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Prevalence of Common Disease Conditions in a Large Cohort of Individuals With Down Syndrome in the United States

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Purpose	Given the current life expectancy and number of individuals living with Down syndrome (DS), it is important to learn common occurrences of disease conditions across the developmental lifespan. This study analyzed data from a large cohort of individuals with DS in an effort to better understand these disease conditions, inform future screening practices, tailor medical care guidelines, and improve utilization of health care resources.
Methods	This retrospective, descriptive study incorporated up to 28 years of data, compiled from 6078 individuals with DS and 30,326 controls matched on age and sex. Data were abstracted from electronic medical records within a large Midwestern health system.
Results	In general, individuals with DS experienced higher prevalence of testicular cancer, leukemias, moyamoya disease, mental health conditions, bronchitis and pneumonia, gastrointestinal conditions, thyroid disorder, neurological conditions, atlantoaxial subluxation, osteoporosis, dysphagia, diseases of the eyes/adnexa and of the ears/mastoid process, and sleep apnea, relative to matched controls. Individuals with DS experienced lower prevalence of solid tumors, heart disease conditions, sexually transmitted diseases, HIV, influenza, sinusitis, urinary tract infections, and diabetes. Similar rates of prevalence were seen for lymphomas, skin melanomas, stroke, acute myocardial infarction, hepatitis, cellulitis, and osteoarthritis.
Conclusions	While it is challenging to draw a widespread conclusion about comorbidities in individuals with Down syndrome, it is safe to conclude that care for individuals with DS should not automatically mirror screening, prevention, or treatment guidelines for the general U.S. population. Rather, care for those with DS should reflect the unique needs and common comorbidities of this population. (<i>J Patient Cent Res Rev.</i> 2021;8:86-97.)
Keywords	Down syndrome; epidemiology; comorbidities; family medicine; population health

Down syndrome (DS) is the most frequent chromosomal abnormality among live-born infants and the most common genetic cause of intellectual disability in the world.^{1,2} Due to improved screening and advances in medical technology and care, the lifespan for an individual with DS has more than doubled to age 60 in the past few decades.³⁻⁷ Recent U.S.-based population estimates of major birth defects

concluded that, while prevalence of most birth defects has remained stable over the past 15 years, prevalence of DS is increasing.⁸ With increasing prevalence and longer lifespans of individuals with DS, it is important to understand common occurrences of co-occurring conditions, or comorbidities, across the developmental lifespan for more appropriate screening practices, tailored medical care guidelines, improved utilization of health care resources, and up-to-date planning and management of care for individuals with DS.

Individuals with DS represent a unique population in need of health care guidelines that address their specific medical care.⁹⁻¹³ A high prevalence of comorbidity has been documented among adults with DS, with types

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and patterns that differ from the general population;^{11,13} specifically, individuals with DS experience lower prevalence of many solid tumors¹⁴ and many cardiovascular issues, particularly atherosclerosis, hypertension, and acute myocardial infarction¹⁵ as well as coronary heart disease and heart failure.¹⁶ On the contrary, individuals with DS experience higher prevalence of stroke,¹⁵ endocrine disorders (eg, diabetes),¹⁵ thyroid disorders,¹⁷ Alzheimer's disease,¹⁸ sleep apnea,^{15,19} and leukemia.²⁰ Most of this literature comes from countries with vastly different demographics and medical care that routinely track health conditions in centralized, linked databases or registries; however, comprehensive comorbidity data on individuals with DS within the United States is still lacking.

Comorbidity in general requires complex medical management, but care complexity is compounded for those with DS by limitations in communication and understanding.¹³ Furthermore, the United States' noncentralized, nonstandardized, and on-demand record system results in fragmented information that is often difficult for health care providers to share for more consistent care.^{21,22} Most individuals with DS receive their care in settings that do not specialize in DS care and are subsequently less familiar with common comorbidities and the unique needs of this group.^{9,10} These issues create barriers to consistent and comprehensive care for individuals with DS. They also hinder national research documenting comorbidities specific to individuals with DS. Guidelines for youth with DS recommend that parents become experts of DS in order to best support medical care for their children;²³ however, more widely available U.S.-based literature would help guide providers and better inform individuals with DS as they continue to age and support their own care.

Evidence-based clinical guidelines for primary care of adults with DS were very recently published,²⁴ but U.S.-based research on comorbidity prevalence could complement the guidelines and fill a significant gap in the literature.^{9,10,24} Providing critical information on conditions unique to individuals with DS in the United States may better guide general practitioners and enhance specialized care for DS. The clinical data set used in this study represents the largest sample of individuals with DS in the United States to date. Patients were treated across a single Midwestern health system that includes the largest U.S. center of care for adults with DS. The study aims to document prevalence of a broad range of comorbidities in individuals with DS and provide relative comparisons to age- and sex-matched individuals without DS.

METHODS

This retrospective, descriptive cohort study utilized 28 years of available encounter data abstracted from electronic medical records collected from all sites within a large Midwestern nonprofit health system. The system included 10 acute care hospitals, including 2 children's hospitals, a specialty hospital for extended care needs, 3 large medical groups, and comprehensive home health and hospice services to serve the greater metropolitan area of a populous city. The study was determined to be non-human subjects research by the Advocate Aurora Health institutional review board.

Participants

For study inclusion, cases were identified using the International Classification of Diseases (ICD)-9, diagnosis code of 758.0 ("Down syndrome") or equivalent ICD-10 diagnosis codes of Q90 ("Down syndrome"), Q90.0 ("Trisomy 21, nonmosaicism [meiotic nondisjunction]"), Q90.1 ("Trisomy 21, mosaicism [mitotic nondisjunction]"), Q90.2 ("Trisomy 21, translocation"), or Q90.9 ("Down syndrome, unspecified") in the electronic medical records. A data analyst identified 6078 eligible cases based on at least one encounter with an ICD code of DS. All 68,299 case encounters in the health system, prior to and after the DS diagnosis code, were reviewed for this study.

Controls included up to 5 individuals without a diagnosis of DS identified and matched to each case on year of birth (± 1 year) and sex by the data analyst. The analyst identified 30,326 eligible controls. All 341,716 control encounters in the health system were reviewed for this study; 64 cases had only 4 matched controls.

Procedures

This study preidentified specific conditions of interest to assess prevalence among individuals with DS compared to individuals without DS. Conditions were chosen based on literature and clinical expertise. A coding system of ICD-9 diagnosis codes developed as part of the Healthcare Cost and Utilization Project, sponsored by the Agency for Health Research and Quality (AHRQ), was used to represent the conditions of interest. The coding system, the Clinical Classifications Software (CCS) for ICD-9, is one of a family of databases and software tools designed to be employed in projects analyzing diagnosis data. The AHRQ CCS collapsed ICD-9 codes into clinically meaningful categories that are more useful for presenting descriptive statistics of clinical conditions than are individual ICD-9 codes.²⁵ A few conditions of interest did not align with AHRQ CCS categories and, instead, were assigned ICD-9 codes by the research team. Table 1²⁵ provides a complete list

Table 1. Conditions of Interest and Associated Codes

Conditions	Codes ²⁵
Cancer conditions	
Breast	AHRQ 24
Cervix	AHRQ 26
Testis	AHRQ 30
Colorectal	AHRQ 14-15
Leukemia	AHRQ 39
Lymphoma (Hodgkin's and non-Hodgkin's)	AHRQ 37-38
Melanomas of skin	AHRQ 22
Heart disease conditions	
High blood pressure/hypertension	AHRQ 98-99
Late effects of cerebrovascular disease (stroke)	AHRQ 113
Coronary atherosclerosis and other heart disease	AHRQ 101
Acute myocardial infarction	AHRQ 100
Moyamoya	ICD-9 4375
Mental health conditions	
Anxiety	AHRQ 651
Obsessive-compulsive disorder	ICD-9 3003
Attention-deficit, conduct, disruptive behavior disorders	AHRQ 652
Mood disorders	AHRQ 657
Schizophrenia and other psychoses	AHRQ 659
Impulse control disorders, NEC	AHRQ 656
Catatonia	ICD-9 78199, 29389, 2948
Infections	
Sexually transmitted diseases (not including HIV or hepatitis)	AHRQ 9
HIV	AHRQ 5
Hepatitis	AHRQ 6
Influenza	AHRQ 123
Bronchitis	AHRQ 125
Sinusitis	ICD-9 461*, 473*
Pneumonia	AHRQ 122
Urinary tract infection	AHRQ 159
Cellulitis	ICD-9 681*-682*
Gastrointestinal conditions	
Intestinal obstruction without hernia	AHRQ 145
Esophageal disorders	AHRQ 138
Gastroduodenal ulcer except hemorrhage	AHRQ 139
Celiac	ICD-9 5790
Endocrine conditions	
Thyroid	AHRQ 48
Diabetes	AHRQ 49-50
Neurology conditions	
Epilepsy; convulsions	AHRQ 83
Alzheimer's disease	ICD-9 3310, 2941*
Myelopathy, cervical	ICD-9 7211, 72271
Orthopedic conditions	
Atlantoaxial subluxation	ICD-9 83900-83902, 83910-83912
Osteoporosis	AHRQ 206
Osteoarthritis	AHRQ 203
Miscellaneous conditions	
Dysphagia	ICD-9 7872*
Diseases of the eyes and adnexa	ICD-9 360-379
Diseases of the ears and mastoid process	ICD-9 380-389
Sleep apnea	ICD-9 32720-32721, 32723, 32727, 32729

Asterisks (*) indicate the full range of numbers were explored in this place.

AHRQ, Agency for Health Research and Quality; ICD-9, International Classification of Diseases, Ninth Revision; NEC, not elsewhere classified.

of clinical conditions of interest and their associated AHRQ CCS categories or ICD-9 codes.

Study data consisted of all ICD-9 codes. All ICD-10 codes documented after October 1, 2015, were converted to ICD-9 codes by the study data analyst. Prevalence of clinical conditions was assessed by totaling unique cases and controls, respectively, with at least one AHRQ ICD-9 code in each category in any encounter. At least one ICD-9 code in an encounter indicated the condition represented by the category of codes was prevalent. Odds and odds ratios (OR) with 95% confidence intervals were calculated across each clinical condition of interest.

Demographic factors, including age, total number of encounters, sex, race, ethnicity, and insurance, were assessed separately for cases and controls (Table 2). Odds, OR, and corresponding P-values were calculated to compare prevalence of conditions among cases (ie,

individuals with DS) relative to matched controls (ie, individuals without DS) (Table 3).

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 are reported as counts with percentages. Clinical conditions are reported as counts with percentages and corresponding OR representing the ratio of odds of cases having a comorbidity relative to controls. Corresponding P-values represent statistically significant differences between prevalence of diagnoses among cases relative to controls. Pearson's chi-squared P-values were interpreted, except when any cell count was <5, in which case Fisher's exact test P-values were interpreted.

Data management and analysis of the DS sample were conducted with SAS 9.4 statistical software (SAS

Table 2. Demographics and Baseline Characteristics of Cases and Controls

	DS Sample (N=6078)	Control Sample (N=30326)	P
Age in years, mean (SD) and median (IQR)	27.88 (20.37); 25.00 (9–46)	29.04 (20.96); 25.00 (11–48)	<0.0001*
Total encounters, mean (SD) and median (IQR)	11.23 (15.19); 6.00 (2–14)	11.27 (16.27); 7.00 (3–13)	0.8440
Sex	n=6075	n=30,324	
Male	3171 (52.19%)	15,816 (52.15%)	0.9536
Female	2904 (47.79%)	14,508 (47.84%)	
Race	n=4495	n=21,296	
White	3477 (77.35%)	13,198 (61.97%)	<0.0001*
Black	650 (14.46%)	6667 (31.31%)	
Asian	150 (3.34%)	1183 (5.56%)	
American Indian	57 (1.27%)	174 (0.82%)	
Other	161 (3.58%)	74 (0.35%)	
Ethnicity	n=3212	n=21,066	
Hispanic	851 (26.49%)	3851 (18.28%)	<0.0001*
Non-Hispanic	2361 (73.51%)	17,215 (81.72%)	
Insurance	n=5991	n=29,666	
Private	2848 (47.54%)	22,532 (75.95%)	<0.0001*
Medicare	2090 (34.89%)	1464 (4.93%)	
Medicaid	644 (10.75%)	4097 (13.82%)	
Other	409 (6.83%)	1573 (5.30%)	

*Statistically significant per Pearson's chi-squared test.

DS, Down syndrome; IQR, interquartile range; SD, standard deviation.

Table 3. Prevalence of Conditions of Interest Among Cases and Controls

Conditions	Cases (N=6078)	Controls (N=30,326)	Odds Ratio (Cases:Controls)	P
Cancer conditions				
Breast	10 (0.16%)	246 (0.81%)	0.20 (0.11, 0.38)	<0.0001*
Cervix	38 (0.63%)	653 (2.15%)	0.29 (0.21, 0.40)	<0.0001*
Testis	10 (0.16%)	19 (0.00%)	2.63 (1.22, 5.66)	0.0102*
Colorectal	3 (0.05%)	115 (0.38%)	0.13 (0.04, 0.41)	<0.0001**
Leukemia	50 (0.82%)	59 (0.19%)	4.26 (2.92, 6.21)	<0.0001*
Lymphoma (Hodgkin's and non-Hodgkin's)	11 (0.18%)	67 (0.22%)	0.82 (0.43, 1.55)	0.5387
Melanomas of skin	6 (0.10%)	59 (0.19%)	0.51 (0.22, 1.17)	0.1063
Heart disease conditions				
High blood pressure/hypertension	345 (5.68%)	18,139 (59.81%)	0.04 (0.04, 0.05)	<0.0001*
Late effects of cerebrovascular disease (stroke)	36 (0.59%)	138 (0.46%)	1.30 (0.90, 1.88)	0.1568
Coronary atherosclerosis and other heart disease	109 (1.80%)	1035 (3.41%)	0.52 (0.42, 0.63)	<0.0001*
Acute myocardial infarction	40 (0.66%)	213 (0.70%)	0.94 (0.67, 1.31)	0.7046
Moyamoya	14 (0.23%)	4 (0.00%)	17.50 (5.76, 53.19)	<0.0001**
Mental health conditions				
Anxiety	850 (13.98%)	3757 (12.39%)	1.15 (1.06, 1.25)	0.0006*
Obsessive-compulsive disorder	445 (7.32%)	124 (0.41%)	19.24 (15.74, 23.53)	<0.0001*
Attention-deficit, conduct, disruptive behavior disorders	233 (3.83%)	1563 (5.15%)	0.73 (0.64, 0.84)	<0.0001*
Mood disorders	761 (12.52%)	3247 (10.71%)	1.19 (1.10, 1.30)	<0.0001*
Schizophrenia and other psychoses	99 (1.63%)	176 (0.58%)	2.84 (2.21, 3.63)	<0.0001*
Impulse control disorders, NEC	27 (0.44%)	34 (0.11%)	3.98 (2.40, 6.59)	<0.0001*
Catatonia	73 (1.20%)	70 (0.23%)	5.25 (3.78, 7.30)	<0.0001*
Infections				
STD (not including HIV or hepatitis)	12 (0.20%)	304 (1.00%)	0.20 (0.11, 0.35)	<0.0001*
HIV	10 (0.16%)	105 (0.35%)	0.47 (0.25, 0.91)	0.0212*
Hepatitis	46 (0.76%)	217 (0.72%)	1.06 (0.77, 1.46)	0.7288
Influenza	125 (2.06%)	1004 (3.31%)	0.61 (0.51, 0.74)	<0.0001*
Bronchitis	210 (3.46%)	479 (1.58%)	2.23 (1.89, 2.63)	<0.0001*
Sinusitis	389 (6.40%)	4624 (15.25%)	0.38 (0.34, 0.42)	<0.0001*
Pneumonia	680 (11.19%)	964 (3.18%)	3.84 (3.46, 4.25)	<0.0001*
Urinary tract infection	286 (4.71%)	2068 (6.82%)	0.67 (0.59, 0.77)	<0.0001*
Cellulitis	480 (7.90%)	2344 (7.73%)	1.02 (0.92, 1.13)	0.6550
Gastrointestinal conditions				
Intestinal obstruction without hernia	82 (1.35%)	167 (5.51%)	2.47 (1.89, 3.22)	<0.0001*
Esophageal disorders	1054 (17.34%)	3679 (12.13%)	1.52 (1.41, 1.64)	<0.0001*
Gastroduodenal ulcer except hemorrhage	71 (1.17%)	249 (0.82%)	1.43 (1.10, 1.86)	0.0082*
Celiac	328 (5.40%)	93 (0.31%)	18.54 (14.70, 23.39)	<0.0001*
Endocrine conditions				
Thyroid	2362 (38.86%)	2282 (7.52%)	7.81 (7.31, 8.35)	<0.0001*
Diabetes	630 (10.37%)	4011 (13.23%)	0.76 (0.69, 0.83)	<0.0001*
Neurology conditions				
Epilepsy; convulsions	804 (13.23%)	878 (2.90%)	5.11 (4.63, 5.65)	<0.0001*
Alzheimer's disease	739 (12.16%)	114 (0.38%)	36.68 (30.05, 44.78)	<0.0001*
Myelopathy, cervical	51 (0.84%)	102 (0.34%)	2.51 (1.79, 3.51)	<0.0001*
Orthopedic conditions				
Atlantoaxial subluxation	137 (2.25%)	9 (0.00%)	77.68 (39.55, 152.57)	<0.0001*
Osteoporosis	12 (0.20%)	26 (0.09%)	2.31 (1.16, 4.57)	0.0138*
Osteoarthritis	380 (6.25%)	1841 (6.07%)	1.03 (0.92, 1.16)	0.5898
Miscellaneous conditions				
Dysphagia	824 (13.56%)	743 (2.45%)	6.24 (5.63, 6.92)	<0.0001*
Diseases of the eyes and adnexa	1710 (28.13%)	6177 (20.37%)	1.53 (1.44, 1.63)	<0.0001*
Diseases of the ears and mastoid process	2484 (40.87%)	8117 (26.77%)	1.89 (1.79, 2.00)	<0.0001*
Sleep apnea	581 (9.56%)	1713 (5.65%)	1.77 (1.60, 1.95)	<0.0001*

*Statistically significant based on alpha of 0.05.

†Fisher's exact test was interpreted. All other P-values interpreted by Pearson's chi-squared test.

NEC, not elsewhere classified; STD, sexually transmitted disease.

Institute Inc.). All analysis of the sample data was performed by research personnel at Advocate Lutheran General Hospital (Park Ridge, IL).

RESULTS

Case population was predominantly White (77.35%) and of non-Hispanic ethnicity (73.51%). Cases in the data set had a median of 6 total encounters (ie, clinical visits in the health system). Controls in the data set were predominantly White (61.97%), of non-Hispanic ethnicity (81.72%), and had a median of 7 total encounters. Cases and controls were matched on sex and year of birth, with both groups approximately 52% male and (median) 25.0 years old. Table 2 displays the demographics of the DS sample and the matched control sample.

The following results will describe OR associated with statistically significant P-values when comparing prevalence of clinical conditions of interest among cases to matched controls, specifically related to cancer, heart disease, mental health, infections, and gastrointestinal, endocrine, neurological, orthopedic, and other miscellaneous conditions. See Table 1 for a full list of the specific conditions of interest within these broad categories and Table 3 for full results and P-values.

Cancer Conditions

Relative to controls, cases had greater odds of experiencing testicular cancer (OR: 2.63 [1.22, 5.66]) and leukemia (OR: 4.26 [2.92, 6.21]). Relative to controls, cases had lesser odds of experiencing breast (OR: 0.20 [0.11, 0.38]), cervical (OR: 0.29 [0.21, 0.40]), and colorectal (OR: 0.13 [0.04, 0.41]) cancers. There was not a statistically significant difference in OR for melanoma or lymphoma.

Heart Disease Conditions

Relative to controls, cases had greater odds of experiencing moyamoya disease, a chronic and progressive condition resulting in narrowing of the arteries in the brain (OR: 17.50 [5.76, 53.19]). Relative to controls, cases had lesser odds of experiencing hypertension (OR: 0.04 [0.04, 0.05]) and coronary atherosclerosis or other heart disease (OR: 0.52 [0.42, 0.63]). There was not a statistically significant difference in OR for acute myocardial infarction or stroke.

Mental Health Conditions

Relative to controls, cases had greater odds of experiencing anxiety (OR: 1.15 [1.06, 1.25]), obsessive-compulsive disorder (OR: 19.24 [15.74, 23.53]), mood disorders (OR: 1.19 [1.10, 1.30]), schizophrenia or other

psychoses (OR: 2.84 [2.21, 5.63]), impulse control disorders (OR: 3.98 [2.40, 6.59]), and catatonia (OR: 5.25 [3.78, 7.30]). Relative to controls, cases had lesser odds of experiencing attention-deficit, conduct, or disruptive behavior disorders (OR: 0.73 [0.64, 0.84]).

Infections

Relative to controls, cases had greater odds of experiencing bronchitis (OR: 2.23 [1.89, 2.63]) and pneumonia (OR: 3.84 [3.46, 4.25]). Relative to controls, cases had lesser odds of experiencing sexually transmitted diseases (OR: 0.20 [0.11, 0.35]), HIV (OR: 0.47 [0.25, 0.91]), influenza (OR: 0.61 [0.51, 0.74]), sinusitis (OR: 0.38 [0.34, 0.42]), and urinary tract infections (OR: 0.67 [0.59, 0.77]). There was not a statistically significant difference in OR for cellulitis or hepatitis.

Gastrointestinal Conditions

Relative to controls, cases had greater odds of experiencing intestinal obstruction without hernia (OR: 2.47 [1.89, 3.22]), esophageal disorders (OR: 1.52 [1.41, 1.64]), gastroduodenal ulcers (OR: 1.43 [1.10, 1.86]), and celiac disease (OR: 18.54 [14.70, 23.39]).

Endocrine Conditions

Relative to controls, cases had greater odds of experiencing thyroid disorders (OR: 7.81 [7.31, 8.35]). Relative to controls, cases had lesser odds of experiencing diabetes (OR: 0.76 [0.69, 0.83]).

Neurology Conditions

Relative to controls, cases had greater odds of experiencing epilepsy convulsions (OR: 5.11 [4.63, 5.65]), Alzheimer's disease (OR: 36.68 [30.05, 44.78]), and cervical myelopathy (OR: 2.51 [1.79, 3.51]).

Orthopedic Conditions

Relative to controls, cases had greater odds of experiencing atlantoaxial subluxation (OR: 77.68 [39.55, 152.57]) and osteoporosis (OR: 2.31 [1.16, 4.57]). There was not a statistically significant difference in OR for osteoarthritis.

Miscellaneous Conditions

Relative to controls, cases had greater odds of experiencing dysphagia (OR: 6.24 [5.63, 6.92]), diseases of the eye and adnexa (OR: 1.53 [1.44, 1.63]), diseases of the ears and mastoid process (OR: 1.89 [1.79, 2.00]), and sleep apnea (OR: 1.77 [1.60, 1.95]).

DISCUSSION

Based on our review of the literature, this study reports on one of the largest cohorts of individuals with DS with matching controls in the United States. The prevalence

of nearly all conditions of interest in this study were statistically significantly higher or lower in individuals with DS compared to the control population. Our findings support similar data of this range and magnitude available from the United Kingdom.¹² This section will look at this study's findings for each condition category separately for clarification.

Cancer

Our U.S.-based results support previous research documenting increased leukemias among individuals with DS,^{14,20,26,27} increased testicular cancer among males with DS,¹⁴ and lower prevalence of solid tumors (ie, breast, cervix, colorectal) among individuals with DS relative to non-DS counterparts.^{14,28} It should be noted that, while the prevalence of colorectal cancer in this study is low, the data on colorectal cancer are mixed, suggesting inconveniences versus benefits of colonoscopy — the American standard for screening — be weighed more carefully in this group.²⁷ Given barriers to examining for cancers among individuals with DS, future research could explore the extent to which fewer examinations and subsequent diagnosis of cancer may be responsible for low prevalence of cancers observed among individuals with DS.

Heart Disease

Since congenital heart disease is well documented as more prevalent in individuals with DS,²⁹⁻³¹ our study did not explore it. As expected, hypertension, coronary atherosclerosis, and other heart disease were significantly lower in individuals with DS relative to non-DS counterparts.^{12,15,16} Prevalence differences in acute myocardial infarction and stroke were both considered nonsignificant. Regarding myocardial infarction, it should be noted that this study's cases and controls were matched on age, with medians of 25 years and means of 28 years, so it is not a surprising that rate of myocardial infarction was low in both groups and nonsignificant. Further study is required to explain the lower prevalence of atherosclerotic heart disease but similar prevalence of acute myocardial infarction among individuals with DS. While similar relative prevalence would be expected, increased congenital heart disease or sleep apnea among individuals with DS could have increased myocardial infarction events in this sample.^{12,32-35}

Regarding stroke, while individuals with DS experienced more stroke clinically, the difference was not significant. Prior research has suggested that increased stroke risk is moderated by cardioembolic risk (eg, congenital heart disease, cardiac arrhythmia),¹⁵ but this study did not

explore these additional risk factors. Increased stroke may be explained partly by the higher prevalence of congenital heart disease common among individuals with DS¹⁵ or due to the higher prevalence of moyamoya disease reflected in our DS sample.

Mental Health Conditions

Overall, individuals with DS were more likely than their non-DS counterparts to experience a wide variety of mental health conditions, including anxiety, obsessive-compulsive disorder, mood disorders (major depression and bipolar disorder), schizophrenia and other psychoses, impulse control disorders, and catatonia. While anxiety and mood disorders³⁶⁻³⁸ and obsessive-compulsive disorder³⁹ have been documented as more common among individuals with DS, bipolar disorder has been documented as less common.⁴⁰ It should be noted that our study looked at mood disorder broadly, as bipolar disorder and depression, finding it more prevalent among individuals with DS relative to non-DS counterparts. Catatonia was more prevalent in our sample of individuals with DS, but catatonia has only recently been recognized in individuals with DS;⁴¹⁻⁴³ thus, there are no previous data of which we are aware regarding its prevalence.

In our cohort, attention-deficit, conduct, and disruptive behavior disorders were found to be less prevalent among individuals with DS relative to non-DS counterparts. Prior research that did not use a comparison group has shown it to be highly prevalent.^{44,45} Additionally, it has been noted that diagnosis of these types of behavior conditions can be inaccurate^{45,46} given common symptoms, like sensory deficits caused by other comorbid medical conditions.⁴⁵ Contrary to one prior study,⁴⁰ we found a higher prevalence of schizophrenia in individuals with DS. Research has noted that schizophrenia and psychoses may be overdiagnosed in people with intellectual disabilities due to symptoms associated with mood disorders or other mental health conditions that are misinterpreted as psychoses.⁴⁷ Overall, individuals with DS are more vulnerable to mental health issues and also more diagnoses, due to deficits in language, communication, cognition, problem-solving, and coping,⁴⁸ and there is limited literature on the diagnosis of psychiatric comorbidities among this group.⁴⁹

Due to the diagnostic challenges and limited literature, we recommend cautious interpretation of mental illness data in individuals with DS. Future research should attempt to mitigate these challenges.

Infections

Individuals with DS had lower prevalence of sexually transmitted diseases, HIV, and urinary tract infections, which could be due to less sexual activity contributed to by noted delays in sexual maturity.⁵⁰ However, there is limited data on sexual activity of individuals with intellectual disabilities, including individuals with DS, and data are often reported by caregivers rather than the individual with DS.⁵¹⁻⁵³

Specific to respiratory infections, individuals with DS had lower prevalence of influenza and sinusitis but, consistent with other findings, higher prevalence of bronchitis and pneumonia.⁵⁴⁻⁵⁶ Immune defects, airway anatomical abnormalities, and an inability to handle secretions have been noted to explain increased infections among individuals with DS.⁵⁴ The higher prevalence of dysphagia noted among individuals with DS in our sample could be contributing to the increased pneumonia seen in our and previously reported studies.^{10,57} Furthermore, encounter-level provider documentation habits also may explain discrepancies; specifically, if a more severe condition (eg, bronchitis, pneumonia) is diagnosed, then less severe conditions (eg, influenza, sinusitis) may be left undocumented. Additional research to understand prevalence of varying infections is necessary.

Gastrointestinal Conditions

Our research found that individuals with DS are more likely to experience a variety of gastrointestinal conditions, including intestinal obstructions, esophageal disorders, gastroduodenal ulcers, and celiac disease. This supports extensive prior research documenting more common structural and functional disorders of the gastrointestinal tract among individuals with DS.^{12,58-63}

Endocrine Conditions

Individuals with DS had higher prevalence of thyroid disorder relative to non-DS counterparts. Hypothyroidism and hyperthyroidism are known to be more prevalent among individuals with DS than individuals without DS.^{9,12,64} Our study found that individuals with DS had lower prevalence of diabetes mellitus relative to non-DS counterparts. Other studies have shown an increased prevalence of type I diabetes among individuals with DS.^{64,65} Previous data are less clear on prevalence of type II diabetes, with studies showing increased, similar, and decreased rates compared with individuals without DS.^{10,64} The coding framework used in this study did not separate ICD codes by type, so this study did not explore thyroid disorder or diabetes by type.

Neurological Conditions

Our findings corroborate prior research that individuals with DS experience more epilepsy convulsions, Alzheimer's disease, and cervical myelopathy relative to non-DS counterparts.^{12,66,67} Higher prevalence of epilepsy and related seizures and Alzheimer's disease type of dementia have been documented in individuals with DS,^{18,68-70} separately and also as associated conditions.⁷¹ Cervical myelopathy is often caused by compression of the spinal cord, which may be associated with the increased prevalence of atlantoaxial subluxation seen in our DS sample.⁷²

Orthopedic Conditions

As mentioned, we found that individuals with DS experience more atlantoaxial subluxation relative to non-DS counterparts. The prevalence of osteoporosis also was higher among individuals with DS in our sample, which is consistent with data from other studies.^{13,73} Further study is needed to understand the significance of this finding. It has been suggested that bone density scans may not be as accurate in individuals with DS due to bone length differences between those with and without DS.⁷⁴ A more recent study adjusted for bone length differences and found that individuals with DS, especially men, had lower volumetric bone mineral density.⁷⁵ We could not identify research on fracture rates associated with osteoporosis in individuals with DS specifically; thus, the clinical significance of osteoporosis is unclear.

Miscellaneous Conditions

Finally, our study indicated that individuals with DS are more likely to experience a number of miscellaneous conditions focused on sense organs and other organs in the head and neck, including dysphagia, diseases of the eye and adnexa, diseases of the ears and mastoid process, and sleep apnea. This has been supported by prior research.^{9,10,12,13,66} As suggested in the infections subsection, it is possible that airway anatomical abnormalities could contribute to increased prevalence of these conditions, too.⁵⁴

Strengths and Limitations

This study is one of the largest to date overall, and particularly in the United States, to investigate the prevalence of comorbidities in individuals with DS, making it suitable for the analysis of relatively rare morbidities of interest. Our data set incorporated the earliest available data, which represented 28 years of patient data and 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 could

be representative of non-DS patients in U.S. health care. As our goal was to compare individuals with DS to a large sample of controls representative of the population of hospital patients, matching across all pertinent demographic factors would have been ideal; however, we chose not to match on race or body mass index (BMI), as neither are well- or accurately captured variables in most medical records. Furthermore, adjusting for race or BMI would have likely resulted in selection bias, as race is collected differently by group and BMI is only collected at certain visit types (ie, inpatient) within our health system. We plan to consider these variables in future analyses.

While these findings represent data from only one health system, this large integrated system may provide the most accurate and available review of prevalence among a U.S.-based cohort, given the country's fragmented storage of data. Furthermore, much of this data set comes from a specialized care center specifically serving adults with DS, which may improve diagnostic accuracy of ICD coding and subsequent prevalence findings. A minority of the data set comes from other system sites less familiar with serving adults with DS, potentially affecting diagnostic consistency. While life expectancy has increased rapidly over the past few decades, it has seemed to plateau in recent years, reducing the potential for change in identified common comorbid conditions.⁷⁶

It should be noted that diagnostic accuracy in general can be difficult with individuals with DS for a variety of reasons.⁷⁷ Additionally, observed prevalence among patients receiving only specialty care versus primary care within the health system could be different. Also, observed prevalence within patients with DS, particularly by level of function or intelligence, could be different. However, these designations were too difficult to parse out in this study.

While this study utilized an established coding framework of ICD-9 diagnosis codes to represent the conditions of interest specifically for research,²⁵ it is acknowledged that these codes may not be ones most commonly used to diagnose comorbid conditions among individuals with DS, introducing potential for underrepresentation of conditions. It is also possible that these particular codes could be used to diagnose individuals with DS more or less than individuals without DS. It is also possible that conditions coded among one single patient could be due to error instead of reality.

Future Research

We looked at all individuals with DS, including youth and adults, and reported prevalence of conditions among them relative to controls. The types of comorbid conditions, as well as the pattern of occurrence over time, have been noted as different. It is important to highlight the fact that this paper does not explore differences in examination for or diagnosis of health conditions, and it is certainly possible that inequalities exist due to inherent differences in individuals with and without DS. Future analyses should consider looking at prevalence of conditions among individuals with DS relative to individuals without DS but with more comparable intellectual and/or developmental disabilities. Youth and adults should be looked at separately and across time to track the course of conditions seen at difference stages of the increasing lifespan of individuals with DS.

While these prevalence findings are a jumping-off point for remodeled care specific to individuals with DS, they also compel new research. For one, a deeper investigation into the broad range of highly prevalent mental health conditions is merited. Comorbid mental and physical health conditions likely impact treatment progress in both areas, so understanding the relationship between them is critical in this group. Furthermore, the varied prevalence of infections warrants further exploration into differences in how individuals with DS experience infections. Finally, further analysis of endocrine disorders, specifically thyroid disorder and diabetes, is required to better understand if certain condition subtypes are driving prevalence findings.

CONCLUSIONS

This study describes prevalence of clinical conditions assessed by comparing total unique cases and controls, respectively, with at least one AHRQ ICD-9 code in each category in any encounter in a large health system's electronic medical records. Our findings show that observed prevalence of comorbid conditions seen in individuals with Down syndrome are vastly different compared to their non-DS-matched counterparts. While it is a challenge to draw widespread conclusions about comorbidities in individuals with DS, generally speaking, it is safe to conclude that care for individuals with DS should not automatically mirror screening, prevention, or treatment guidelines for the general U.S. population. Instead, care for those with DS should reflect the unique needs and common comorbidities of this population.

Patient-Friendly Recap

- People with Down syndrome are living longer than in decades past and thus more susceptible to longer durations of unique health problems.
- Authors reviewed data from an exceptionally large Down syndrome cohort to compare a litany of diagnoses to a general U.S.-based patient population matched for age and sex.
- Individuals with Down syndrome were *more likely* to be diagnosed with testicular or blood cancer, mental health conditions, bronchitis, pneumonia, and gastrointestinal, neurological, thyroid, and bone diseases, among others. They were *less likely* to be diagnosed with solid tumors, heart disease, sexually transmitted disease, influenza, sinusitis, and diabetes.
- Health care for those with Down syndrome should reflect the unique needs and commonly occurring conditions of this population.

Author Contributions

Study design: Chicoine, Rzhetsky. Data acquisition or analysis: Chicoine, Rivelli, Fitzpatrick. Manuscript drafting: all authors. Critical revision: all authors.

Conflicts of Interest

None.

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