Comprehensive Description of Comorbidity for Autism Spectrum Disorder in a General Population

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ABSTRACT

Context: Few published studies of autism spectrum disorder (ASD) and comorbidity are population based.

Objective: To describe the comorbidity of ASD and disorders listed in the main classes of the International Classification of Diseases, Ninth Revision (ICD-9) in a general population.

Design: Direct physician billing data for the city of Calgary, Alberta, Canada, for the treatment of any presenting concern in the Calgary Health Zone (n = 763,449) from 1994 to 2009 were extracted. Diagnosed ICD-9 disorders (independent variable) were grouped into 17 categories using ICD-9 diagnosis codes. ASD (dependent variable) was classified under ICD-9 Code 299. Individuals with and without independent disorder classes were counted by the presence or absence of any ASD. Odds ratios (ORs) and 95% confidence intervals of the association were calculated.

Main Outcome Measures: ORs of ASD comorbidities.

Results: Annual rates of ASD increased 3.9-fold for males and 1.4-fold for females. Diagnosed disorders ranked by OR in the independent ICD-9 categories indicated that males with ASD had overall higher ORs (> 1.0) in 11 main ICD-9 classes, and females with ASD had higher ORs (> 1.0) in 12 main ICD-9 classes. Males with ASD had lower ORs in 4 main ICD-9 disease classes; females with ASD had lower ORs related only to the main class "complications of pregnancy and childbirth." Five main ICD-9 classes were not significant for males or females.

Conclusions: Patients with ASD have significant comorbidity of physical disorders. This finding may inform other areas of research and assessment in clinical management.

INTRODUCTION

The annual prevalence of autistic spectrum disorder (ASD) is increasing and in 2014 was found to be 2.24% in children[1] and 1% in the general population.[2] Often, these disorders are long term and debilitating. A literature review of ASD focusing on comorbidity revealed few articles that were based on population studies.[3,4] Studies of comorbidity with ASD focus primarily on other psychiatric disorders,[5-23] neurologic disorders,[24-28] or congenital disorders.[29-32] Few studies focused on physical disorders,[33-35] and fewer still focused on adults.[36] In this study, the physical comorbidities associated with ASD and the main disorder classes from the International Classification of Diseases, Ninth Revision (ICD-9) were examined in a population including children and adults.

METHODS

Using a population-based sample, the unique identifiers of 763,449 individuals (46% male) were selected from the regional health service registry in the Calgary Health Zone (Calgary, Alberta, Canada). These identifiers were merged with all direct physician billings (n = 90,611,984) from 1993 to 2010 for treatment of any presenting concern, resulting in 16 years of data (1994-2009). Each billing record pertained to services rendered to patients on specified dates, resulting in the assignment of an ICD diagnostic code, including V-codes. This study employed an anonymous data set that included ICD-9 diagnoses, visit date, age at index visit, sex, and visit cost paid to the attending physician.

The annual population rates were calculated for ASD using the number of unique individuals who received a diagnosis from a physician in any given year, denominated by the annual civic census from 1994 to 2009. The 16-year prevalence rate was based on a standard population estimate (eg, 2002). Additionally, the average 16-year cost per patient for ASD was calculated and compared with those costs for any other mental disorder and those for patients with no mental disorders.

The data were collapsed into 2 groups representing the dependent variable. Counts in the major class ICD-9 diagnostic groupings given the presence or absence of any ASD were expressed as the odds ratio (OR = [AD/BC]) of the remaining classes of ICD-9 disorders (independent variables) compared to those without ASD. A, B, C, and D (columns in Table 1) refer to the corresponding 2 X 2 cells in the OR formula (as defined in the footnote to Table 1 and used to calculate the ORs in Table 2). Differences were based on the comparison of overlapping and nonoverlapping 95% confidence intervals (95% CIs). For rates, significant statistical differences between proportions in any given year were estimated by comparison of the 95% CIs using the standard formula, wherein nonoverlapping 95% CIs represent significant differences ($p < 0.05$, with z set to 1.96). The comorbidity of ASD within the main ICD-9 classes of disorders was examined. Diagnosed ICD-9 disorders (independent variable) were grouped into 17 categories on the basis of ICD-9 Codes 001 to 319 and 360 to 999. The dependent variable, ASD, was classified as ICD-9 Codes 320 to 359. Data for each sex was analyzed separately.

RESULTS

The sample consisted of 583 females (286 < 19 years old) and 1457 males (1207 < 19 years old) with ASD. On the first

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diagnosis for all ages, females' age averaged 29 years (median = 19 years) and males' age averaged 14 years (median = 11 years). On the first diagnosis for those younger than age 19 years, females' age averaged 11 years (median = 10.7 years) and males' age averaged 10 years (median = 9.6 years).

The 16-year cumulative rate of ASD in the population was 2.1 per 1000 for females and 8.7 per 1000 for males younger than age 19 years. The total population annual rate between 1994 and 2009 increased 4.5-fold for males from 2 to 9 per 10,000 and for females 1.6-fold from 2.5 to 4 per 10,000.

As shown in Table 3, the group with ASD had a greater overall 16-year average total visit cost per patient than those with any other mental disorder or those without any mental disorder (eg, only somatic or biomedical disorders).

Table 1 provides the counts in each cell constructing the OR calculation for males and females. The counts in each cell represent the unique individuals in that group required to calculate the OR. A indicates patients with neither ASD nor ICD-9 disorder; B and C, those with one and not the other; and D, those with both disorders. Note in Table 1 that complications of pregnancy and childbirth (ICD-9 Codes 630-679) refer in males to newborns or fetuses (n = 32), whereas in females it refers to both newborns or fetuses and adolescent females of childbearing age (n = 97).

Table 2 shows the ORs for males and females across 17 independent ICD-9 physical/biomedical disorder categories. The ORs were based on the cell values in Table 1 used in the OR formula (mentioned in the Methods section) given the presence or absence of ASD. Males with ASD were significantly less likely than males without ASD to have disorders related to the endocrine system, musculoskeletal system and connective tissue, neoplasms, or circulatory system. Females with ASD were significantly less likely to have disorders related to complications of pregnancy and childbirth.

Males with ASD were significantly more likely to have perinatal conditions; diseases of the sense organs or the respiratory system; congenital anomalies; symptoms, signs, and ill-defined conditions; diseases of the skin and subcutaneous tissue; infectious diseases; nervous system diseases, complications of pregnancy and childbirth, diseases of the digestive system or the genitourinary system, or injury and poisoning. Females with ASD were significantly more likely to have disorders related to congenital anomalies; sense organs; symptoms, signs, and ill-defined conditions; respiratory system; skin and subcutaneous tissue; injury and poisoning; digestive system; infectious diseases; nervous system; perinatal conditions; endocrine, nutritional, and metabolic diseases, and immunity disorders; and blood and blood-forming organs. ORs for males were greater overall for males compared with females, because males more frequently had ASD (see Table 2).

DISCUSSION

The literature reports ASD occurring in 1% to 4% of the population.[1] The present study summarized the 16-year cumulative

Table 1. Counts in respective cells constructing odds ratio formula[a]

	A		B		C		D	
Main ICD-9 diagnostic class	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**
Infectious and parasitic diseases	319,191	296,266	374	1123	94,994	52,240	209	334
Neoplasms	250,405	253,349	373	1208	163,780	95,157	210	249
Endocrine, nutritional, and metabolic diseases, and immunity disorders	247,105	235,070	292	1116	167,080	113,436	291	341
Diseases of the blood and blood-forming organs	341,750	317,074	453	1309	72,435	31,432	130	148
Mental disorders	306,559	291,110	366	1104	107,626	57,396	217	353
Diseases of the nervous system and sense organs	119,376	121,085	74	169	294,809	227,421	509	1288
Diseases of the circulatory system	238,083	225,425	344	1183	176,102	123,081	239	274
Diseases of the respiratory system	57,965	66,822	35	89	356,220	281,684	548	1368
Diseases of the digestive system	199,818	185,619	183	630	214,367	162,887	400	827
Diseases of the genitourinary system	89,960	228,306	128	894	324,225	120,200	455	563
Complications of pregnancy, childbirth, and the puerperium[b]	303,519	343,418	486	1425	110,666	5088	97	32
Diseases of the skin and subcutaneous tissue	108,172	118,487	74	310	305,888	230,019	509	1147
Diseases of the musculoskeletal system and connective tissue	109,204	113,812	158	649	304,981	234,694	425	808
Congenital anomalies	389,222	330,859	493	1224	24,963	17,647	90	233
Certain conditions originating in the perinatal period	385,130	336,072	522	1208	29,055	12,434	61	249
Symptoms, signs, and ill-defined conditions	34,564	47,690	19	79	379,621	300,816	564	1378
Injury and poisoning	89,306	69,540	68	258	324,879	278,966	515	1199

[a] Odds ratio formula: Odds ratio = (AD/BC), where A = patients with neither autism spectrum disorder (ASD) nor that ICD-9 disorder; B = those with ASD but not the ICD-9 disorder; C = those without ASD but with the ICD-9 disorder; and D = those with both disorders.

[b] Complications of pregnancy and childbirth (ICD-9 Codes 630-679) refer in males to newborns or fetuses (n = 32), whereas in females it refers to both newborns or fetuses and adolescent females of childbearing age (n = 97).

ICD-9 = International Classification of Diseases, Ninth Revision.

Table 2. Odds ratios with 95% confidence intervals for females and males with autism spectrum disorder

Main ICD-9 class	Odds ratio (95% CI)	
	Females	Males
Perinatal conditions	1.55 (1.19-2.02)	5.57 (4.86-6.39)
Sense organs	2.79 (2.18-3.55)	4.06 (3.46-4.76)
Respiratory system	2.55 (1.81-3.59)	3.65 (2.94-4.52)
Congenital anomalies	2.85 (2.27-3.56)	3.57 (3.1-4.11)
Symptoms, signs, ill-defined conditions	2.7 (1.71-4.27)	2.77 (2.2-3.47)
Skin and subcutaneous tissue	2.43 (1.91-3.1)	1.91 (1.68-2.16)
Infectious diseases	1.88 (1.59-2.22)	1.69 (1.49-1.91)
Nervous system	1.69 (1.43-2.0)	1.62 (1.44-1.83)
Complications of pregnancy, childbirth	0.55 (0.44-0.68)	1.52 (1.07-2.15)
Digestive system	2.04 (1.71-2.43)	1.5 (1.35-1.66)
Genitourinary system	0.99 (0.81-1.2)	1.2 (1.08-1.33)
Injury and poisoning	2.08 (1.62-2.68)	1.16 (1.01-1.33)
Blood and blood-forming organs	1.35 (1.11-1.65)	1.14 (0.96-1.35)
Endocrine, nutritional, and metabolic diseases, and immunity disorders	1.47 (1.25-1.73)	0.63 (0.56-0.71)
Musculoskeletal system and connective tissue	0.96 (0.8-1.16)	0.6 (0.54-0.67)
Neoplasms	0.86 (0.73-1.02)	0.55 (0.48-0.63)
Circulatory system	0.94 (0.8-1.11)	0.42 (0.37-0.48)

CI = confidence interval; ICD-9 = International Classification of Diseases, Ninth Revision.

prevalence and overall changes in annual rates of ASD. The cumulative rate reported here is closest to the lower limit reported in the literature. The differences may be because the higher rates reported in the literature were based on results of a national survey, whereas this study was based on a physician-assigned diagnosis. The rate of all physician-diagnosed mental disorders has increased for children.[37] Similarly, there has been an increase in the annual rate of ASD that was greater for males than females, although not as great as that reported in the literature. The reasons for the increased ASD rates are multifold and include any or all of the following: more diagnostic precision (reduction in false-negatives), increased public awareness (inflation of false-positives), or a real increase in the ASD rate.

Table 3. Average 16-year index of total cost of physician visit per patient by group

Group	Sex	Average cost (CAD)
Autism spectrum disorder	Female	1802
	Male	1329
Any mental disorder	Female	1532
	Male	1166
No mental disorder	Female	669
	Male	518

CAD = Canadian dollars.

Recent studies focusing on the relationship between ASD and comorbid disorders have tended, in part, to focus on general psychiatric comorbidity,[38] with most studies focusing on specific psychiatric disorders, such as primarily attention deficit-hyperactivity disorder[39-41]and, less frequently, anxiety, epilepsy, and neurologic disorders.[41] One study of physical disorders focused only on motor skills.[34] Although less frequent, genetic studies tended to examine comorbidity in relation to identifying potential overlapping phenotypic or genetic homology, or both.

Most comparable to the results of the present study was a time-series study of an electronic health record.[33] However, that study focused on distinguishing between fragile X syndrome and other ASD-associated syndromes. Aligned with this finding is the relatively high occurrence of congenital anomalies in patients with ASD for both sexes. Congenital defects are beyond the scope of the present study, which has described the physical and biomedical comorbidities of ASD, nevertheless each broad diagnostic category includes the range of subsumed diagnoses. When studied in a single large population, the interrelationship of comorbid disorders is revealed, and these patterns may be compared between disorders such as other ASD syndromes and disorders, such as fragile X. The present population-based description of the physical and biomedical disorders of ASD makes such comparative study possible. Most focused comparative study of symptom comorbidity, such as with epilepsy, has been used to provide insight into the origin of ASD, yet, unlike the present study, the samples have been too small to provide conclusive evidence of association.

Studies of ASD comorbidity have sought to understand issues of etiology[42] and mechanism. For example, disruption of the microbiota-gut-brain axis has recently become a focus of study in ASD.[38,43-46] The ability to examine ASD comorbidities in a population over time holds the potential to rank-order the relative importance of a specific comorbid disorder associated with ASD and to inform research. Being able to accomplish the ranked comparison, as illustrated in Table 2, in terms of the comorbidity of ASD and the main ICD-9 classes of disorder, permits more precise examination related to the comparative magnitude and prevalence of the comorbidities.

Importance of Present Findings

The present study examined comorbidity in the population. As it stands, this study makes an original contribution to the study of ASD comorbidity, against which there are few, if any, studies to compare. Substantial differences and similarities were found between males and females (see Table 2). For example, perinatal conditions are comparatively high for males, whereas females are less likely than males to have complications of pregnancy and childbirth. The present work supports the contention that there is a relationship between perinatal conditions, complications of pregnancy and childbirth, and ASD.[47,48] Otherwise, although males with ASD are more intensely affected than females, males and females are comparable on the basis of the relative order of sensory organ and respiratory disorders.

The results of the present study comparing the relationship between ASD and the main classes of ICD-9 disorders suggest that a great deal of research must yet be undertaken to understand the intricacies of these relationships in more precise terms. For example, there are about 1000 main diagnoses and more than 13,000 subdiagnoses within 19 main categories of disorder. This article serves as a simple example of a method for proceeding with further study. The broad-stroke approach to analysis has revealed that more precise relationships must exist within these data.

Study Limitations

The limitations of the approach taken to the study of comorbidity in this study have been described.[37] The usual threat to validity is the reliability of physician-assigned diagnoses, which is assumed to be a normally distributed source of error.

Another limitation lies in examining only main categories of ICD-9 disorders. This approach reveals associations observable within these broad categories, yet masks relationships between ASD and more specific subclasses of disorder. The present study points to the need for a more detailed disorder-specific analysis.

Examination of the temporal order of the classes of disorders and specific disorders associated with ASD was beyond the scope of the present study. Analysis of temporal order has for other disorders revealed potential mechanisms underpinning disease processes.[49] Comprehensive temporal-order analysis represents an important next step in the evolution of the presented approach to the population-based analysis of comorbidity.

CONCLUSIONS

Traditionally, study of comorbidity has largely focused on the relationship between one comorbid disorder, or only a few comorbid disorders, and a primary disorder of interest. With the advent of large integrated data repositories, it is possible to comprehensively examine comorbidity. For example, an examination of comorbidity has given rise to a novel population health index and provided evidence in support of the Adverse Childhood Experiences Study.[50-52]

This article provides a thumbnail sketch of ASD comorbidity. For every individual with an ASD, there is a temporal order in which the patterns of disease arise, and understanding these patterns may help elucidate a more formal understanding of the etiology and prognosis of sets of disorders within given groups of individuals. The results of such future research may serve to inform other approaches to the study of ASD. At the very least, the present study orients clinicians to the need to consider the physical and biomedical comorbidities in relation to ASD assessment, care, and service integration planning. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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A Neurological Disorder

Autism is a neurological disorder. It's not caused by bad parenting. It's caused by, you know, abnormal development in the brain. The emotional circuits in the brain are abnormal. And there also are differences in the white matter, which is the brain's computer cables that hook up the different brain departments.

— Temple Grandin, PhD, b 1947, author of *The Autistic Brain: Thinking Across the Spectrum* and autism spokesperson; American professor of animal science, consultant to the livestock industry on animal behavior