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Clinical Research Article

Multicenter Analysis of Cardiometabolic-Related Diagnoses in Youth With Congenital Adrenal Hyperplasia: A PEDSnet Study

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Abstract

Context: Small cohorts of youth with congenital adrenal hyperplasia (CAH) demonstrate increased risk of obesity and poor cardiometabolic health.

Objective: To determine the odds of cardiometabolic-related diagnoses in youth with CAH compared with matched controls in a cross-sectional analysis in a large, multisite database (PEDSnet).

Methods: Electronic health record data (2009-2019) from 6 PEDSnet sites were used to determine odds of cardiometabolic-related outcomes based on diagnosis, anthropometric, and laboratory data using logistic regression among youth with CAH vs controls. Youth with CAH and ≥1 outpatient visit in PEDSnet (n = 1647) were propensity score–matched on 8 variables to controls (n = 6588). A subset of youth with classic CAH (n = 547, with glucocorticoid and mineralocorticoid prescriptions) were matched to controls (n = 2188). Odds of having cardiometabolic-related diagnoses among youth over 2 years with CAH were compared with matched controls.

Results: Outcomes were calculated for all individuals with CAH (median age at last visit 12.9 years [7.3, 17.6]) and a subset with classic CAH (median age at last visit 11.6 years [4.7, 17.5]) compared with their matched controls. All individuals with CAH had higher odds of overweight/obesity (odds ratio [95% CI] 3.63 [3.24,4.07]), hypertension (3.07 [2.60,3.64]), dysglycemia (1.95 [1.35,2.82], dyslipidemia (2.28 [1.79,2.91]), and liver dysfunction (2.30 [1.91,2.76]) than matched controls. Individuals with classic CAH had higher odds of overweight/obesity (3.21 [2.61,3.93]), hypertension (8.22 [6.71,10.08]), and liver dysfunction (2.11 [1.55,2.89]) than matched controls.

Conclusion: Overall, youth with CAH are at increased risk of diagnoses related to worse cardiometabolic health.

Key Words: congenital adrenal hyperplasia, obesity, overweight, hypertension, cardiometabolic

Abbreviations: 21OH, 21-hydroxylase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAH, congenital adrenal hyperplasia; EHR, electronic health record.

Congenital adrenal hyperplasia (CAH) refers to a group of autosomal recessive disorders caused by pathogenic variants in specific genes, thereby altering the function of adrenal steroidogenic enzymes. The most common form of CAH is secondary to 21-hydroxylase (21OH) deficiency. The phenotype of 21OH deficiency is variable depending on the degree of 21OH enzyme activity. Cortisol and aldosterone secretion are reduced, potentially leading to adrenal insufficiency and salt-wasting. Inadequate cortisol feedback leads to elevated adrenocorticotropic hormone, which promotes accumulation of steroid precursors proximal to the 21OH enzyme action, resulting in excessive androgen secretion and virilization. The phenotypic spectrum of CAH ranges from the life-threatening, salt-wasting, classic form with virilization in XX fetuses, to the

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nonclassic form without glucocorticoid or mineralocorticoid deficiency and later-onset virilization The classic form is a rare disease, and its frequency in most populations varies between 1 in 14 000 and 1 in 18 000 (1).

The aims of CAH treatment are to replace glucocorticoid and/or mineralocorticoid deficiencies and to reduce adrenal androgen excess. This is achieved with glucocorticoid treatment that re-establishes negative feedback on the hypothalamus and pituitary gland (1). Individuals with classic CAH also require mineralocorticoid therapy (fludrocortisone) along with appropriate salt intake (1). The introduction of glucocorticoid replacement in the 1950s improved the lifespan of people with CAH. The average age of death increased from 21 years during the 1980s to 57 years in 2010 (2). However, as no regimen can perfectly replicate the physiologic circadian rhythm of cortisol, individuals with CAH typically experience alternating periods of hyperandrogenism and hypercortisolism (3, 4). Both hypocortisolism and hypercortisolism may increase the risk of adverse metabolic and cardiovascular profiles (3, 5). Cardiovascular disease is a leading cause of death, after adrenal crisis, in CAH (2). A growing body of evidence suggests that cardiometabolic comorbidities start in childhood and adolescence (6). Children with classic CAH are at high risk for early-onset overweight and obesity (7), and increased risk of hypertension, insulin resistance, and metabolic syndrome (8). However, studies are limited by evaluation in a single center (7, 8) with relatively small sample sizes (<250 children) (7, 8). Furthermore, little is known about cardiovascular risk factors among individuals with nonclassic CAH.

We aimed to address this gap in the literature by utilizing PEDSnet, a national clinical research network that compiles electronic health record (EHR) data from large pediatric health systems, to evaluate cardiometabolic health outcomes in a large cohort of youth with CAH. Furthermore, we aimed to identify a subset of youth with classic CAH to determine whether risks differed from the overall cohort (which would include milder forms of CAH).

Materials and Methods

Patients

Deidentified EHR data were acquired from the PEDSnet Data Coordinating Center, covering over 6 million children under a Common Data Model (9). Data were extracted from the 6 large pediatric health systems in PEDSnet at the time: Children's Hospital Colorado, Children's Hospital of Philadelphia, Nemours Children's Health (locations in Florida and Delaware), Nationwide Children's Hospital, St. Louis Children's Hospital, and Seattle Children's Hospital. PEDSnet is a Partner Network Clinical Data Research Network in PCORnet, the National Patient Centered Clinical Research Network, an initiative funded by the Patient Centered Outcomes Research Institute.

Clinical data are available from the EHR of these health systems from 2009 onward for patients with at least 1 in-person encounter with a provider. All youth (any age) with a diagnosis of CAH (by PEDSnet concept ID; Table S1 includes codes extracted from the EHR problem list or diagnosis code from any encounter (10)) and at least 1 outpatient visit between 2009 and 2019 were extracted from the PEDSnet database in November 2019. Controls were selected randomly from a sample of 197 039 patients with at least 1 outpatient visit during the same time period who did not have a diagnosis of CAH, a difference of sex development, gender dysphoria, or a sex chromosome aneuploidy case, populations associated with cardiometabolic dysfunction (and previously described in separate publications) (11-14). Detailed descriptions of the criteria for the control population have previously been published (12, 13).

To identify patients with classic CAH, we extracted data for a subset of individuals with any CAH diagnosis (Table S1 (10)), and both a glucocorticoid and mineralocorticoid prescription in the chart. We included hydrocortisone (RXCUI code 5492), prednisolone (8638), prednisone (8640), methylprednisolone (6902), dexamethasone (3264), and fludrocortisone (H02AA). We also evaluated the number of people prescribed an antihypertensive, lipid-lowering, or blood glucose–regulating medications (Table S3 (10)).

Outcomes

Cardiometabolic-related outcomes investigated in this study included overweight/obesity, dyslipidemia, liver dysfunction, hypertension, and dysglycemia/hyperglycemia. These outcomes were captured using SNOMED concept codes. A cardiometabolic health risk factor was considered present/abnormal if there was (1) a diagnosis related to the outcome of interest (billing code, problem list) or (2) at least 2 abnormal measurements at different time points (anthropometric or laboratory value) recorded in the EHR. Full criteria for these outcomes are shown in supplemental materials (Table S2 (10)) and previously published (11, 12)). These continuous variables were then dichotomized into normal or abnormal values. Patients under age 2 at the last visit were excluded for cardiometabolic outcomes.

If anthropometric measures were not readily available in the dataset, they were calculated based on available height, weight, or body mass index (BMI). For continuous variables, normal and abnormal values were defined using academic society guidelines related to each outcome and the Centers for Disease Control definition of overweight and obesity in youth and adolescents (15-18). Z-scores were calculated for systolic and diastolic blood pressure.

Statistical Analysis

We identified 1647 youth with any type of CAH (all ages) for analysis (Table S1 (10)). Propensity scores were used to match 4 controls to each case. The details of the propensity score match along with a plot of the standardized differences for the entire cohort with CAH has previously been published (13). The propensity score match for the subset with classic CAH is shown in Fig. 1. Covariates chosen a priori for matching include year of birth, age at last PEDSnet visit for our study period, sex listed in the chart (EHR sex), race, ethnicity, insurance status (public vs private vs none), duration in the PEDSnet database (time between first and last encounter for our study period), and site (13).

Demographic and other descriptive characteristics were compared using either a chi-square test of proportions or a Wilcoxon rank sum test. Our primary analyses examined the differences in odds of having a diagnosis related to cardiometabolic health between those with CAH and controls. These were examined using logistic regression with generalized estimating equations to account for potential correlation among the matched cases and controls. This was performed twice, first for the entire cohort with CAH and second for the subset that

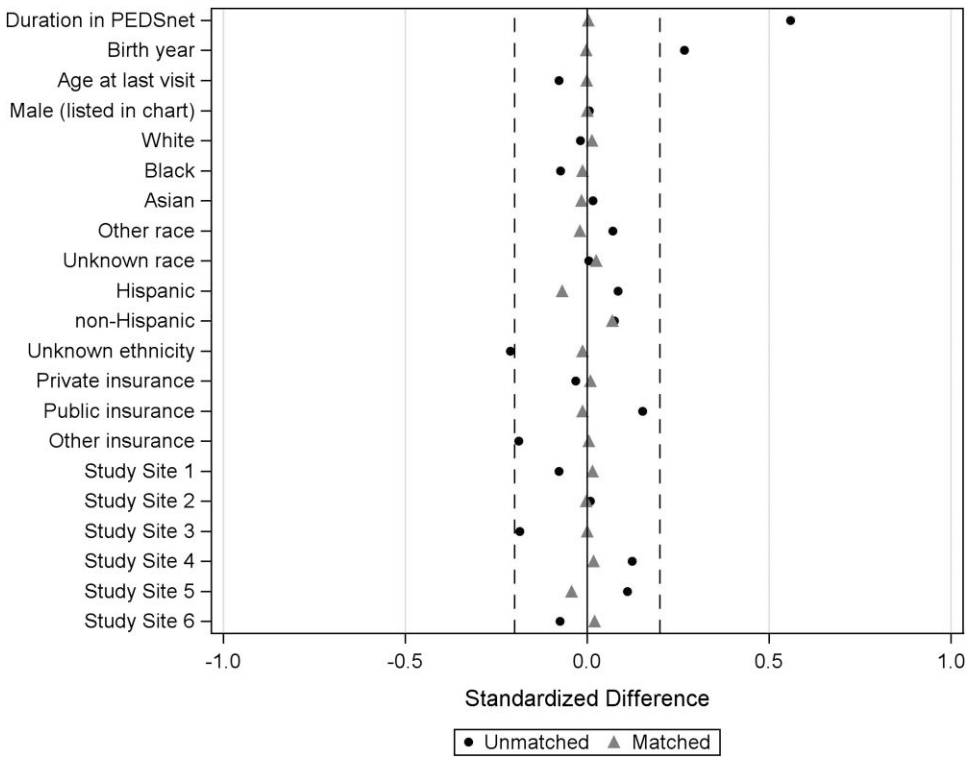

Figure 1. Standardized differences in population baseline characteristics in youth with CAH and a prescription for both a glucocorticoid and mineralocorticoid before (dots) and after (triangles) matching. Dotted lines are at 0.2.

best approximates those with classic CAH. An interaction term was used in the model for EHR sex to evaluate whether the association between outcomes and case/control status differed by sex. All analyses were performed using SAS v9.4 (SAS Institute, Cary, NC). We utilized a more conservative P value of $< .01$ to account for multiple comparisons. Data with $n < 11$ in any cell were not reported as per PEDSnet policy.

Results

Demographic data of all individuals with CAH and their matched controls (n = 1647 and 6588, respectively) have previously been published (13). Demographics of the subset with classic CAH and their matched controls are in Table 1. The group was predominantly female and white with half having private insurance. The propensity score match for the subset with classic CAH is in Fig. 1 (and the entire cohort with CAH was previously published (13)). The CAH diagnosis codes for the entire cohort and the subset with classic CAH (on a glucocorticoid and mineralocorticoid) are shown in supplemental materials (Table S1 (10)). There were 3 individuals in the classic CAH group who had a diagnosis other than 21OH deficiency (2 with 3-beta-hydroxysteroid dehydrogenase deficiency and 1 with STAR deficiency).

Overall, all individuals with CAH over the age of 2 years at the last visit had higher odds of overweight/obesity ($P < .0001$), hypertension ($P < .0001$), dysglycemia ($P = .0004$), dyslipidemia ($P < .0001$), and liver dysfunction ($P < .0001$) than controls (Table 2 and Fig. 2). The subset of individuals with classic CAH had higher odds of overweight/obesity ($P < .0001$), hypertension ($P < .0001$), and liver dysfunction ($P < .0001$) than controls (Table 2 and Fig. 2). In the entire cohort, 17 individuals had type 1 diabetes (1%) and 12 had type 2 diabetes (0.7%); in the subset with classic CAH, 1 individual had type 1 diabetes, and none had type 2 diabetes. There were neither significant interactions by sex in the entire CAH cohort, nor in the subset with classic CAH (data not shown).

Table 3 shows the number of individuals over age 2 years with documented anthropometric or laboratory measurements in the chart, as well as the median and interquartile range (25th-75th percentiles) anthropometric or laboratory measurements. There were more individuals with CAH who had documented anthropometric or laboratory values than controls. There were statistically significant differences in the median values, with individuals with CAH (overall cohort) having a higher median BMI ($P < .0001$ for calculated BMI and percentile), median systolic and diastolic blood pressures and Z-scores ($P < .0001$ for both), and triglycerides ($P < .0001$), and a lower median hemoglobin A1c ($P < .0001$) and aspartate aminotransferase (AST, $P = .0095$). There were no significant differences in median alanine aminotransferase (ALT) or lipid values.

The subset with classic CAH had significantly higher median BMI percentile and calculated BMI ($P < .0001$ for both) than matched controls (Table 3). They had higher median systolic and diastolic blood pressure and Z-scores ($P < .0001$ for both). There were no significant differences in aminotransferases, lipids, or hemoglobin A1c.

The number of individuals on an antihypertensive, lipid-lowering, or blood glucose–regulating medications are shown in supplemental materials (Table S3 (10)).

Discussion

Overall, patients with all types of CAH and classic CAH in PEDSnet had higher odds of overweight/obesity, hypertension,

and liver dysfunction. Roughly two-thirds of the cohort had an elevated BMI. The overall group of CAH included both classic and nonclassic forms of 21OH deficiency, as well as other more rare forms of CAH (3-beta hydroxysteroid dehydrogenase deficiency, 11-beta hydroxylase deficiency, 17-hydroxylase deficiency, StAR). Among those with classic CAH, roughly two-thirds had hypertension.

Table 1. Demographics of individuals with classic CAH compared with controls

	Classic CAH n = 547	Controls n = 2188	*P* value
Sex			
Female	314 (57.4)	1256 (57.4)	>.99
Male	233 (42.6)	932 (42.6)	
Race			
White	366 (66.9)	1451 (66.3)	.97
Black	37 (6.8)	155 (7.1)	
Asian	18 (3.3)	78 (3.6)	
Other	78 (14.3)	327 (14.9)	
Unknown	48 (8.8)	177 (8.1)	
Hispanic ethnicity	79 (14.4)	371 (17.0)	.33
Insurance			
Public	222 (40.6)	901 (41.2)	.30
Private	283 (51.7)	1122 (51.3)	
Other	36 (6.6)	118 (5.4)	
Unknown	6 (1.1)	47 (2.1)	
Site			
1	68 (12.4)	262 (12.0)	.97
2	121 (22.1)	487 (22.3)	
3	31 (5.7)	124 (5.7)	
4	163 (29.8)	634 (29.0)	
5	109 (19.9)	474 (21.7)	
6	55 (10.1)	207 (9.5)	
Age at first visit (yrs)	0.3 (0.0, 5.5)	1.2 (0.1, 4.5)	<.01
Age at last visit (yrs)	11.6 (4.7, 17.5)	12.3 (6.6, 16.0)	.82
Total # outpatient visits	25.0 (12.0, 42.0)	9.0 (3.0, 23.0)	<.01
Duration in PEDSnet (yrs)	7.9 (2.9, 12.6)	8.5 (2.9, 12.9)	.94

Data shown as n (%) or median (25th, 75th percentile).
Abbreviations: CAH, congenital adrenal hyperplasia.

Obesity

Our study aligns with several others showing increased rates of obesity among adults and youth with CAH (19-22). Several factors contribute to obesity in this population including need for higher doses of glucocorticoids than other forms of adrenal insufficiency (21). There is a positive correlation between hydrocortisone dose and BMI in individuals with CAH (21). Moreover, overtreatment with glucocorticoids, which is often necessary to suppress adrenal androgens, which can also result in Cushing syndrome (4, 21). In our study, we were unable to calculate daily doses relative to body surface area as exact daily doses could not be extracted from PEDSnet.

Hypertension

In our study, individuals with CAH including those with classic CAH, had an increased risk of hypertension. However, the median blood pressure Z-scores were in the normal range in the CAH cohorts. Hypertension in those with CAH has been associated with administration of fludrocortisone and glucocorticoids (23). We were not able to assess whether the increased rate of hypertension in this study was related to overtreatment with fludrocortisone, which is a known risk factor (23). Studies evaluating an association between

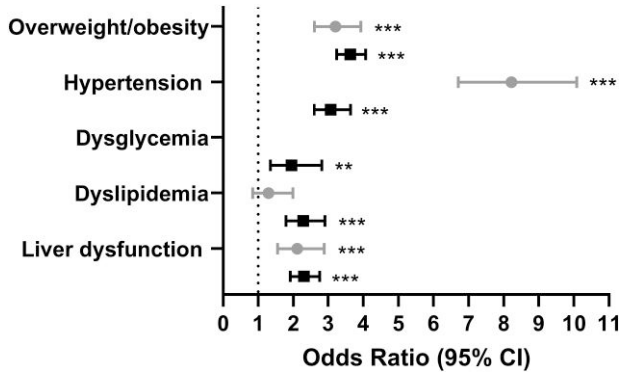

Figure 2. Odds of cardiometabolic health diagnoses among youth with congenital adrenal hyperplasia (CAH) compared with matched controls. The forest plots show the odds ratios and 95% CI of cardiometabolic health diagnoses among all youth with CAH (black squares) and classic CAH (gray circles) compared with controls. Higher odds ratios (>1) indicate that youth with CAH are more likely to have the listed diagnosis. Lower odds ratios (<1) indicate that youth with CAH are less likely to have the listed diagnosis. $^{***}P < 0.001$, $^{**}P < 0.01$.

Table 2. Odds of cardiometabolic outcomes between youth with CAH and controls over age 2

	CAH (n = 1513)	Controls (n = 6181)	OR (95% CI)	Classic CAH (n = 487)	Controls (n = 2017)	OR (95% CI)
Overweight/ obesity	963 (63.6)	2011 (32.5)	3.63 (3.24, 4.07)***	324 (66.5)	772 (38.3)	3.21 (2.61, 3.93)***
Hypertension	253 (16.7)	379 (6.1)	3.07 (2.60, 3.64)***	310 (63.7)	354 (17.6)	8.22 (6.71, 10.08)***
Dysglycemia	41 (2.7)	87 (1.4)	1.95 (1.35, 2.82)**	3 (0.6)	22 (1.1)	N/A
Dyslipidemia	114 (7.5)	213 (3.4)	2.28 (1.79, 2.91)***	28 (5.7)	91 (4.5)	1.29 (0.84, 1.99)
Liver dysfunction	189 (12.5)	362 (5.9)	2.30 (1.91, 2.76)***	61 (12.5)	128 (6.3)	2.11 (1.55, 2.89)***

Both in the overall group and in the subset, this includes youth over age 2 years at the last visit. The "classic CAH" group includes individuals with specific diagnosis codes (Table S1 (10) and both a glucocorticoid and mineralocorticoid prescription). There is no value in the dysglycemia OR category as the n was too small to generate an OR.
Abbreviations: CAH, congenital adrenal hyperplasia; N/A, not available; OR, odds ratio.
$^{**}P < .01$, $^{***}P < .0001$.

Table 3. Number of individuals over age 2 with CAH with measured anthropometric or laboratory value and median values compared with controls

	CAH n = 1513		Controls n = 6182		Classic CAH n = 487		Controls n = 2017	
	n (%)	Median (IQR)	n (%)	Median (IQR)	n (%)	Median (IQR)	n (%)	Median (IQR)
BMI (kg/m^2)	1435 (94.8)	22.1 (17.8, 27.6)	5056 (81.8)	20.3 (17.0, 24.4)***	470 (96.5)	21.5 (17.4, 27.7)	1682 (83.4)	19.9 (16.6, 24.1)***
BMI (%ile)	1435 (94.8)	85.0 (56.9, 96.8)	5056 (81.8)	69.6 (41.0, 91.1)***	470 96.5)	83.7 (54.6, 96.9)	1682 (83.4)	69.8 (42.1, 92.3)***
Systolic pressure (mmHg)	1357 (89.7)	115 (106, 122)	4031 (65.2)	112 (102, 120)***	441 (90.6)	116 (106, 123)	1357 (67.3)	110 (102, 119)***
Systolic pressure (% or Z-score)	1357 (89.7)	0.23 (−0.46, 0.77)	4031 (65.2)	0.00 (−0.77, 0.62)***	441 (90.6)	0.31 (−0.46, 0.85)	1357 (67.3)	−0.15 (−0.77, 0.54)***
Diastolic pressure (mmHg)	1357 (89.7)	66 (60, 72)	4031 (65.2)	64 (59, 70)***	441 (90.6)	67 (60, 74)	1357 (67.3)	64 (59, 70)***
Diastolic pressure (% or Z-score)	1357 (89.7)	0.11 (−0.56, 0.79)	4031 (65.2)	−0.11 (−0.67, 0.56)***	441 (90.6)	0.22 (−0.56, 0.99)	1357 (67.3)	−0.11 (−0.72, 0.56)***
ALT (IU/L)	572 (37.8)	21 (14, 30)	1386 (22.4)	21 (15, 30)	205 (42.1)	20 (13, 28)	435 (21.6)	21 (15, 30)
AST (IU/L)	577 (38.1)	25 (20, 33)	1362 (22.0)	27 (20, 35)**	215 (44.1)	26 (20, 36)	451 (22.4)	27 (21, 36)
Total cholesterol (mg/dL)	267 (17.6)	158 (138, 180)	595 (9.6)	155 (136, 177)	65 (13.3)	153 (142, 186)	208 (10.3)	158 (140, 182)
HDL (mg/dL)	256 (16.9)	47 (39, 55)	563 (9.1)	48 (40, 57)	65 (13.3)	47 (39, 56)	199 (9.9)	46 (40, 55)
LDL (mg/dL)	199 (13.2)	87 (73, 105)	423 (6.8)	88 (72, 106)	49 (10.0)	85 (72, 99)	162 (8.0)	91 (72, 110)
Triglycerides (mg/dL)	283 (18.7)	103 (67, 146)	619 (10.0)	86 (60, 119)***	69 (14.1)	97 (73, 133)	220 (10.9)	89 (63, 132)
HbA1c (%)	218 (11.4)	5.3 (5.1, 5.6)	288 (4.7)	5.4 (5.2, 5.9)**	75 (15.4)	5.3 (5.0, 5.5)	100 (5.0)	5.4 (5.1, 5.7)

Patients over age 2 years at the last visit are included here. Data shown as n (%) or median (25, 75th percentile). N = number of individuals who had a documented anthropometric or laboratory measurement listed in their chart.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAH, congenital adrenal hyperplasia; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IQR, interquartile range.
**$P < .01$, ***$P < .0001$.

hypertension and 17-hydroxyprogesterone concentration have shown conflicting results (23-25). Over two-thirds of our group with classic CAH had a diagnosis of hypertension (either by diagnosis code or blood pressure value) and only 16% of the overall cohort with CAH did. According to previous studies, the prevalence of hypertension in individuals with CAH ranges from 3.9% to 87.7% (19, 20, 26-28). The prevalence of hypertension is higher among salt-wasting compared with simple-virilizing CAH (23). We used treatment with both a glucocorticoid and mineralocorticoid as a proxy for classic CAH. This definition may have excluded some people with simple virilizing CAH not on mineralocorticoid treatment.

Dyslipidemia

In the PEDSnet cohort, all youth with CAH had higher odds of dyslipidemia, but not the cohort with classic CAH. A higher percentage of individuals in the overall cohort had a lipid panel than those with classic CAH. Those with classic CAH were, on average, younger than those in the overall group (median age at last visit 11.6 vs 12.9 years). The odds of dyslipidemia may change as individuals progress through adolescence and into adulthood when lipid panels are more likely to be checked. Dyslipidemia was broadly defined as a diagnosis of "dyslipidemia" or "hyperlipidemia" or 2 low high-density lipoprotein, or 2 high triglyceride, low-density lipoprotein, or total cholesterol measurements (Table S2, (10)) (12). The only significant differences in laboratory values were higher triglycerides among all youth with all types of CAH than controls. Notably, triglycerides may be the first elevated lipid value in children treated with prednisolone (29). However, there were no significant differences among those with classic CAH (and they were not more likely to be treated with prednisolone; Table S3 (10)) and controls, although we may have been underpowered to find a difference. Overall, there are conflicting data about the risk of dyslipidemia among individuals with CAH (29-31). Some studies suggest that among individuals with CAH, the prevalence of dyslipidemia increases with age, and adults with CAH are more prone to dyslipidemia (19). The median age at the last visit in the PEDSnet cohort was only 11-13 years, so the prevalence of dyslipidemia may change over time. Furthermore, lipid measures increase throughout childhood but decline during adolescence (32).

Dysglycemia

Individuals in the overall CAH group had higher odds of dysglycemia, but the number in the classic group was too small to calculate an odds ratio. A small number of individuals in the overall CAH group had diabetes (1% with type 1 and 0.7% with type 2). Hemoglobin A1c was higher among controls than in individuals with CAH. However, more patients with CAH had a measured A1c compared with controls, so controls may have been more likely to have an A1c measured for a specific indication, with a bias towards higher values. However, the odds of dysglycemia were still higher in the overall CAH group than in controls, as this diagnosis was defined as either a listed diagnosis code (Table S2 (10)) or a hemoglobin A1c over 5.7%. Various studies have reported an increased risk of insulin resistance in patients with CAH (20, 33), and a bidirectional relationship between hyperandrogenism and insulin resistance (34, 35). Moreover, pharmacological agents that target insulin resistance in patients with CAH can also help reduce circulating androgens (36-38). Hyperandrogenism in women contributes to impaired insulin action (34). Newer agents have been developed to target reducing hyperandrogenism in patients with CAH (39), although it is not yet known whether these will also improve or alter insulin resistance.

Liver Dysfunction

Individuals with CAH (entire cohort and classic CAH) had an increased odds of liver dysfunction. However, there was no significant difference in ALT values between individuals with CAH and controls, and the overall CAH cohort actually had a lowed median AST than controls. A higher proportion of individuals with CAH had aminotransferase measurement compared with controls, so there may be a bias towards higher values in controls. A diagnosis of liver dysfunction as reflected in the odds ratio is a combination of both diagnosis codes and laboratory values. Patients who had laboratory tests elsewhere would not have been captured in PEDSnet, but a diagnosis code may still reflect known liver dysfunction. This is an area where data are sparse, though at least 1 study has shown elevated transaminases and gamma-glutamyl transpeptidase among adult women with CAH (40).

There are several limitations to this study. This is a large retrospective study involving multiple institutions in several geographic regions around the country. One significant limitation is that only laboratory values obtained at a PEDSnet institution would be captured here. Patients who had laboratory tests drawn outside of their PEDSnet institution would not be included in this dataset. Furthermore, the methods used by laboratories at PEDSnet institutions may differ. We used a combination of diagnosis/problem list codes and laboratory and anthropometric values to classify the cardiometabolic health outcomes and address the limitations of the laboratory tests. However, if a diagnosis was only listed in the medical history (not in the problem list or as a diagnosis code), it would not be captured. We were also limited in our assessment of glucocorticoid dose relative to body surface area, as the total daily doses were not available. We report a high prevalence of hypertension, which may be related to fludrocortisone dose. However, a high blood pressure reading may have also been used to justify lowering the fludrocortisone dose, and therefore future blood pressure measurements may be normal. Overall, despite increased odds of many cardiometabolic risk factors, the median blood pressure Z-scores, aminotransferases, lipid, and A1c values were normal. A smaller subset of individuals in this cohort may have driven the increased odds for the overall group, and additional research is needed to determine who is at highest cardiometabolic risk and outcomes by age. Text variables are not currently available in PEDSnet, so genetic test results and bone age image results were not available. Finally, it is possible, some patients, such as those with 11-beta hydroxylase deficiency, could have been misclassified as having classic 21OH deficiency in this cohort, as many diagnosis codes are not specific. We tried to overcome this by including a fludrocortisone prescription in the definition for those with classic CAH (as patients with 11-beta hydroxylase deficiency should not be prescribed fludrocortisone). Future studies will evaluate and validate a more robust algorithm to differentiate the different types of CAH, as well as risk by specific diagnosis.

To our knowledge, this is the largest study to date evaluating markers of cardiometabolic risk among pediatric patients

with CAH in the United States. Over 60% of children with classic CAH had obesity or hypertension. Current Endocrine Society guidelines do not recommend routine screening for cardiac and metabolic disease among patients with CAH aside from general population recommendations (1) and should be reconsidered in future guidelines.

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Disclosures

N.J.N. is a consultant for Neurocrine Biosciences, Inc. and Ionis Pharmaceuticals and is on an Expert Panel for World Athletics. M.G.V. is a consultant for Neurocrine Bioscience, Spruce Bioscience, and Crinetics Pharmaceuticals. P.Y.F. has received research funding has served as a consultant to Neurocrine Biosciences; research funding from Spruce Biosciences and Diurnal; consulting fees from Eton Pharmaceuticals. The other authors have indicated that they have no financial relationships relevant to this article to disclose.

Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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.
2. Falhammar H, Frisén L, Norrby C, *et al.* Increased mortality in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Clin Endocrinol Metab*. 2014;99(12):E2715-E2721.
3. Merke DP, Auchus RJ. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *N Engl J Med*. 2020;383(13):1248-1261.
4. Mallappa A, Merke DP. Management challenges and therapeutic advances in congenital adrenal hyperplasia. *Nat Rev Endocrinol*. 2022;18(6):337-352.
5. Mnif MF, Kamoun M, Mnif F, *et al.* Metabolic profile and cardiovascular risk factors in adult patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Indian J Endocrinol Metab*. 2012;16(6):939.
6. Kim MS, Fraga NR, Minaeian N, Geffner ME. Components of metabolic syndrome in youth with classical congenital adrenal hyperplasia. *Front Endocrinol*. 2022;13:848274.
7. Sarafoglou K, Forlenza GP, Yaw Addo O, *et al.* Obesity in children with congenital adrenal hyperplasia in the Minnesota cohort: importance of adjusting body mass index for height-age. *Clin Endocrinol*. 2017;86(5):708-716.
8. Finkielstain GP, Kim MS, Sinaii N, *et al.* Clinical characteristics of a cohort of 244 patients with congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2012;97(12):4429-4438.
9. PEDSnet: A Pediatric Learning Health System. Accessed April 17, 2024. https://pedsnet.org/
10. Data from: Open Science Forum. https://osf.io/zxf7y/?view_only=a4e54a7a16f7483894564ef3fb7e797a
11. Davis SM, Nokoff NJ, Furniss A, *et al.* Population-based assessment of cardiometabolic-related diagnoses in youth with Klinefelter syndrome: a PEDSnet study. *J Clin Endocrinol Metab*. 2022;107(5):e1850-e1859.
12. Valentine A, Davis S, Furniss A, *et al.* Multicenter analysis of cardiometabolic-related diagnoses in transgender and gender diverse youth: a PEDSnet study. *J Clin Endocrinol Metab*. 2022;107(10):e4004-e4014.
13. Sewell R, Buchanan CL, Davis S, *et al.* Behavioral health diagnoses in youth with differences of sex development or congenital adrenal hyperplasia compared with controls: a PEDSnet study. *J Pediatr*. 2021;239:175-181.e172.
14. Nunes-Moreno M, Buchanan C, Cole FS, *et al.* Behavioral health diagnoses in youth with gender dysphoria compared with controls: a PEDSnet study. *J Pediatr*. 2022;241:147-153.e141.
15. 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.
16. Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. *Am J Gastroenterol*. 2017;112(1):18-35.
17. Arnett DK, Blumenthal RS, Albert MA, *et al.* 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74(10):e177-e232.
18. Kuczmarski RJ, Ogden CL, Guo SS, *et al.* 2000 CDC growth charts for the United States: methods and development. *Vital Health Stat*. 2002;11(246):1-190.
19. Torky A, Sinaii N, Jha S, *et al.* Cardiovascular disease risk factors and metabolic morbidity in a longitudinal study of congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2021;106(12):e5247-e5257.
20. Falhammar H, Frisén L, Hirschberg AL, *et al.* Increased cardiovascular and metabolic morbidity in patients with 21-hydroxylase deficiency: a Swedish population-based national cohort study. *J Clin Endocrinol Metab*. 2015;100(9):3520-3528.
21. Völkl TM, Simm D, Beier C, Dörr HG. Obesity among children and adolescents with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Pediatrics*. 2006;117(1):e98-e105.
22. Righi B, Ali SR, Bryce J, *et al.* Long-term cardiometabolic morbidity in young adults with classic 21-hydroxylase deficiency congenital adrenal hyperplasia. *Endocrine*. 2023;80(3):630-638.
23. Maccabee-Ryaboy N, Thomas W, Kyllo J, *et al.* Hypertension in children with congenital adrenal hyperplasia. *Clin Endocrinol (Oxf)*. 2016;85(4):528-534.
24. Hashemi Dehkordi E, Khaheshi S, Mostofizadeh N, Hashemipour M. Cardiovascular risk factors in children and adolescents with Congenital Adrenal Hyperplasia. *Adv Biomed Res*. 2021;10:19.
25. Abdel Meguid SE, Soliman AT, De Sanctis V, *et al.* Growth and metabolic syndrome (MetS) criteria in young children with classic Congenital Adrenal Hyperplasia (CAH) treated with corticosteroids (CS). *Acta Biomed*. 2022;93(5):e2022304.
26. Bonfig W, Roehl F-W, 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*. 2015;29(2):266-272.

27. 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.
28. 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.
29. Botero D, Arango A, Danon M, Lifshitz F. Lipid profile in congenital adrenal hyperplasia. *Metab Clin Exp*. 2000;49(6):790-793.
30. Gomes LG, Mendonca BB, Bachega TASS. Long-term cardiometabolic outcomes in patients with classical congenital adrenal hyperplasia: is the risk real? *Curr Opin Endocrinol Diabetes Obes*. 2020;27(3):155-161.
31. Tamhane S, Rodriguez-Gutierrez R, Iqbal AM, *et al.* Cardiovascular and metabolic outcomes in congenital adrenal hyperplasia: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2018; 103(11):4097-4103.
32. Schienkiewitz A, Truthmann J, Ernert A, Wiegand S, Schwab KO, Scheidt-Nave C. Age, maturation and serum lipid parameters: findings from the German Health Survey for Children and Adolescents. *BMC Public Health*. 2019;19(1):1-14.
33. Charmandari E, Weise M, Bornstein SR, *et al.* Children with classic congenital adrenal hyperplasia have elevated serum leptin concentrations and insulin resistance: potential clinical implications. *J Clin Endocrinol Metab*. 2002;87(5):2114-2120.
34. Moghetti P, Tosi F, Castello R, *et al.* The insulin resistance in women with hyperandrogenism is partially reversed by antiandrogen treatment: evidence that androgens impair insulin action in women. *J Clin Endocrinol Metab*. 1996;81(3):952-960.
35. Unluhizarci K, Karaca Z, Kelestimur F. Role of insulin and insulin resistance in androgen excess disorders. *World J Diabetes*. 2021;12(5):616-629.
36. Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome P450c17 alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. *N Engl J Med*. 1996;335(9):617-623.
37. la Marca A, Egbe TO, Morgante G, Paglia T, Cianci A, De Leo V. Metformin treatment reduces ovarian cytochrome P-450c17alpha response to human chorionic gonadotrophin in women with insulin resistance-related polycystic ovary syndrome. *Hum Reprod*. 2000;15(1):21-23.
38. Krysiak R, Okopien B. The effect of metformin on androgen production in diabetic women with non-classic congenital adrenal hyperplasia. *Exp Clin Endocrinol Diabetes*. 2014;122(10): 568-571.
39. Auer MK, Nordenström A, Lajic S, Reisch N. Congenital adrenal hyperplasia. *Lancet*. 2023;401(10372):227-244.
40. Falhammar H, Filipsson H, Holmdahl G, *et al.* Increased liver enzymes in adult women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Endocr J*. 2009;56(4):601-608.