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Behavioral Health Diagnoses in Youth With Difference of Sex Development or Congenital Adrenal Hyperplasia Compared With Controls: A PEDSnet Study

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Abstract

Objective: To evaluate the odds of a behavioral health diagnosis among youth with a difference of sex development (DSD) or congenital adrenal hyperplasia (CAH) compared with matched controls in the PEDSnet database.

Study design: All youth with a diagnosis of DSD (n=1,216) or CAH (n=1,647) and at least one outpatient encounter were extracted from the PEDSnet database and propensity-score matched on 8 variables (1:4) to controls (n=4,864 and 6,588, respectively) using multivariable logistic regression. The likelihood of having behavioral health diagnoses was examined using generalized estimating equations.

Results: Youth with a DSD had higher odds of a behavioral health diagnosis (OR: 1.7 [95% CI: 1.4, 2.1], p<0.0001) and neurodevelopmental diagnosis (1.7 [95% CI: 1.4, 2.0], $P < .0001$ compared with matched controls. Youth with CAH did not have increased odds of a behavioral

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health diagnosis (1.0 [95% CI: 0.9, 1.1], p=0.9) compared with matched controls but did have higher odds of developmental delay (1.8 [95% CI: 1.4, 2.4], p<0.0001).

Conclusions: Youth with a DSD diagnosis have higher odds of a behavioral health or neurodevelopmental diagnosis compared with matched controls. Youth with CAH have a higher odds of developmental delay, highlighting the need for screening in both groups.

Keywords

congenital adrenal hyperplasia; disorder of sex development; difference of sex development; psychiatric; neurodevelopmental; depression; anxiety; developmental delay; intellectual disability

Introduction

Individuals with a difference of sex development (DSD) or congenital adrenal hyperplasia (CAH) may be at increased risk of behavioral health comorbidities. We separated these two diagnoses because we included males with a diagnosis of CAH (who would not be considered to have a DSD) and CAH has been shown to be associated with a higher risk of neurodevelopmental conditions.[1-3] Furthermore, other studies have shown that families affected by CAH do not identify with the term DSD.[4] Individuals with DSD are at increased risk of having central nervous system conditions or learning difficulties.[5, 6] adults with a DSD have a high prevalence of psychiatric disorders and suicide attempts.[7, 8] Individuals with CAH, particularly those with the salt-wasting form, have been found to have a lower intelligence quotient (IQ) than controls or unaffected siblings.[1-3] women and men with CAH have higher odds of psychiatric disorders compared with controls.[9, 10] Furthermore, there are known sex differences in the prevalence of behavioral health conditions in the general population,[11-13] and sex chromosomes and sex steroids play important roles in brain development and differentiation.[14-16]

There are limited data on the behavioral health outcomes of youth with DSD or CAH receiving care at large pediatric health centers in the United States (U.S). We aim to fill this gap by utilizing a large pediatric database, to evaluate the odds of having any behavioral health diagnosis (primary outcome) and specific behavioral health diagnoses (secondary outcomes) among youth with a DSD or CAH compared with matched controls.

Methods

Patients

Data for this analysis were obtained from PEDSnet (https://pedsnet.org/), a pediatric Learning Health System and a clinical research network in PCORnet, a national, patient-centered resource, with a Common Data Model. Six pediatric health systems participated in this PEDSnet dataset, collectively including over 6 million children: Children's Hospital Colorado, Children's Hospital of Philadelphia, Nemours Children's Health System (locations in Florida and Delaware), Nationwide Children's Hospital, St. Louis Children's Hospital, and Seattle Children's Hospital. Clinical data are available from the electronic health record (EHR) of these health systems from 2009 onward for patients with an in-person encounter with a provider. All youth (any age) with a diagnosis of a DSD or

CAH (by PEDSnet concept ID, Table 4 [available at www.jpeds.com]) includes codes extracted from the EHR problem list or diagnosis code from any encounter) and at least one outpatient visit from 2009-2019 were extracted from the PEDSnet database in November 2019. We chose one outpatient visit as a criterion for cases and controls to not oversample from those who were only seen in the health systems for urgent/emergent care. Although individuals with sex chromosome aneuploidies are classified as having a DSD by the 2006 guidelines,[17] we did not include them here and performed separate analyses for those with Turner Syndrome and Klinefelter Syndrome (data not shown). We did include those with a diagnosis of mixed gonadal dysgenesis (45,X/46,XY). We excluded diagnosis codes for late-onset or non-classic CAH but based on the vagueness of some of the diagnosis codes, cannot be certain exactly which types of CAH were included. A random sample of 197,042 patients with at least one outpatient visit who did not have a diagnosis of CAH or other DSD were used as a pool of controls. To ensure these controls were representative of the general PEDSnet population, we evaluated the prevalence of well characterized pediatric diagnoses (asthma, type 1 diabetes, and acute lymphoid leukemia) to ensure the prevalence in the controls was similar to PEDSnet as a whole.

Outcomes

Composite diagnoses were created for behavioral health diagnoses based on SNOMED clinical terms concept terminology (medical term codes). SNOMED codes are used in U.S. Federal Government systems for exchange of electronic clinical health information (www.snomed.org). PEDSnet concept IDs were mapped to Athena Ancestor Tables (developed by Observational Health Data Sciences and Informatics, Columbia University). Athena is the application that contains standardized vocabularies used in PEDSnet. In addition to an overall neurodevelopmental composite, we created additional composites for developmental delay, feeding delay, learning disorders, motor delay, and speech and language disorders (Table 5; available at www.jpeds.com). Similarly, a self-harm composite comprised of all codes reflective of self-injurious behavior and suicidality was made. If n was <10 in any cell, that cell was omitted. Controls did not have a diagnosis of gender dysphoria as this group was also used as a control group for a related study evaluating mental health in individuals with gender dysphoria. Therefore, the prevalence of gender dysphoria is presented in the results, but no odds ratios were generated, as the controls did not have gender dysphoria.

Statistical analysis

Propensity scores were generated for cases (individuals with a DSD or CAH code) via multivariable logistic regression and used to match every 1 case to 4 controls.[18] The propensity score was defined as the probability of having DSD or CAH given the following youth characteristics: sex listed in chart, year of birth, age at last medical visit, PEDSnet site, race, ethnicity, payer status (public/private/none), and duration in the PEDSnet database (time between first and last encounter). Cases and controls were matched on the predicted probability of having the diagnosis (DSD or CAH) using a greedy match algorithm and a caliper of width 0.10.[19] The balance of covariates between the cases and control groups (ie, the similarity of the covariate distributions) was evaluated as a reduction in standardized mean difference, using a decision criterion of <0.20 to indicate that a covariate was balanced

(Figure 1; available at www.jpeds.com).[20] Variable missingness was handled by the widely accepted approach of including missing as another category for the variable.[21]

Differences in diagnoses of interest between cases and controls were examined using generalized estimating equations (GEE), which accounted for potential correlation between the cases and matched controls.[22] Sex listed in the chart was included as interaction term in the regression model to evaluate whether the associations between diagnoses and case/control status differed by sex (a p-value cutoff of <0.05 was used for interaction terms). Descriptive statistics including the prevalence of outcomes in the cases versus control groups, odds ratios and 95% confidence intervals, were computed. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc). A conservative p-value of <0.0025 was considered significant given the multiple comparisons.

Results

Demographics are in Table I for those with a DSD (n=1,216) or CAH (n=1,647) and their matched controls (n=4,864 and n=6,588, respectively).

A behavioral health diagnosis was listed in the EHR for 382 individuals with a DSD (31.4%), which includes all mental health and neurodevelopmental conditions. Individuals in PEDSnet with a DSD had higher odds of having any behavioral health diagnosis (OR 1.7 [95% CI: 1.4, 2.1], p<0.0001) and higher odds of any neurodevelopmental diagnosis compared with matched controls (1.7 [95% CI: 1.4, 2.0], p<0.0001, Table 2 and Figure 2, A). Individuals with a DSD had higher odds of developmental delay, feeding delay, intellectual disability, motor delay, and a speech language disorder than matched controls. Thirteen (1.1%) individuals with a DSD had a diagnosis of gender dysphoria. There were significant interactions by sex listed in the chart aside for some of the secondary outcomes including depressive disorder (p=0.04), feeding delay (p=0.03) and intellectual disability (p=0.03). Neither males nor females with DSD had a significantly higher odds of depressive disorder than their respective controls. Males with DSD had higher odds of intellectual disability compared with males without DSD (3.9 [95% CI: 2.2, 7.1], p<0.0001); but females with DSD did not (1.4 [95% CI: 0.7, 2.9], p=0.4). Males with DSD had higher odds of feeding delay compared with males without DSD (4.4 [95% CI: 3.2, 6.1], p<0.0001); females also had higher odds of feeding delay than females without DSD (2.6 [95% CI: 1.7, 3.8], p<0.0001).

A behavioral health diagnosis was listed in the EHR for 388 individuals with CAH (23.6%). Individuals in PEDSnet with CAH did not have higher odds of having a behavioral health diagnosis (1.0 [95% CI: 0.9, 1.1], p=0.9) compared with controls. However, individuals with a CAH had higher odds of developmental delay (1.8 [95% CI: 1.4, 2.4], p<0.0001) and feeding delay (1.6 [95% CI: 1.2, 2.2], p=0.002, Table 3 and Figure 2, B). Eleven (0.7%) individuals with CAH had a diagnosis of gender dysphoria. There was a significant interaction by sex for anxiety (p=0.03). Females with CAH had lower odds of anxiety disorder compared with females without CAH (0.7 [95% CI: 0.5, 0.9], p=0.007); but males did not (1.2 [95% CI: 0.8, 1.7], p=0.5).

Discussion

In this large EHR-based study, youth with a DSD in the PEDSnet database had higher odds of having a behavioral health diagnosis, particularly neurodevelopmental diagnoses compared with matched controls. Those with CAH had higher odds of developmental delay but did not have higher odds of an overall behavioral health diagnosis.

Although much attention is given to the initial gender assignment[23, 24] and controversies about surgical intervention in patients with DSD and CAH,[25-29] there is less attention given to neurodevelopment. Individuals with DSD may be at increased risk for neurodevelopmental conditions, likely primarily related to the underlying genetic cause of the DSD. Some DSD conditions are isolated to development of the genital or reproductive organs, but others may be a result of a large gene deletion or duplication, sex chromosome aneuploidies (as in 45,X/45,XY mosaicism causing mixed gonadal dysgenesis), or from mutations in a gene that affects multiple developmental pathways.[30] In the European I-DSD Registry, about a quarter of cases had an additional associated condition; over 10 times the prevalence of congenital anomalies at birth in the general population.[5, 31] The Deciphering Developmental Disorders study in the UK found that DSD phenotypes (including cryptorchidism and hypospadias) occur in 5% of patients with learning difficulties,[6] and among the 603 children with a DSD, 61% had at least one neurodevelopmental delay diagnosis, a prevalence much higher than what we report here.[6] However, their cohort was enriched for individuals with intellectual disability or developmental delay. An improved understanding of the risk of neurodevelopmental conditions, along with a specific molecular diagnosis, when possible, will improve counseling and screening for patients and families. Specific considerations are warranted for medical and surgical management, and future decision-making capacity should be evaluated in children with a DSD and a neurodevelopmental condition. These children, in particular, would be best served in a multidisciplinary clinic or care center where psychosocial support, genetic counseling and testing, and neurodevelopmental screening and assessment are available on an ongoing basis.

Patients in PEDSnet with CAH had higher odds of developmental delay and feeding delay, but not intellectual disability or a neurodevelopmental diagnosis overall. Others have shown that individuals with CAH, particularly those with the salt-wasting form, have a lower IQ than controls or unaffected siblings.[1-3] Risk factors for low IQ in CAH include higher glucocorticoid dose, higher 17-hydroxyprogesterone concentrations, and higher number of hyponatremic episodes,[2] which may indicate more severe disease. Those who have poorly controlled disease have lower IQ and higher risk of cognitive deficits compared with well-controlled patients.[2] Others have shown that those with the more severe salt-wasting form have lower IQs than those with simple virilizing form,[1-3] and those with adrenal crises or abnormal electrolytes in neonatal life may be particularly at risk for future learning problems.[32-34] There have been several studies evaluating the effect of prenatal hormonal imbalances in CAH (androgen excess, hypocortisolemia) on brain development.[35-38] Finally, although considered experimental, the use of prenatal dexamethasone administered to pregnant mothers of children at risk of having CAH may negatively impact their visual working memory and visual perception.[39, 40] Finally, as some of the codes for CAH were

non-specific that were included here, the cohort here reflects a range of phenotypes, and results may be different if only those with the salt wasting form are included.

Unlike other studies, we did not show an increased risk of mental health diagnoses in those with DSD or CAH. In fact, in this cohort, those with CAH had lower odds of self-harm than matched controls. A large study in Sweden found that women and girls with CAH had higher odds of any psychiatric disorder compared with male and female controls.[9] And women and girls with CAH had higher odds of mood disorder, anxiety disorder, and eating disorders compared with male, but not female, controls.[9] Studies are more limited in men with CAH, but one study found that men with CAH had higher odds of psychiatric disorders and suicidality compared with controls.[10] The dsd-LIFE consortium (6 European countries, n=1,040) reported psychiatric disorders in 45% of the study cohort and a suicide attempt in 6.8% of individuals.[7] However, Turner Syndrome and Klinefelter syndrome, which are not always classified as a DSD, represented 50% of the cohort.[7] In the dsd-LIFE study, 19.5% of adults met clinical cutoff symptom scores for anxiety, 7.1% for depression, 4.1% for ADHD and 9.1% for autism. Other smaller studies (n<100) of adults with a DSD that excluded sex chromosome aneuploidies have also shown a prevalence of severe psychological symptoms of 26% (vs 14% in controls) and suicidal thoughts and attempts at 38% and 12%, respectively (about 3x that in controls);[8] or a prevalence of suicidal tendencies and self-harm comparable with women without a DSD but a history of abuse.[41] A recent survey of adults in the U.S. with DSD demonstrated that half rated their mental health as fair or poor.[42] Data in the pediatric population are limited. The prevalence of these behavioral health diagnoses is lower in this pediatric cohort than what has been reported in adults. It is unknown if that is secondary to ascertainment bias in our sample, or if the risk of psychiatric diagnoses in young kids (average age ~11 years at most recent follow up) receiving care at large pediatric health centers is actually lower than what is reported in adults. The Pediatric Psychosocial Preventative Health Model can be utilized in DSD/CAH to prevent and accurately diagnosed and treat mental health concerns as they arise.[43] Finally, many psychiatric conditions emerge in adolescence and we do not yet know how many children in this cohort will go on to be diagnosed with a psychiatric condition later in life. It is important to note that there may be a subset of individuals who are at higher psychiatric risk,[7-10, 42] and more work is needed to understand specific risk factors.

Small studies suggest a prevalence of gender dysphoria of 5% among 46,XX individuals with congenital adrenal hyperplasia, the most common 46,XX DSD[44] and as high as >50% for some rare DSDs.[45-47] The prevalence of a diagnosis of gender dysphoria in the medical chart was 1.1% for DSD (n=13) and 0.7% of CAH (n=11). Recent studies in the U.S. suggest that 0.6% of adults[48] and up to 1.8% of youth[49] identify as transgender in the general population, although it is uncertain what percent of people who self-identify as transgender would have a diagnosis of gender dysphoria in their medical record.

There are several limitations to our study. As this study utilized EHR data, cases and outcomes were only captured if a diagnosis was listed in either the problem list or as a billing diagnosis at any point in the EHR. Past medical history is not available in PEDSnet; therefore, individuals with an outcome diagnosis of interest may have been missed if it was not also documented in the problem list or as a billing code. If codes of interest

were entered erroneously or omitted, this could alter the prevalence/risk of our outcomes, although we would expect this would be similar for both cases and controls. If an individual only received a diagnosis of interest at a non-PEDSnet site, this would not be captured in the outcomes. This may result in an underreporting of outcomes for individuals with a DSD or CAH. However, the converse may also be true. All six PEDSnet sites presented here (minus the Nemours Delaware location) have a DSD multidisciplinary clinic that includes either a psychologist or psychiatrist (and a social worker in some cases). If children with a DSD or CAH are receiving their care in a multidisciplinary clinic that includes regular behavioral health screening and support, they may be more likely to receive a psychiatric or neurodevelopmental diagnosis. Although we do not know what percentage of patients here received care in a multidisciplinary setting. The age of the patients, particularly those in the DSD cohort, is relatively young. As these participants age, some may go on to be diagnosed with one of the behavioral health conditions here or express gender dysphoria. The risk of these outcomes may change over time or as participants age. Prospective, multi-site data, such as those collected in the DSD Translational Research Network (DSD-TRN, which includes two PEDSnet sites: Children's Hospital Colorado and Seattle Children's),[50] will help address some of the limitations of the PEDSnet database. Future work will also focus on clarifying how sex is recorded in the chart at each site. Several sites use an EHR smart form that captures gender identity, sex assigned at birth and pronouns. When it becomes possible to capture SNOMED codes that reflect these fields, we will also evaluate differences based on stated gender identity. Finally, although our sample size of youth with DSD or CAH is large and diverse, it may not be representative of patients with these diagnoses in the U.S. as the PEDSnet sites represent large pediatric health systems.

In conclusion, this large PEDSnet sample shows higher odds of behavioral health diagnoses, in particular those affecting neurodevelopment, among youth with DSD and a similar odds of behavioral health diagnoses among youth with CAH compared with rigorously matched controls. However, both groups had higher odds of developmental delay than controls, highlighting the need for appropriate screening and referrals for these groups.

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Abbreviations:

DSD	difference of sex development

CAH	congenital adrenal hyperplasia
EHR	electronic health record
IQ	intelligence quotient

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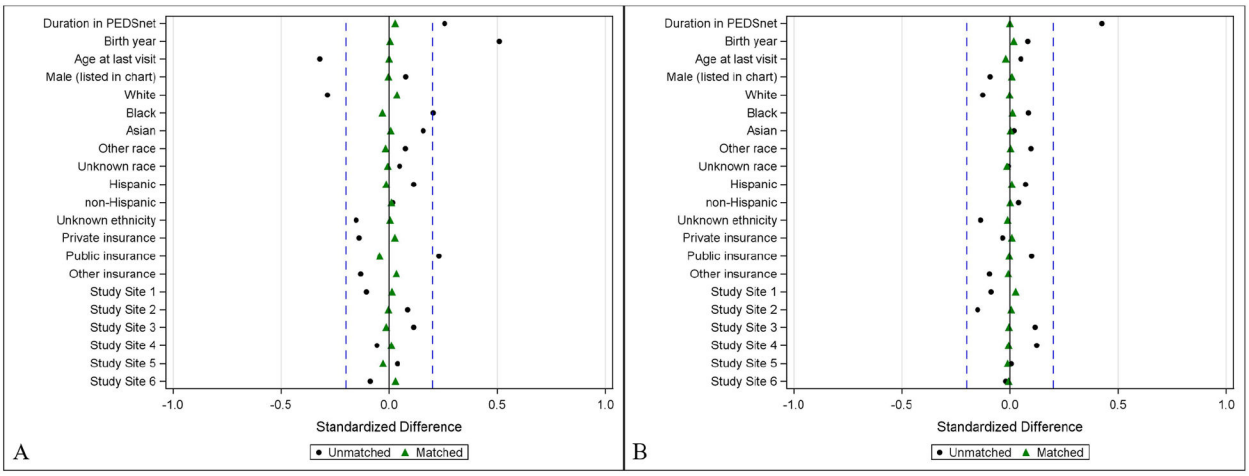

Figure 1: Standardized differences in population baseline characteristics in youth with a difference of sex development (A) or congenital adrenal hyperplasia (B) vs. controls before (dots) and after (triangles) matching.

Dotted lines are at 0.2.

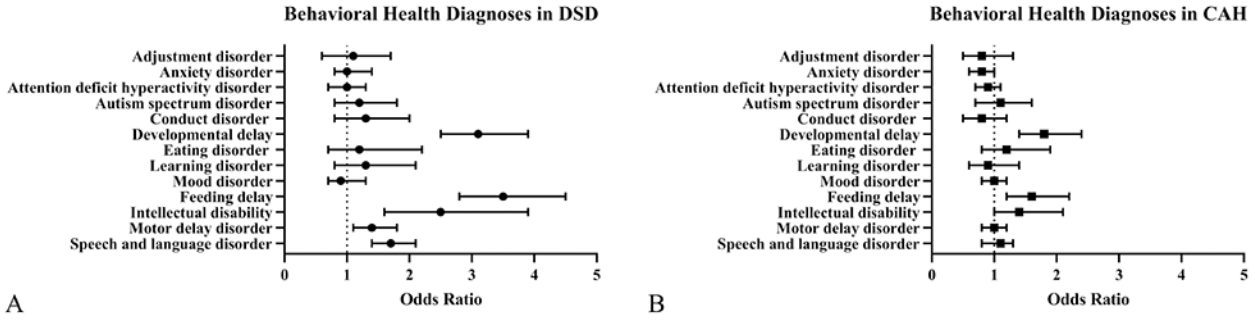

Figure 2: Odds of behavioral health diagnoses among youth with a difference of sex development (DSD) or congenital adrenal hyperplasia (CAH) compared to matched controls.

The forest plots show the odds ratios and 95% confidence intervals of behavioral health diagnoses in DSD (A) and CAH (B) compared to controls. Higher odds ratios (>1) indicate that youth with DSD or CAH are more likely to have the listed diagnosis. Lower odds ratios (<1) indicate that youth with DSD or CAH are less likely to have the listed diagnosis. Note that developmental delay, feeding delay, learning disorder, motor delay disorder and speech and language disorder are composite scores.

Table 1.

Demographics

	DSD n=1,216	Controls n=4,864	CAH n=1,647	Controls n=6,588
Sex listed in chart				
Female	655 (53.9)	2,613 (53.7)	1,025 (62.2)	4,124 (62.6)
Male	561 (46.1)	2,251 (46.3)	622 (37.8)	2,464 (37.4)
Race				
White	656 (53.9)	2,539 (52.2)	1,017 (61.7)	4,074 (61.8)
Black	186 (15.3)	798 (16.4)	186 (11.3)	720 (10.9)
Asian	77 (6.3)	300 (6.2)	55 (3.3)	218 (3.3)
Other	175 (14.4)	729 (15.0)	250 (15.2)	995 (15.1)
Unknown	122 (10.0)	498 (10.2)	139 (8.4)	581 (8.8)
Ethnicity				
Non-Hispanic	939 (77.2)	3,736 (76.8)	1,288 (78.2)	5,151 (78.2)
Hispanic	188 (15.5)	777 (16.0)	231 (14.0)	907 (13.8)
Unknown	89 (7.3)	351 (7.2)	128 (7.8)	530 (8.0)
Insurance type				
Private	564 (46.4)	2,196 (45.1)	850 (51.6)	3,374 (51.2)
Public	539 (44.3)	2,261 (46.5)	626 (38.0)	2,513 (38.1)
Other	92 (7.6)	282 (5.8)	142 (8.6)	461 (7.0)
Unknown	21 (1.7)	125 (2.6)	29 (1.8)	240 (3.6)
Age at first visit (years)	0.2 (0.0, 4.3)	1.0 (0.1, 5.0)	2.9 (0.1, 8.0)	3.0 (0.4, 8.2)
Age at last visit (years)	8.8 (3.9, 15.4)	10.1 (4.2, 15.3)	12.9 (7.3, 17.6)	13.6 (8.3, 16.7)
Duration in PEDSnet (years)	5.3 (2.2, 10.2)	5.4 (1.5, 10.7)	7.1 (2.7, 11.4)	7.2 (2.0, 12.2)
Saw a provider who could make a behavioral health diagnosis	452 (37)	1,073 (22)	429 (26)	1,508 (23)
Age at first diagnosis (years)	1.0 (0.0, 9.0)	---	6.0 (0.0, 11.0)	---
Age at last diagnosis (years)	6.0 (1.0, 14.0)	---	10.0 (5.0, 15.0)	---

Data are shown as n (%), mean ± standard deviation or median (25-75th %ile). Age at first visit refers to the age at the first visit in PEDSnet (not necessarily a visit related to DSD/CAH). Age at first diagnosis refers to the first diagnosis of DSD or CAH in the chart.

Table 2.

Prevalence and odd ratios of behavioral health diagnoses in those with DSD vs. matched controls

	DSD n=1,216 (%)	Control n=4,864 (%)	OR (95% CI)	p-value
Behavioral Health Diagnoses *	**382 (31.4)**	**1,130 (23.2)**	**1.7 (1.4, 2.1)**	**<0.0001**
Adjustment disorder	20 (1.6)	76 (1.6)	1.1 (0.6, 1.7)	0.8
Anxiety disorder	68 (5.6)	263 (5.4)	1.0 (0.8, 1.4)	0.8
Conduct disorder	28 (2.3)	89 (1.8)	1.3 (0.8, 2.0)	0.3
Eating disorder	15 (1.2)	50 (1.0)	1.2 (0.7, 2.2)	0.5
Mood disorder	50 (4.1)	220 (4.5)	0.9 (0.7, 1.3)	0.5
Depressive disorder	40 (3.3)	170 (3.5)	0.9 (0.7, 1.3)	0.7
Neurodevelopmental Diagnoses	**288 (23.7)**	**763 (15.7)**	**1.7 (1.4, 2.0)**	**<0.0001**
Attention deficit hyperactivity disorder	64 (5.3)	261 (4.9)	1.0 (0.7, 1.3)	0.9
Autism spectrum disorder	27 (2.2)	92 (1.9)	1.2 (0.8, 1.8)	0.5
Developmental delay composite	132 (10.9)	183 (3.8)	3.1 (2.5, 3.9)	<0.0001
Feeding delay composite	130 (10.7)	160 (3.3)	3.5 (2.8, 4.5)	<0.0001
Intellectual disability	32 (2.6)	52 (1.1)	2.5 (1.6, 3.9)	<0.0001
Learning disorder composite	22 (1.8)	68 (1.4)	1.3 (0.8, 2.1)	0.3
Motor delay composite	116 (9.5)	333 (6.8)	1.4 (1.1, 1.8)	0.002
Speech/language disorder composite	151 (12.4)	375 (7.7)	1.7 (1.4, 2.1)	<0.0001

Data are shown as n (%), mean ± standard deviation or median (25-75th %ile).

*Behavioral health diagnoses include a composite of all outcomes including neurodevelopmental outcomes.

Table 3.

Prevalence and odd ratios of behavioral health diagnoses in those with CAH vs. matched controls

	CAH n=1,647 (%)	Control n=6,588 (%)	OR (95% CI)	p-value
Behavioral Health Diagnoses *	**388 (23.6)**	**1,561 (23.7)**	**1.0 (0.9, 1.1)**	**0.9**
Adjustment disorder	24 (1.5)	119 (1.8)	0.8 (0.5, 1.3)	0.3
Anxiety disorder	84 (5.1)	414 (6.3)	0.8 (0.6, 1.0)	0.07
Conduct disorder	28 (1.7)	137 (2.1)	0.8 (0.5, 1.2)	0.3
Eating disorder	24 (1.5)	80 (1.2)	1.2 (0.8, 1.9)	0.4
Mood disorder	93 (5.6)	383 (5.8)	1.0 (0.8, 1.2)	0.8
Depressive disorder	73 (4.4)	325 (4.9)	0.9 (0.7, 1.2)	0.4
Bipolar disorder	13 (0.8)	46 (0.7)	1.1 (0.6 2.1)	0.7
Tic disorder	15 (0.9)	44 (0.9)	1.4 (0.8, 2.5)	0.3
Self-Harm composite	16 (1.0)	137 (2.1)	0.5 (0.3, 0.8)	0.004
Neurodevelopmental Diagnoses	**240 (14.6)**	**970 (14.7)**	**1.0 (0.9, 1.2)**	**0.9**
Attention deficit hyperactivity disorder	98 (6.0)	429 (6.5)	0.9 (0.7, 1.1)	0.4
Autism spectrum disorder	31 (1.9)	117 (1.8)	1.1 (0.7, 1.6)	0.8
Developmental delay composite	91 (5.5)	203 (3.1)	1.8 (1.4, 2.4)	<0.0001
Feeding delay composite	55 (3.3)	139 (2.1)	1.6 (1.2, 2.2)	0.002
Intellectual disability	34 (2.1)	97 (1.5)	1.4 (1.0, 2.1)	0.09
Learning disorder composite	26 (1.6)	111 (1.7)	0.9 (0.6, 1.4)	0.8
Motor delay composite	121 (7.3)	493 (7.5)	1.0 (0.8, 1.2)	0.9
Speech/language disorder composite	108 (6.6)	414 (6.3)	1.1 (0.8, 1.3)	0.7

Data are shown as n (%), mean ± standard deviation or median (25-75th %ile).

*Behavioral health diagnoses include a composite of all outcomes including neurodevelopmental outcomes.

Table 4.

SNOMED codes and linked PEDSnet concept IDs

SNOMED Name	PEDSnet Concept ID
Difference of Sex Development (DSD)	
46,XX disorder of sex development with anorectal anomalies syndrome	37116741
46,XX disorder of sex development with skeletal anomalies syndrome	37116740
46, XX true hermaphrodite	4004776
Ambiguous genitalia	4062097
Androgen receptor absent	4035130
Androgen resistance - infertile male	4127074
Androgen resistance syndrome	440359
Chimera 46, XX; 46, XY	4007565
Chondrodysplasia with disorder of sex development syndrome	36715303
Complete androgen insensitivity syndrome	45770921
Complete testicular feminization syndrome	4176428
Disorder of androgen receptor	4322687
Disorder of sex development with intellectual disability syndrome	36714286
Dysmorphism, short stature, deafness, disorder of sex development syndrome	37118645
Female pseudohermaphroditism	4338827
Gynandromorphism syndrome	4048536
Hermaphroditism	4028941
History of intersex surgery	4323227
Incomplete testicular feminization syndrome	442636
Indeterminate sex	46270485
Indeterminate sex and pseudohermaphroditism	73584
Intersex	46273637
Male pseudohermaphroditism	4009631
Male pseudohermaphroditism due to 5-alpha-reductase deficiency	42538057
Mixed gonadal dysgenesis	4308443
Meacham syndrome	36716451
Mosaic XO/XY	4005274
Ovotestis	4077758
Partial androgen insensitivity syndrome	45757367
Pseudohermaphroditism	4326589
Pure gonadal dysgenesis	4316871
Pure gonadal dysgenesis 46,XX	4317840
Pure gonadal dysgenesis 46,XY	4317951
Receptor-positive androgen resistance syndrome	4289899
Reifenstein syndrome	4242435

SNOMED Name	PEDSnet Concept ID
Testicular feminization	436379
Testosterone 17-beta-dehydrogenase deficiency	4174657
XX males	4251774
XY females	4219609
XY, female phenotype	4004649
XY type gonadal dysgenesis with associated anomalies syndrome	37116728
Congenital Adrenal Hyperplasia (CAH)	
3 beta-Hydroxysteroid dehydrogenase deficiency	4182535
17 alpha-Hydroxyprogesterone aldolase deficiency	4169253
Adrenogenital disorder	196369
Adrenal virilism	4156662
CAH - desmolase deficiency	4028928
Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency	37397203
Cholesterol monooxygenase (side-chain cleaving) deficiency	4195771
Congenital adrenal hyperplasia	4029573
Congenital adrenal hyperplasia due to cytochrome P450 oxidoreductase deficiency	37396060
Congenital lipoid adrenal hyperplasia due to STAR deficiency	37397202
Deficiency of steroid 11-beta-monooxygenase	4051374
Deficiency of steroid 17-alpha-monooxygenase	4050764
Feminization-adrenogenital syndrome	4028925
Feminizing syndrome of adrenal origin	4150530
Pseudohermaphrodite, female with adrenocortical disorder	4035119
Pseudohermaphrodite, male with adrenocortical disorder	4035118
Salt-losing congenital adrenal hyperplasia	4029574
Salt-losing congenital adrenal hyperplasia with virilism	45757615
Steroid 21-monooxygenase deficiency, salt wasting type	4324258
Virilization-adrenogenital syndrome	4028926
Virilizing syndrome of adrenal origin	4066281

Table 5.

SNOMED codes for outcomes

	SNOMED code
Behavioral Health Diagnoses	74732009, 700364009, 229729009, 231543005, 268734000, 29164008, 27172100, 248290002, (exclude 123526007, 129104009 & 66936004)
Adjustment disorder	17226007
Anxiety disorder	197480006
Obsessive compulsive disorder	191736004
Panic disorder	371631005
Post-traumatic stress disorder	47505003
Conduct disorder *	430909002
Eating disorder	72366004 (exclude 192016008, 426881004)
Impulse control disorder	66347000
Mood disorder	46206005
Bipolar disorder	13746004
Depressive disorder	35489007
Neurosis	111475002
Personality disorder	33449004
Psychotic disorder	69322001
Tic disorder	568005
Self-Harm Composite (not a subcategory of psychiatric disorders)	248062006, 6471006, 82313006, 77434001, 276853009
Neurodevelopmental Diagnoses	700364009, 229729009, 231543005, 268734000, 29164008, 27172100, 248290002, (exclude 123526007)
Attention deficit hyperactivity disorder	406506008
Autism spectrum disorder	408856003
Developmental delay composite	442059001, 716710007, 609225004, 248290002 (exclude 307653008, 123526007, 703477003, 430099007)
Feeding delay composite	78164000, 426881004
Intellectual disability	110359009
Learning disorder composite	1855002, 59770006, 192138007
Motor delay composite	268674003, 4949009, 302289002
Speech/language disorder composite	229729009, 231543005, 268734000, 29164008, 271721006

* in SNOMED, conduct disorder is classified as both a mental disorder and a neurodevelopmental disorder. Psychiatric diagnoses are termed “mental disorder” in SNOMED.