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Prevalence of Endocrine Disorders Among 6078 Individuals With Down Syndrome in the United States

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Abstract Findings from a recent study describing prevalence of common disease conditions in the largest documented cohort of individuals with Down syndrome (DS) in the United States strongly suggested significant disparity in endocrine disorders among these individuals when compared with age- and sex-matched individuals without DS. This retrospective, descriptive study is a follow-up report documenting prevalence of 21 endocrine disorder conditions, across 28 years of data, from 6078 individuals with DS and 30,326 age- and sex-matched controls, abstracted from electronic medical records within a large integrated health system.

Overall, individuals with DS experienced higher prevalence of adrenal insufficiency and Addison's disease; thyroid disorders, including hypothyroidism, hyperthyroidism, Hashimoto's disease, and Graves' disease; prolactinoma/hyperprolactinemia; diabetes insipidus; type I diabetes mellitus; and gout. Conversely, those with DS had lower prevalence of polycystic ovary syndrome and type II diabetes mellitus. Many prevalences of endocrine conditions seen in individuals with DS significantly differ relative to their non-DS matched counterparts. These varied findings warrant further exploration into how screening for and treatment of endocrine conditions may need to be approached differently for individuals with DS. (*J Patient Cent Res Rev.* 2022;9:70-74.)

Keywords Down syndrome; prevalence; endocrine diseases; thyroid disorder; diabetes mellitus; adrenal insufficiency

A recent study of the largest documented cohort of individuals with Down syndrome (DS) in the United States described the prevalence of a broad range of disease conditions.[1] Findings strongly suggested significant disparity in endocrine-specific conditions among individuals with DS as compared with age- and sex-matched individuals without DS.[1] It is well-supported in current research that thyroid disorder and diabetes mellitus, specifically, are more prevalent among individuals with DS, meriting a closer look at these and other endocrine conditions.[2-7]

To explore respective prevalence of a more comprehensive set of endocrine conditions among individuals with DS, this follow-up brief report to a broader study[1] utilizes clinical data representing the largest sample of individuals with DS in the United States, treated across a single Midwestern integrated health system that includes the largest center of care for adolescents and adults with DS. The objective was to provide critical information on endocrine-specific conditions in individuals with DS, thereby adding to the sparsely available clinical research into this unique but growing patient population and ultimately to enhance practitioner knowledge and specialized care.

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METHODS

This retrospective, descriptive cohort study utilized 28 years of available inpatient and outpatient encounter data (May 1991–September 2019) abstracted from electronic medical records of one of the largest nonprofit health systems in the United States. As a follow-up to a larger study conducted with this patient population, it was determined to be non-human subjects research by the local institutional review board. Full details on the data collection methods for this and the more generalized prevalence study can be found in the previously published parent report.[1]

Participants

In all, 6078 eligible cases with at least 1 encounter with an International Classification of Diseases (ICD) code of DS were identified. Controls included up to 5 individuals without a diagnosis of DS matched to each case on year of birth (±1 year) and sex by a data analyst. There were 30,326 eligible controls. Overall, 64 cases were assigned only 4 (as opposed to 5) matched controls.

Procedures

Preidentified endocrine conditions of interest among individuals with DS were chosen based on the existing literature as well as clinical expertise and experience, with corresponding ICD codes reviewed by a clinical expert (B.C.). To assess prevalence, this study used the U.S. Clinical Modification (CM) codes for medical diagnoses based on the statistical classification of disease denoted in the World Health Organization's publication of the ICD.[8] Specifically, 10th Revision (ICD-10-CM) and 9th Revision (ICD-9-CM) codes were utilized. See Table 1 for a complete list of endocrine-specific conditions of interest and associated ICD codes.

Statistical Methods

Demographics are reported as means with standard deviations and medians with ranges for age and total encounters per sample. Sex, race, ethnicity, and insurance type are reported as counts with percentages. Clinical conditions are reported as counts with percentages and odds ratios (OR) representing the odds of cases having an endocrine condition relative to controls. Corresponding Pearson's chi-squared P-values represent statistically significant differences (at an alpha of <0.05) in prevalence of diagnoses between cases and controls. Fisher's exact P-value was interpreted when any sample count was less than 5.

Table 1. Endocrine Conditions of Interest and Associated Codes

Endocrine condition	ICD-10-CM codes	ICD-9-CM codes
Acromegaly	E220	2530
Panhypopituitarism	E230	2522
Adrenal insufficiency/Addison's disease	E27	2554, 25541, 25542, 2555
Cushing's syndrome and increased adrenal function	E24	2550, 2551, 2553
Cystic fibrosis	E84	27700
Creutzfeldt-Jakob disease	A810	04619
Hypothyroidism	E02, E030–E033, E038, E039, E063, E890	243, 244, 2452
Hashimoto's disease	E063	2452
Hyperthyroidism	E05	242
Graves' disease	E050	2420
Multiple endocrine neoplasia type 1	E3120–E3123	25801, 25802, 25903
Polycystic ovary syndrome	E282	2564
Hyperparathyroidism	E210	25200, 25201, 25202, 58881
Hypoparathyroidism	E209	2521
Prolactinoma/Hyperprolactinemia	E221	2521
Turner syndrome	Q96	7586
Diabetes insipidus	E232, N251	2535, 5881
Secondary diabetes mellitus	E089, E099	249
Type I diabetes mellitus	E109, E1065, E1069	25001, 25003, 25211, 25013, 25021, 25023, 25031, 25033, 25041, 25043, 25051, 25053, 25061, 25063, 25071, 25073, 25081, 25083, 25091, 25093
Type II diabetes mellitus	E119, E1165, E1169	25000, 25002, 25010, 25012, 25020, 25022, 25030, 25032, 25040, 25042, 25050, 25052, 25060, 25062, 25070, 25072, 25080, 25082, 25090, 25092
Gout	M10	2740, 2741, 2748, 2749

CM, Clinical Modifications; ICD, International Classification of Diseases.

RESULTS

The DS case population was predominantly White (77.35%) and of non-Hispanic/Latino ethnicity (73.51%). Cases had a median of 6 total encounters (ie, clinical visits in the health system) in the dataset. The control population was also predominantly White (61.97%) and of non-Hispanic/Latino ethnicity (81.72%), with a median of 7 total encounters in the dataset. Both groups were approximately 52% male and had a median age of 25 years. For complete demographics of the DS and matched control cohorts, the reader is referred to the relevant table published within the parent article describing this project.[1]

Table 2 of this brief report displays complete results for all endocrine conditions analyzed. Statistically significant findings of OR (95% CI) and P-value derived from comparing prevalence of clinical endocrine conditions of interest among individuals with DS (ie, cases) to matched controls are highlighted in the following paragraphs.

Relative to controls, individuals with DS had *greater* odds of experiencing adrenal insufficiency (OR: 1.68 [1.18, 2.40]; P=0.0037); hypothyroidism (OR: 10.94 [10.17, 11.78]; P<0.0001); hyperthyroidism (OR: 2.46 [2.03, 2.99]; P<0.0001); Hashimoto's disease (OR: 2.41 [1.80, 3.21]; P<0.0001); Graves' disease (OR: 1.89 [1.22, 2.93]; P=0.0035); prolactinoma/hyperprolactinemia (OR: 2.60 [1.33, 5.08]; P=0.0038); diabetes insipidus (OR: 2.91 [1.15, 7.40]; P=0.0185); type I diabetes mellitus (OR: 1.63 [1.23, 2.15]; P=0.0005); and gout (OR: 2.67 [2.29, 3.10]; P<0.0001).

Other statistically significant results revealed that, relative to controls, individuals with DS had *lesser* odds of experiencing polycystic ovary syndrome (OR: 0.48 [0.28, 0.81]; P=0.0049) and type II diabetes mellitus (OR: 0.56 [0.49, 0.64]; P<0.0001).

DISCUSSION

These findings show that prevalences of endocrine disorders seen in individuals with DS vastly differ from their non-DS matched counterparts. While it is a challenge to draw a widespread conclusion about comorbidities in individuals with DS, generally speaking, it is reasonable to conclude that care for individuals with DS should not mirror recommendations or clinical guidelines for

Table 2. Prevalence of Endocrine Conditions Among Cases vs Controls

Endocrine condition	DS sample (n=6078)	Controls (n=30,326)	OR (95% CI)	*P*[a]
Acromegaly	0	0	–	–
Panhypopituitarism	8	51	0.78 (0.37, 1.65)	0.5179
Adrenal insufficiency/Addison's disease	41	122	1.68 (1.18, 2.40)	0.0037
Cushing's syndrome and increased adrenal function	0	11	–	0.2301[b]
Cystic fibrosis	4	6	3.33 (0.94, 11.80)	0.0701[b]
Creutzfeldt-Jakob disease	0	0	–	–
Hypothyroidism	2212	1507	10.94 (10.17, 11.78)	<0.0001
Hashimoto's disease	69	144	2.41 (1.80, 3.21)	<0.0001
Hyperthyroidism	155	319	2.46 (2.03, 2.99)	<0.0001
Graves' disease	28	74	1.89 (1.22, 2.93)	0.0035
Multiple endocrine neoplasia type 1	0	1	–	1.0000[b]
Polycystic ovary syndrome	15	157	0.48 (0.28, 0.81)	0.0049
Hyperparathyroidism	3	45	0.33 (0.10, 1.07)	0.0524[b]
Hypoparathyroidism	3	9	1.66 (0.45, 6.15)	0.4353[b]
Prolactinoma/Hyperprolactinemia	13	25	2.60 (1.33, 5.08)	0.0038
Turner syndrome	1	10	0.50 (0.06, 3.90)	0.7038[b]
Diabetes insipidus	7	12	2.91 (1.15, 7.40)	0.0185
Secondary diabetes mellitus	6	19	1.58 (0.63, 3.95)	0.3273
Type I diabetes mellitus	66	203	1.63 (1.23, 2.15)	0.0005
Type II diabetes mellitus	240	2066	0.56 (0.49, 0.64)	<0.0001
Gout	261	502	2.67 (2.29, 3.10)	<0.0001

[a]*Statistical significance was reached at an alpha of <0.05.*

[b]*Fisher's exact test P-value was interpreted due to low sample count.*

DS, Down syndrome; OR, odds ratio.

screening, prevention, diagnoses (including assessment of pretest probability), or treatment for the general U.S. population and, instead, should reflect the unique needs and common comorbidities of this population.

Our parent study found that individuals with DS had lower prevalence of overall diabetes mellitus relative to age- and sex-matched counterparts without DS.[1] Other studies have shown an increased prevalence of type I diabetes among individuals with DS.[6,7] Previously reported data are less clear on prevalence of type II diabetes, with studies showing increased, similar, and decreased rates as compared to those without DS.[2,6] The coding framework used in this study allowed us to separate ICD codes by type, which did then demonstrate that while type I diabetes is more common in those with DS, type II diabetes is less common. This is despite the parent study showing obesity is more common in people with DS.[3] Moreau et al provided a review of factors that may clarify our findings, including that obesity is often related to functional differences in multiple hormones and that, despite more obesity in those with DS, other factors could be associated with lesser type II diabetes found in this study.[9]

Etiology or cause for the differences in prevalence of endocrine conditions, including diagnosis differences, were not explored in this study. For instance, the diagnosis of gout, which has traditionally been thought of as a rheumatologic disorder but was included here due to its possible link to metabolic syndrome,[10] highlights some of the challenges of diagnostic accuracy in individuals with DS. Specifically, individuals with DS tend to have higher levels of serum uric acid,[11] but compliance with an arthrocentesis to examine joint fluid to confirm the diagnosis can be limited among this patient population. This can result in a presumptive, rather than confirmed, diagnosis based on elevated serum uric acid and the clinical picture.

While these prevalence findings highlight a need for remodeled care specific to individuals with DS, it also compels new research. For one, a deeper investigation into the broad range of more and less prevalent endocrine conditions, and the reasons and etiologies behind those differences, could be informative. Furthermore, the variations in prevalence warrant exploration into how screening and treatment for endocrine conditions may need to be different for individuals with DS. Finally, further analysis of the effects of endocrine disorders, specifically thyroid disorder and diabetes, in people with DS is required to better understand if certain condition subtypes are driving the findings seen in this work.

Strengths/Limitations

Our study's patient sample is one of the largest to date overall, and particularly in the United States, in which prevalence of disease conditions in individuals with DS was investigated, making it suitable for the analysis of relatively rare morbidities of interest. Our dataset incorporated the earliest available clinical data, representing a 28-year time span, which allowed for a very comprehensive look at prevalence. Our analysis also included a large group of controls matched by age and sex, a sample that can be representative of patients without DS in the United States.

While these findings represent data from only one U.S. Midwest-based health system, the consistency of data collected from a single large system may provide the most accurate and available review of prevalence among a DS sample population, given the United States' fragmented storage of data. Of importance, 34% of our DS cohort were seen by our institution's DS care center, likely a higher ratio of specialized care than that provided by most U.S. health systems without a large, centralized, dedicated DS clinic. This fact may have led to comparatively better diagnostic accuracy of ICD coding and, subsequently, more precise prevalence findings among individuals with DS. It should be noted that diagnostic accuracy in the setting of DS in general can be difficult for a variety of reasons, including limitations of some patients' ability to cooperate with evaluations, limited communication skills in some patients, and differences in presentations of some conditions.[12] While the codes used to represent the conditions of interest in this study were carefully chosen and reviewed by a clinical expert on DS, it is acknowledged that these codes may not be ones most commonly used to represent corresponding conditions. It is also possible that these codes over- or underrepresent diagnoses among individuals with DS relative to those without DS.

Although our study included both youths and adults with DS when determining prevalence of endocrine disorders, patterns of occurrence over time were not analyzed. Future research should look at conditions across time, report on youths and adults separately, and track the course of conditions seen at different stages of the increasing lifespan of individuals with DS.

CONCLUSIONS

In this endocrine condition-focused follow-up report to a previously published study of comprehensive differences in disease conditions prevalent among individuals with Down syndrome relative to matched controls,[1] numerous differences between cohorts were identified.

Adrenal insufficiency, thyroid disorders, prolactinoma/hyperprolactinemia, diabetes insipidus, type I diabetes mellitus, and gout, were significantly more prevalent in individuals with DS. Polycystic ovary syndrome and type II diabetes mellitus were significantly less prevalent. This information can be used to better guide practitioners, enhance specialized DS care, and potentially change screening protocols for this unique population.

Patient-Friendly Recap

- Broader research previously reported by the authors suggested various endocrine disorders may be more or less prevalent in individuals with Down syndrome (DS).
- To better characterize this population, authors used patient records from a single health system to compare diagnosis of endocrine conditions in those with DS to a control cohort of similar patients without DS.
- Most significantly, individuals with DS were *more* likely to have thyroid disorders, type I diabetes, and gout and *less* likely to have type II diabetes than their age- and sex-matched counterparts.

Author Contributions

Study design: Rivelli, Fitzpatrick, Jia, Rzhetsky, B. Chicoine. Data acquisition or analysis: Rivelli, Fitzpatrick, Wales, L. Chicoine, B. Chicoine. Manuscript drafting: Rivelli, Fitzpatrick, Wales, L. Chicoine, B. Chicoine. Critical revision: Rivelli, Fitzpatrick, Wales, L. Chicoine, B. Chicoine.

Conflicts of Interest

None.

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