graph to avoid bias introduced by conditioning on mediating variables or ancestors of the variable of interest (Figure S1[19]).
[b]Statistically significant estimates as estimated by Bayesian joint modelling across 400 iterations with 10 bootstrap replications of each of 10 imputed datasets and combining estimates using Rubin's rules.
Abbreviations: BP , blood pressure; 17OHP , 17-OH progesterone; CI , confidence interval. Full model estimates and sensitivity analyses in Table S8.[19]

Conclusion

Higher BP in children with CAH is commonly observed and is particularly pronounced at a younger age. These higher readings are not explained by excessive mineralocorticoid or salt replacement alone, nor are they associated with poor disease control, higher levels of 17OHP and androstenedione being associated with lower BP. There is currently no evidence that BP is a significant problem in children with 21OHD CAH, although there is a need to further our understanding of the determinants of the raised BP in younger children with CAH, and whether this has any long-term consequences. Future research assessing the impact of different dosing regimens on cardiac function would further our understanding of the underlying pathophysiological processes.

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Supplementary material

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Data availability

All code and supplementary material associated with this analysis can be found at:
https://github.com/neilxlawrence/I-CAH_Blood_Pressure
Requests for access to data must be sought through SDM Registries:
https://sdmregistries.org/data-access/

References

1. Speiser PW, Arlt W, Auchus RJ, *et al.* Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088. https://doi.org/10.1210/jc.2018-01865
2. 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. https://doi.org/10.1210/endrev/bnab016
3. Bonfig W, Roehl F, Riedl S, *et al.* Blood pressure in a large cohort of children and adolescents with classic adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. *Am J Hypertens*. 2016;29(2):266-272. https://doi.org/10.1093/ajh/hpv087
4. Bonfig W, Roehl F, Riedl S, *et al.* Sodium chloride supplementation is not routinely performed in the majority of German and Austrian infants with classic salt-wasting congenital adrenal hyperplasia and has No effect on linear growth and hydrocortisone or fludrocortisone dose. *Horm Res Paediatr*. 2018;89(1):7-12. https://doi.org/10.1159/000481775
5. Krysiak R, Claahsen-van der Grinten HL, Reisch N, Touraine P, Falhammar H. Cardiometabolic aspects of congenital adrenal hyperplasia. *Endocr Rev*. 2024; doi:10.1210/endrev/bnae026
6. Mooij C, Kapusta L, Otten B, Claahsen-van der Grinten H. Blood pressure in the first year of life in children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency: a pilot study. *Horm Res Paediatr*. 2010;74(5):28-332. https://doi.org/10.1159/000308891
7. Ubertini G, Bizzarri C, Grossi A, *et al.* Blood pressure and left ventricular characteristics in young patients with classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Int J Pediatr Endocrinol*. 2009;2009:383610. https://doi.org/10.1155/2009/383610
8. Liivak K, Tillmann V. 24-hour blood pressure profiles in children with congenital adrenal hyperplasia on two different hydrocortisone treatment regimens. *J Pediatr Endocrinol Metab*. 2009;22(6):511-517. https://doi.org/10.1515/JPEM.2009.22.6.511
9. Akyürek N, Atabek ME, Eklioğlu BS, Alp H. Ambulatory blood pressure and subclinical cardiovascular disease in patients with congenital adrenal hyperplasia: a preliminary report. *J Clin Res Pediatr Endocrinol*. 2015;7(1):13-18. https://doi.org/10.4274/jcrpe.1658
10. Roche EF, Charmandari E, Dattani MT, Hindmarsh PC. Blood pressure in children and adolescents with congenital adrenal hyperplasia (21-hydroxylase deficiency): a preliminary report. *Clin Endocrinol (Oxf)*. 2003;58(5):589-596. https://doi.org/10.1046/j.1365-2265.2003.01757.x
11. Bonfig W, Schwarz HP. Blood pressure, fludrocortisone dose and plasma renin activity in children with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency followed from birth to 4 years of age. *Clin Endocrinol (Oxf)*. 2014;81(6):871-875. https://doi.org/10.1111/cen.12498
12. Jääskeläinen J, Voutilainen R. Growth of patients with 21-hydroxylase deficiency: an analysis of the factors influencing adult height. *Pediatr Res*. 1997;41(1):30-33. https://doi.org/10.1203/00006450-199701000-00005

13. Whitworth J, Brown M, Kelly J, Williamson P. Mechanisms of cortisol-induced hypertension in humans. *Steroids*. 1995;60(1):76-80. https://doi.org/10.1016/0039-128X(94)00033-9
14. Balagamage C, Lawrence NR, Krone R, Bacila IA, Krone NP. Blood pressure in children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Horm Res Paediatr*. 2024;97(4):315-325. https://doi.org/10.1159/000533465
15. Roth GA, Mensah GA, Johnson CO, *et al*. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol*. 2020;76(25):2982-3021. https://doi.org/10.1016/j.jacc.2020.11.010
16. Tseretopoulou X, Bryce J, Chen M, *et al*. The I-CAH registry: a platform for international collaboration for improving knowledge and clinical care in congenital adrenal hyperplasia. *Clin Endocrinol (Oxf)*. 2024;101(4):397-404. https://doi.org/10.1111/cen.14961
17. National Heart Lung and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128 Suppl 5(Suppl\ 5):S213-S256. https://doi.org/10.1542/peds.2009-2107C
18. Carpenter JR, Bartlett JW, Morris TP, Wood AM, Quartagno M, Kenward MG. *Multiple Imputation and its Application*. John Wiley & Sons; 2023.
19. Lawrence NR, Bacila I, Tonge J, *et al*. Supplementary Materials: Blood pressure and its associations in 554 children and young people with CAH. Github. Accessed March 23, 2025. https://github.com/neilxlawrence/I-CAH_Blood_Pressure.
20. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ*. 2007;85(09):660-667. https://doi.org/10.2471/BLT.07.043497
21. Gemelli M, Manganaro R, Mamì C, De Luca F. Longitudinal study of blood pressure during the 1st year of life. *Eur J Pediatr*. 1990;149(5):318-320. https://doi.org/10.1007/BF02171556
22. Joint Formulary Committee. *Equivalent Anti-Inflammatory Doses of Corticosteroids. British National Formulary. Vol. 88*. Pharmaceutical Press; 2024.
23. Trenkel S, Seifarth C, Schobel H, Hahn E, Hensen J. Ratio of serum aldosterone to plasma renin concentration in essential hypertension and primary aldosteronism. *Exp Clin Endocrinol Diabetes*. 2002;110(02):80-85. https://doi.org/10.1055/s-2002-23491
24. Tennant PW, Murray EJ, Arnold KF, *et al*. Use of directed acyclic graphs (DAGs) to identify confounders in applied health research: review and recommendations. *Int J Epidemiol*. 2021;50(2):620-632. https://doi.org/10.1093/ije/dyaa213
25. Neumann U, Van Der Linde A, Krone RE, *et al*. Treatment of congenital adrenal hyperplasia in children aged 0–3 years: a retrospective multicenter analysis of salt supplementation, glucocorticoid and mineralocorticoid medication, growth and blood pressure. *Eur J Endocrinol*. 2022;186(5):587-596. https://doi.org/10.1530/EJE-21-1085
26. Han TS, Conway GS, Willis DS, *et al*. Relationship between final height and health outcomes in adults with congenital adrenal hyperplasia: United Kingdom congenital adrenal hyperplasia adult study executive (CaHASE). *J Clin Endocrinol Metab*. 2014;99(8):E1547-E1555. https://doi.org/10.1210/jc.2014-1486
27. Mooij CF, van Herwaarden AE, Sweep FGCJ, *et al*. Cardiovascular and metabolic risk in pediatric patients with congenital adrenal hyperplasia due to 21 hydroxylase deficiency. *J Pediatr Endocrinol Metab*. 2017;30(9):957-966. https://doi.org/10.1515/jpem-2017-0068
28. Gidlöf S, Hogling DE, Lönnberg H, Ritzén M, Lajic S, Nordenström A. Growth and treatment in congenital adrenal hyperplasia: an observational study from diagnosis to final height. *Horm Res Paediatr*. 2024;97(5):445-455. https://doi.org/10.1159/000535403
29. Pofi R, Prete A, Thornton-Jones V, *et al*. Plasma renin measurements are unrelated to mineralocorticoid replacement dose in patients with primary adrenal insufficiency. *J Clin Endocrinol Metab*. 2019;105(1):314-326. https://doi.org/10.1210/clinem/dgz055
30. Al-Zoubaidi DF, Johannsen TH, Jørgensen NR, Main KM. The effect of 30 min of supine rest on plasma renin concentrations in paediatric patients. *Acta Paediatrica*. 2024;113(11):2473-2478. https://doi.org/10.1111/apa.17360
31. Fukushige J, Shimomura K, Ueda K. Influence of upright activity on plasma renin activity and aldosterone concentration in children. *Eur J Pediatr*. 1994;153(4):284-286. https://doi.org/10.1007/BF01954521
32. Maccabee-Ryaboy N, Thomas W, Kyllo J, *et al*. Hypertension in children with congenital adrenal hyperplasia. *Clin Endocrinol (Oxf)*. 2016;85(4):528-534. https://doi.org/10.1111/cen.13086
33. Quinkler M, Meyer B, Bumke-Vogt C, *et al*. Agonistic and antagonistic properties of progesterone metabolites at the human mineralocorticoid receptor. *Eur J Endocrinol*. 2002;146(6):789-799. https://doi.org/10.1530/eje.0.1460789
34. Flynn JT, Kaelber DC, Baker-Smith CM, *et al*. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3):e20171904. https://doi.org/10.1542/peds.2017-1904
35. Wasniewska M, Balsamo A, Valenzise M, *et al*. Increased large artery intima media thickness in adolescents with either classical or non-classical congenital adrenal hyperplasia. *J Endocrinol Invest*. 2013;36(2):147. https://doi.org/10.1007/BF03346751