RESEARCH ARTICLE

The Comorbidity of Schizophrenia Spectrum and Mood Disorders in Autism Spectrum Disorder

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Individuals with autism spectrum disorder are often diagnosed with at least one or more accompanying disorders. Most studies reported prevalence of the psychiatric comorbidities among these individuals; however, the incidence of developing comorbidities is unclear. This study used Taiwan's claims database and aimed to investigate the incidence of developing major psychiatric comorbidities in individuals with autism spectrum disorder and whether the incidence was moderated by gender, autism-spectrum disorder subtypes, and autism-associated neurodevelopmental conditions. A total of 3,837 individuals with autism spectrum disorder (2,929 autistic disorder, 447 Asperger syndrome, 461 pervasive developmental disorder-not otherwise specified) and 38,370 comparison subjects, who were matched by age and gender, were included. The incidences of schizophrenia spectrum, bipolar, and major depressive disorders was examined. The results showed that the incidences of schizophrenia spectrum (9.7 per 1,000 person-year), bipolar disorder (7.0 per 1,000 person-year), and major depressive disorder (3.2 per 1,000 person-year) were significantly higher than the comparison group across all three subtypes of autism-spectrum disorder. Individuals with pervasive developmental disorder-not otherwise specified had higher risk for major depressive disorder than autistic disorder. Females with Asperger syndrome had significant higher risk for schizophrenia spectrum than males. The comorbidity rate dramatically dropped when the autism-associated neurodevelopmental conditions were taken into account. Our findings suggested that the incidences of major psychiatric comorbidities were higher in autism spectrum disorder and influenced by autism subtypes, gender, and autism-associated neurodevelopmental conditions. ***Autism Res*** *2020, 00: 1–11.* © 2020 International Society for Autism Research, Wiley Periodicals, LLC

Lay Summary: We examined whether people with autism spectrum disorder (ASD) have higher incidence of schizophrenia, bipolar disorders, and major depression using a large claims database. The results showed the incidences of these mental illness among individual with ASD were significantly higher than those without ASD. In addition, the incidences were influenced by autism subtypes, gender, and comorbid neurodevelopmental conditions.

Keywords: affect/emotion; comorbidity; gender difference; schizophrenia

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by social communication deficits, and repetitive behaviors and interests [American Psychiatric Association, 2013]. Studies show that the majority of ASD individuals are diagnosed with at least one or more accompanying disorders [Croen et al., 2015; Hossain et al., 2020; Houghton, Liu, & Bolognani, 2018; Mazefsky et al., 2012] and are associated with increased risk of severe mental illness such as psychosis spectrum and bipolar spectrum disorders [Selten, Lundberg, Rai, & Magnusson, 2015]. The comorbidities between ASD and schizophrenia spectrum disorder (SSD), bipolar disorder (BD), or major depressive disorder (MDD) often indicate a less favorable outcome [Croen, Shankute, Davignon, Massolo, & Yoshida, 2017; Gurney, McPheeters, & Davis, 2006; Helles, Gillberg, Gillberg, & Billstedt, 2017], higher risk of suicide and early mortality [Borue et al., 2016; Cassidy, Bradley, Shaw, & Baron-Cohen, 2018], and a need of more intensive and longer medical treatment [Mandell et al., 2008].

Studies have investigated the prevalence of comorbidity between ASD and major psychiatric disorders. The rates of comorbid SSD varied from 0% to 34.8% among ASD individuals [Chisholm, Lin, Abu-Akel, & Wood, 2015], a recent umbrella review revealed that the prevalence of SSD and other psychotic disorders ranged from 4% to 67% [Hossain et al., 2020]. The prevalence of BD ranged from 0.7% to 27.3% across studies [Hossain et al., 2020; Leyfer et al., 2006; Munesue et al., 2008; Vannucchi et al., 2014]. Meanwhile, the rate of unipolar depression, the most common mood disorder, was reported to be 50% or even higher [Lugnegard, Hallerback, & Gillberg, 2011]. Meta-analyses of clinical studies showed a pooled estimate of

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current depression was 20% or higher [Hollocks, Lerh, Magiati, Meiser-Stedman, & Brugha, 2018; Wigham, Barton, Parr, & Rodgers, 2017] and lifetime depression was around 37% [Wigham et al., 2017]; likewise, recent reviews suggested a prevalence ranged from 2.5% to 47.1% [Hollocks et al., 2018; Hudson, Hall, & Harkness, 2019; Lai et al., 2019]. Large variations across studies could be accounted by differences in sample source (clinical vs. community), and diagnostic method (clinical diagnosis vs. questionnaires) [Rosenberg, Kaufmann, Law, & Law, 2011]. Additionally, several other factors, such as sample size, patient selections, sample sources, and gender, may also contribute to the controversial findings [Hossain et al., 2020; Lai et al., 2019].

First, the sample sizes of these clinical studies were relatively small [Chisholm et al., 2015; Rosenberg et al., 2011]. Given that the prevalence of ASD, SSD, or BD were around 1–2% [Brugha et al., 2011; Kendler, Gallagher, Abelson, & Kessler, 1996; Leonard, Schwarz, & Myint, 2012; van Os, Hanssen, Bijl, & Vollebergh, 2001], it has been suggested that studies with samples under 100 may report a higher comorbid rate than larger studies [Chisholm et al., 2015]. Hence, a large representative sample is needed for a better estimation on the rates of SSD or BD in the ASD population. Second, the subtypes within autism spectrum may have different risks for developing the psychiatric comorbidities. Rosenberg et al. [2011] have investigated the prevalence of mood disorder among 4,343 ASD individuals aged 5–18 years through the online parent-report database. They reported that BD was much more common in Asperger syndrome (AS) (8.6%) than in autistic disorder (3.0%), implying a different risk of comorbidity within the autism spectrum. Third, gender may be another factor that should be accounted for. Using the adults dataset from Kaiser Permanente Northern California (1,504 ASD vs. 15,040 non-ASD controls), Croen et al. [2015] have shown that the odds ratios of comorbid schizophrenia in females were 2–3 times, compared to males. Meanwhile, in a Swedish sample of 54 AS adult outpatients from Regional Centers of Public Health, patients received a diagnosis of bipolar II disorder showed a slight preponderance in the female gender, compared to their counterpart (11% vs. 8%) [Lugnegard et al., 2011], suggesting that gender may also moderate the risk of developing comorbidity. Moreover, several neurodevelopmental conditions were highly associated with ASD (e.g., ADHD, intellectual disability, etc.) [Rosen, Mazefsky, Vasa, & Lerner, 2018] and may also contribute to the risk of developing schizophrenia spectrum or mood disorders (e.g., epilepsy and cerebral palsy, etc.) [Croen et al., 2015]. However, the ASD-associated neurodevelopmental conditions were rarely controlled in the analysis of comorbidity.

Currently, most aforementioned research is Western studies [Nahar, Thippeswamy, Shanker Reddy, Kishore, & Chaturvedi, 2018], the comorbid rates of ASD in Asian countries are largely unknown until recently one small clinical study ($N = 37$) was published [Nahar et al., 2018]. In addition, there were few cohort studies estimating the incidence of newly-onset major psychiatric disorders and related risk factors among individuals with ASD. The current study aims to investigate the incidence of comorbid SSD, BD, and MDD in ASD using the national insurance database, a representative large sample with clinical diagnoses claimed by physicians. We specifically examine the incidence of each comorbidity across the subtypes within autism spectrum, including autistic disorder, AS, and pervasive developmental disorder, not otherwise specified (PDD-NOS) given the evidence of higher comorbidity rates in ASD subtypes other than autistic disorders. The comorbid rates were compared between males and females, separately. Moreover, considering the common neurodevelopmental conditions that may contribute to the risk of developing schizophrenia spectrum or mood disorders (i.e., ADHD, intellectual disability, epilepsy, cerebral palsy, tic disorders, learning disorder, and obsessive compulsive disorder), we also evaluated the ASD-associated neurodevelopmental conditions to derive the exact comorbid rate attributed to ASD diagnosis alone.

Methods

Data Source

This cohort study used Taiwan's National Health Insurance Research Database (NHIRD). In Taiwan, the government launched a single-payer National Health Insurance program, on March 1, 1995, covering 99% of the Taiwanese population. The physician payment methods for psychiatric illness are fee-for-service, which is not related to the diagnosis, diseases severity, or comorbid conditions. The services are regularly audited by Taiwan's Bureau of National Health Insurance whereby medical professionals reviewed the chart records to assure the quality. (https://www.nhi.gov.tw/english/Content_List.aspx?n=7B24D0240347DAA8&topn=BCB2B0D2433F6491). The validity of the major psychiatric diagnoses in Taiwan's National Health Insurance program has been well-documented [Wu, Kuo, Su, Wang, & Dai, 2020].

The NHIRD was derived from the original reimbursement claims. The database includes patients' demographic characteristics, diagnoses, procedures, and prescription claims data. This cohort study from 2000 to 2012 was carried out using the Longitudinal Health Insurance Database (LHID) 2000, 2005, and 2010 which are three subsets of the NHIRD. Each of them contains all the original claims data of 1,000,000 beneficiaries, randomly sampled from Beneficiaries of the NHIRD in year 2000, 2005, and 2010, respectively. The distribution of age and gender of the sampled subjects in the LHIDs do not differ significantly

from that of the general population. After excluding those with repeated sampling or missing important demographic variables (gender and the year of birthday), there are a total of 2,884,098 individuals in the three LHIDs.

This study protocol was approved by the institutional review board of National Taiwan University Hospital (201412165RINB) before implementation.

Study Sample

We screened all patients with pervasive developmental disorders (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes: autistic disorder (autism) [299.0], Asperger's syndrome (AS) [299.8], and pervasive developmental disorder, not otherwise specified (PDD-NOS) [299.9]) registered in the NHIRD between January 1st, 2000 and December 31th, 2012 for those having at least two ambulatory claims or one in-patient discharge diagnosis of ASD (i.e., autism, AS or PDD-NOS) (N = 4,199). The date of the first ASD diagnosis was also recorded.

Based on the diagnostic criteria, we excluded AS or PDD-NOS patients who were concomitantly diagnosed with intelligence disability (N = 298). In order to have one-year washout period, the cohort entry date was defined as January 1st, 2001. If the individual was born after January 1st, 2001, the cohort entry date was defined as the birth date. Finally, prevalent cases, who had been diagnosed as SSD, BD, or MDD before the cohort entry date, were excluded (N = 64). As a result, 3,837 patients with ASD were included for subsequent data analysis.

Comparison Cohort of Patients without ASD Diagnosis

To assemble comparison group, we randomly selected 10 individuals without an ASD diagnosis for each ASD case and matched by the year of birth and gender. Each comparison subject was assigned a cohort entry date, same as their matching cases. Those who had study outcome before the cohort entry date would not be selected. Finally, a total of 38,370 comparison subjects were included.

ASD-Associated Conditions

The ASD-associated conditions were assessed based on the claims records during the study period. The ASD-associated conditions included mental retardation (ICD-9-CM codes: 317, 318, and 319), obsessive–compulsive disorders (ICD-9-CM code: 300.3), specific learning disorders (ICD-9-CM code: 315), attention-deficit hyperactivity disorder (ADHD; ICD-9-CM code: 314), epilepsy (ICD-9-CM code: 345), cerebral palsy (ICD-9-CM code: 343), and tic disorders (ICD-9-CM code: 307.2).

Main Outcome

Study subjects were followed up until the end of study period, December 31th, 2012. The clinical main outcomes include the development of SSDs (ICD-9-CM code: 295, 297, or 298), BDs (ICD-9-CM code: 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, or 296.8), and MDD (ICD-9-CM code: 296.2 or 296.3).

Statistical Analysis

Descriptive statistics of the baseline characteristics of individuals with ASD and comparison groups were provided. Differences in the characteristics among these two-by-two group comparisons were tested by analysis of variance or chi-square test.

We used multivariate Cox proportional hazards models to estimate the hazard ratios (HRs) of ASD, comorbidities and baseline characteristics for SSD, BD and MDD, respectively. The proportional hazard assumption was examined using Kolmogorov-type supremum test. The HRs of subtype of ASD were also estimated. To study the HRs, we categorized ASD into three subgroups: autistic disorder, AS, and PDD-NOS. Stratified analyses were conducted to explore the gender difference on the association between ASD and major psychiatric disorders. We examined the modifying effect of gender on the association between ASD and major psychiatric disorders by adding the interaction term between gender and ASD in the regression models. If the interaction term was statistically significant, it indicates the associations between ASD and major psychiatric illness are significantly different between males and females. The modifying effect of age at cohort entry date was also examined.

In addition, we explore the order of the diagnosis of autism spectrum disorder and major psychiatric disorder. Individuals might have psychotic or mood symptoms firstly, and then autism spectrum disorder was diagnosed later. On the other hands, the major psychiatric illness is more likely to be detected during the follow-up visits for ASD. Therefore, we divided the person-time into the period before and after ASD diagnosis. The incidence was calculated for the periods before and after ASD diagnosis, respectively. If ASD diagnosis occurred before the cohort entry date, all the follow-up period was classified as the period after ASD diagnosis.

All statistical analyses were conducted with SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). The statistical significance was assessed using 95% confidence intervals (CI) or p values <0.05.

Results

Sample Characteristics

The mean ages of the sample at cohort entry date were 5.6 ± 10.6 years in the autistic disorder, 7.8 ± 11.6 years

in the AS, 12.7 ± 16.5 years in the PDD-NOS, and 6.7 ± 11.8 years in the comparison group. Most ASD patients were diagnosed by psychiatrists (83.8%), pediatricians (18.4%), or rehabilitation physicians (30.7%); yet the percentage was not mutually exclusive. Around 4.0% was diagnosed by physicians other than the above-mentioned specialists. Males are predominant in all three ASD groups (autism 81.6%, AS 81.4%, and PDD-NOS 67.5%). All the three groups had substantial comorbid conditions such as learning disorder, ADHD, and intellectual disability. The autism group also had relatively high rates of epilepsy (14.0%), cerebral palsy (8.7%), and tic disorders (5.8%) compared to the comparison group (see Table 1).

Crude Incidence of Comorbid SSD, BD, or MDD

Overall, the mean of follow-up period was 10.9 ± 2.1 years; ranged from 0 to 12 years. As Table 2 shows, the incidences of SSD, BD, and MDD in the comparison group ranged from 0.3 to 0.4 (per 1,000 person-year). The incidences of newly-diagnosed SSD are 8.1 for autism, 14.9 for AS, and 14.9 for PDD-NOS (per 1,000 person-year). The incidences of comorbid with BD are 6.2 for autism, 11.9 for AS, and 7.8 for PDD-NOS. The incidences of comorbid MDD are 1.9 for autism, 6.1 for AS, and 8.3 for PDD-NOS (per 1,000 person-year). Notably, females with ASD had higher point estimates of incidences of either SSD, BD, or MDD relative to males.

HRs of Developing the Comorbidities in Three Subtypes

Table 3 shows the adjusted HRs of developing the comorbidities of SSD, BD and MDD. Overall, the HRs of developing comorbidities in all ASD were 23.3 (95% CI: 18.5–29.4) for SSD, 9.8 (95% CI: 7.7–12.4) for BD, and 6.6 (95% CI: 5.0–8.8) for MDD. Compared with autism, AS group had a higher risk for SSD (HR = 2.2; 95% CI: 1.6–3.0), BD (HR = 2.0; 95% CI: 1.4–2.8), and MDD (HR = 2.0; 95% CI: 1.2–3.2). Patients with PDD-NOS had a higher risk for developing SSD (HR = 1.5; 95% CI: 1.1–2.0) and MDD (HR = 2.0; 95% CI: 1.3–3.1) than autism. There was no difference between PDD-NOS and autism in the risk of developing BD.

The Effect Modification by Gender and Age

Although the point estimates of the incidence for major psychiatric disorders were higher among female than that among male, there was no statistically significant interaction between gender and ASD (all p-value >0.30). In terms of ASD subtypes, the females with AS had significantly higher HRs than males in developing SSD (HRs of AS: 59.2 in females vs. 29.6 in males; p-value = 0.019). Whereas, the gender difference in developing BD or MDD were not statistically significant in AS or PDD-NOS (all p-value >0.2).

There was no interaction between age at cohort entry date and ASD or ASD subtype (all p-value >0.15).

The Temporal Order between ASD and Major Psychiatric Illness

We found that the incidences of SSD and BD were higher during the period after ASD diagnosis compared with that before ASD (supplementary Table 1). It should be noted that the incidence also increased during the follow-up period among comparison groups (supplementary Table 2). The Kolmogorov-type supremum test showed the proportional hazard assumption was not violated (0.51 for SSD,

TABLE 1. Baseline Characteristics of Study Subjects

	Patients with autism spectrum disorder (n = 3,837) N (%)	Patients with autistic disorder (n = 2,929) N (%)	Asperger's syndrome (n = 447) N (%)	PDD, NOS (n = 461)	Comparison group (n = 38,370) N (%)
Age at cohort entry date, year					
0	1,201 (31.3)	1,008 (34.4)	132 (29.5)	61 (13.2)	12,010 (31.3)
1–5	1,357 (35.4)	1,075 (36.7)	141 (31.5)	141 (30.6)	13,570 (35.4)
6–10	576 (15.0)	412 (14.1)	66 (14.8)	98 (21.3)	5,760 (15.0)
≥11	703 (18.3)	434 (14.8)	108 (24.2)	161 (34.9)	7,030 (18.3)
Gender, male	3,064 (79.9)	2,389 (81.6)	364 (81.4)	311 (67.5)	30,640 (79.9)
Comorbid conditions					
Obsessive compulsive disorder	149 (3.9)	99 (3.4)	25 (5.6)	25 (5.4)	70 (0.2)
Learning disorder	2,341 (61.0)	2,019 (68.9)	181 (40.5)	141 (30.6)	2,302 (6.0)
ADHD	2,096 (54.6)	1,640 (56.0)	253 (56.6)	203 (44.0)	2,382 (6.2)
Mental retardation	1,056 (27.5)	1,056 (36.1)	0 (0.0)	0 (0.0)	516 (1.3)
Epilepsy	498 (13.0)	409 (14.0)	37 (8.3)	52 (11.3)	720 (1.9)
Cerebral palsy	286 (7.5)	254 (8.7)	12 (2.7)	20 (4.3)	180 (0.5)
Tic disorders	226 (5.9)	171 (5.8)	31 (6.9)	24 (5.2)	511 (1.3)

Note. All p-value <0.001.

PDD-NOS: pervasive developmental disorder not otherwise specified; ADHD: attention-deficit hyperactivity disorder.

TABLE 2. The Incidence and Crude Hazard Ratio of Incident Schizophrenia Spectrum, Bipolar Disorder, or Major Depressive Disorder in Individuals With Autism Spectrum Disorder

	Schizophrenia-spectrum disorder		Bipolar affective disorder		Major depressive disorder	
	N (incidence, per 1,000 person-year)	Crude hazard ratio (95% CI)	*N* (incidence, per 1,000 person-year)	Crude hazard ratio (95% CI)	*N* (incidence, per 1,000 person-year)	Crude hazard ratio (95% CI)
Overall						
Autism spectrum disorder	386 (9.7)	30.7 (25.2–37.3)	285 (7.0)	16.8 (13.9–20.2)	131 (3.2)	7.4 (5.9–9.2)
Autistic disorder	246 (8.1)	25.6 (20.7–31.6)	190 (6.2)	14.8 (12.0–18.1)	60 (1.9)	4.4 (3.3–6.0)
Asperger syndrome	67 (14.9)	47.2 (35.2–63.2)	55 (11.9)	28.6 (21.1–38.6)	29 (6.1)	14.2 (9.6–21.0)
PDD-NOS	73 (14.9)	46.9 (35.2–62.3)	40 (7.8)	18.1 (12.9–25.5)	42 (8.3)	19.0 (13.6–26.5)
Comparison groups	134 (0.3)	Reference	178 (0.4)	Reference	181 (0.4)	Reference
Male						
Autism spectrum disorder	271 (8.5)	30.5 (24.1–38.5)	214 (6.6)	16.9 (13.6–21.0)	80 (2.4)	7.5 (5.6–10.1)
Autistic disorder	192 (7.8)	27.9 (21.8–35.7)	150 (6.0)	15.4 (12.2–19.4)	45 (1.8)	5.5 (3.9–7.8)
Asperger syndrome	42 (11.1)	39.7 (27.6–57.2)	39 (10.2)	26.2 (18.3–37.4)	16 (4.1)	12.6 (7.4–21.2)
PDD-NOS	37 (10.9)	38.7 (26.4–56.6)	25 (7.3)	18.1 (11.8–27.8)	19 (5.5)	16.7 (10.2–27.2)
Comparison groups	94 (0.3)	Reference	132 (0.4)	Reference	108 (0.3)	Reference
Female						
Autism spectrum disorder	115 (14.6)	31.4 (21.9–45.0)	71 (8.6)	16.3 (11.2–23.6)	51 (6.1)	7.2 (5.1–10.3)
Autistic disorder	54 (9.5)	20.5 (13.7–30.9)	40 (6.9)	13.2 (8.6–20.2)	15 (2.5)	3.0 (1.7–5.2)
Asperger syndrome	25 (35.2)	74.6 (45.2–123.0)	16 (19.5)	38.0 (21.5–67.1)	13 (15.9)	19.0 (10.5–34.2)
PDD-NOS	36 (24.0)	51.7 (33.0–81.1)	15 (8.8)	16.4 (9.2–29.4)	23 (14.1)	16.7 (10.4–26.6)
Comparison groups	40 (0.5)	Reference	46 (0.5)	Reference	73 (0.8)	Reference

PDD-NOS: pervasive developmental disorder not otherwise specified.

0.19 for BD, and 0.40 for MDD), which indicated that HRs did not change statistically significantly before and after the diagnosis of ASD.

Discussion

As one of the first Asian studies investigating the incidence of major psychiatric comorbidities in ASD, this study presented the incidences of SSD (9.7 per 1,000 person-year), BD (7.0 per 1,000 person-year), and MDD (3.2 per 1,000 person-year) in subtypes within autism spectrum. We found that all the three ASD subtypes had higher risk of SSD, BD, and MDD than the comparison group. We also found comorbid rates varied between different subtypes of autism spectrum. Specifically, AS group had a higher risk for SSD, BD, and MDD than autism group, while the PDD-NOS group had a higher risk for developing SSD and MDD than autism group. In addition, we found female AS had significant higher risk for SSD than males, but had similar risk for developing BD or MMD with males. Lastly, the risk of comorbidity dropped when the ASD-associated neurodevelopmental conditions were controlled. Our findings suggested that the incidences of major psychiatric comorbidities were influenced by ASD subtypes, gender and ASD-associated neurodevelopmental conditions.

The gender ratio and the prevalence of ASD-associated conditions in this study were close to those reported in previous epidemiological studies in Western countries, supporting the diagnosis validity of using NHI claims records. Specifically, the male to female ratio of our database was 4.0:1, close to the findings from previous large-cohort epidemiological studies (e.g., 4.3:1) [Suren et al., 2012] or meta-analysis (overall pooled odds ratio 4.2, 95% CI = 3.8–4.6) [Loomes, Hull, & Mandy, 2017]. As for the rates of ASD-associated neurodevelopmental conditions, the rate of ADHD (ASD 56.0%) was similar to the previous reports that around half of ASD individuals fulfill the diagnosis of ADHD [Sinzig, Walter, & Doepfner, 2009; Yoshida & Uchiyama, 2004]. Likewise, the rate of epilepsy (14.0%) was close to previous reports from medical records (~11.2%) [Croen et al., 2015; Suren et al., 2012]. Meanwhile, the rates of cerebral palsy (0.4%) and intellectual disability (0.7%) in the comparison groups were also consistent with previous reports on cerebral palsy (0.3%) [Suren et al., 2012] and intellectual disability (~1%) [McGuire, Tian, Yeargin-Allsopp, Dowling, & Christensen, 2019]. The similarity between our database and previous studies also implied that medical utilization pattern of these conditions is generally consistent with Western reports.

Instead of reporting prevalence of comorbidities in most studies, our research demonstrated higher incidences of SSD, BD, and MDD in the ASD than the comparison group, supporting an increasing high risk of developing major psychiatric disorders in ASD. Although previous studies suggested high prevalence of MDD in ASD, we found the incidence of developing MDD was lower than those of BD and SSD. This could be partly

TABLE 3. The Adjusted Hazard Ratios of Developing Major Psychiatric Comorbidities

Outcome	Schizophrenia spectrum disorder Adjusted hazard ratio (95% CI)	Bipolar disorder Adjusted hazard ratio (95% CI)	Major depressive disorder Adjusted hazard ratio (95% CI)
Autism spectrum disorder	23.3 (18.5–29.4)	9.8 (7.7–12.4)	6.6 (5.0–8.8)
Autistic disorder	17.4 (13.2–23.0)	8.3 (6.2–11.0)	4.4 (3.0–6.5)
Asperger syndrome	37.6 (27.6–51.3)	16.4 (11.8–22.8)	8.7 (5.7–13.3)
PDD-NOS	25.9 (19.2–34.9)	8.6 (6.0–12.4)	8.8 (6.1–12.5)
Obsessive compulsive disorder	4.6 (3.6–5.9)	2.0 (1.4–2.9)	5.9 (4.0–8.7)
Learning disorder	0.9 (0.7–1.1)	0.7 (0.5–0.9)	0.9 (0.6–1.4)
ADHD	1.1 (0.9–1.4)	3.2 (2.5–4.2)	1.5 (1.0–2.3)
Mental retardation	2.2 (1.7–2.9)	1.6 (1.2–2.1)	0.7 (0.4–1.1)
Epilepsy	1.7 (1.3–2.2)	1.8 (1.3–2.4)	1.4 (0.9–2.2)
Cerebral palsy	0.6 (0.4–0.9)	0.5 (0.3–0.9)	0.6 (0.2–1.5)
Tic disorders	1.1 (0.8–1.7)	1.2 (0.8–1.7)	1.1 (0.6–2.1)
Subgroup analysis, male			
Autism spectrum disorder	20.8 (15.7–27.6)	8.2 (6.1–11.0)	6.5 (4.5–9.4)
Autistic disorder	17.9 (12.9–24.8)	6.8 (4.9–9.4)	5.2 (3.3–8.3)
Asperger syndrome	29.6 (20.1–43.4)	13.7 (9.2–20.3)	8.1 (4.6–14.2)
PDD, NOS	20.7 (13.9–30.7)	8.0 (5.1–12.5)	7.8 (4.7–13.2)
Obsessive compulsive disorder	5.1 (3.8–6.8)	2.0 (1.3–3.0)	4.5 (2.8–7.2)
Learning disorder	0.9 (0.7–1.2)	0.7 (0.5–1.0)	1.1 (0.6–1.8)
ADHD	1.0 (0.8–1.4)	3.7 (2.8–4.9)	1.4 (0.9–2.3)
Mental retardation	2.1 (1.6–2.8)	1.8 (1.3–2.5)	0.7 (0.4–1.3)
Epilepsy	2.0 (1.5–2.7)	1.6 (1.2–2.3)	0.9 (0.5–1.8)
Cerebral palsy	0.8 (0.5–1.3)	0.7 (0.4–1.3)	0.3 (0.0–1.9)
Tic disorders	1.0 (0.6–1.5)	1.2 (0.8–1.8)	1.6 (0.9–3.1)
Subgroup analysis, female			
Autism spectrum disorder	28.4 (19.0–42.6)	14.0 (9.1–21.6)	6.3 (4.1–9.7)
Autistic disorder	15.3 (8.8–26.5)	14.1 (8.2–24.1)	2.7 (1.3–5.6)
Asperger syndrome	59.2 (34.6–101.2)	23.9 (13.0–44.1)	9.6 (5.0–18.5)
PDD-NOS	35.3 (22.1–56.4)	10.0 (5.4–18.4)	9.6 (5.8–15.9)
Obsessive compulsive disorder	4.2 (2.5–7.2)	2.1 (0.9–5.0)	12.3 (6.5–23.2)
Learning disorder	0.7 (0.4–1.2)	0.6 (0.3–1.2)	0.5 (0.2–1.4)
ADHD	1.4 (0.9–2.4)	2.2 (1.2–4.1)	1.9 (0.9–4.3)
Mental retardation	2.5 (1.4–4.4)	1.0 (0.5–2.0)	0.7 (0.3–2.0)
Epilepsy	1.2 (0.7–1.9)	1.9 (1.1–3.2)	2.2 (1.2–3.9)
Cerebral palsy	0.5 (0.2–1.1)	0.4 (0.1–1.1)	1.0 (0.4–3.1)
Tic disorders	2.0 (0.8–4.6)	1.3 (0.4–4.5)	0.0 (0.0–0.0)

Note. The hazard ratios for schizophrenia-spectrum disorder for male and female are significantly different (p-value = 0.019).
PDD-NOS: pervasive developmental disorder, not otherwise specified; ADHD: attention-deficit hyperactivity disorder.

accounted by the relatively later onset [Kessler & Bromet, 2013] and possible lower rate of treatment seeking in MDD compared to schizophrenia or BD. Studies on service utilization rates for MDD in community-based surveys suggested a discrepancy of treatment needs and service utilization, suggesting the untreated rate ranging from 15.9% (12 month, Florence) [Faravelli, Guerrini Degl'Innocenti, Aiazzi, Incerpi, & Pallanti, 1990] to 83.9% (current, UK) [Ohayon, Priest, Guilleminault, & Caulet, 1999] and a median untreated rate 56.3% worldwide [Kohn, Saxena, Levav, & Saraceno, 2004]. Our NHI claimed data indeed reflected the ASD individuals who sought for MDD treatment, the true incidence may be higher. In addition, one may argue that the increased incidence can be caused by detection effect, i.e., the comorbid psychiatric illness might be more likely to be identified during the follow-up visits. However, we found the incidence among the comparison subjects also increased during follow-up, and the HRs of psychiatric comorbidity did not change significantly before and after the diagnosis of ASD.

It has been suggested that AS and PDD-NOS were significantly associated with increased odds of several psychiatric diagnoses compared to autism [Bryson, Corrigan, McDonald, & Holmes, 2008; Rosenberg et al., 2011]. Consistently, our large representative dataset showed that the AS group and PDD-NOS group had a higher risk for SSD and MDD than the autism group, and the AS group also had a higher risk for developing BD than the autism group. The finding of higher risk of BD in AS than in autism was consistent with Rosenberg et al. [2011], and the finding that PDD-NOS had an elevated risk for developing MDD and SSD was also consistent with previous studies that demonstrated a higher prevalence of MDD in individuals with PDD-NOS compared to autistic disorder

[Bryson et al., 2008; Rosenberg et al., 2011] and that children diagnosed with multiple complex developmental disorder, a subtype of PDD-NOS, are at high risk for developing psychosis later in life [Sprong et al., 2008]. These findings support that ASD subtypes or severity may influence the risk of developing major psychiatric comorbidity [Lee & Ousley, 2006; Leyfer et al., 2006] particularly the non-autism ASD. These higher-functioning ASD individuals may have better awareness on their own difficulties, yet higher social expectation and fewer resources compared to autistic disorder [Eaves & Ho, 2008; Esbensen, Bishop, Seltzer, Greenberg, & Taylor, 2010; Howlin, 2000; Howlin, Goode, Hutton, & Rutter, 2004; Rydén & Bejerot, 2008]. Besides, high risk for victimization, unemployment, lack of relationships, loneliness and isolation may also cause higher stress for them that might precipitate psychiatric comorbidities [Cederlund, Hagberg, Billstedt, Gillberg, & Gillberg, 2008; Howlin et al., 2004; Humphrey & Symes, 2010; Lasgaard, Nielsen, Eriksen, & Goossens, 2010]. On the other hand, it is possible that the comorbid psychiatric diagnosis may be harder to establish in the individuals with typical autism given their difficulty in communicating on symptoms. In these cases, the psychiatric diagnosis therefore relies more on behavioral observation and the abnormal behaviors may be misunderstood as associated presentation of ASD.

Gender has been shown to influence the presence of co-occurring symptoms [Chien, Gau, & Gadow, 2011] as well as symptom expression [Kessler et al., 2012]. Studies investigating gender differences in psychiatric comorbidities of ASD have yielded inconclusive results [Hofvander et al., 2009; Holtmann, Bolte, & Poustka, 2007; Mandy et al., 2012]. For example, female gender was shown protective for BD (odds ratio = 0.5, 95% CI: 0.3–0.9) in a study of parent-reported psychiatric comorbidity in 4,343 children [Rosenberg et al., 2011]. But female gender was associated higher risk of mental health conditions and intellectual disabilities (odds ratio = 1.4) in 6,649 adults with autism in Scotland's 2011 Census [Rydzewska et al., 2018]. Moreover, 28 female adults with AS also had higher rate of BD than 26 male adults assessed by the Structured Clinical Interview [Lugnegard et al., 2011]. As for comorbid SSD, an adult autism sample (N = 1,507) of Kaiser Permanente Northern California demonstrated a higher risk for schizophrenia in females [Croen et al., 2015], while a population-based study (4,790 children/adolescents) suggested that male gender increased risk for schizophrenia in adults aged 35 years or more with ASD (25%) compared to females (7.7%) [Supekar, Iyer, & Menon, 2017]. Based on our national data, we found females with AS indeed had higher incidences of SSD than males. Evidence has shown that ASD and SSD may share genetic risks [Guilmatre et al., 2009; Soler et al., 2018; Waltereit, Banaschewski, Meyer-Lindenberg, & Poustka, 2014] and that females with ASD are predicted to carry a more penetrant risk variant load than males and to share this greater genetic liability with their siblings [Werling & Geschwind, 2015]. Our findings imply gender difference of comorbid SSD may specifically swell in AS. On the other hand, our findings of no gender difference on developing BD and MDD in each subtype of ASD were consistent with several studies showing no associations between gender difference concerning the comorbid depression [Greenlee, Mosley, Shui, Veenstra-VanderWeele, & Gotham, 2016; Hurtig et al., 2009; Schwartzman & Corbett, 2020]. As far as we know, most studies focused on the risk of comorbidity in ASD have not adjusted ASD-associated neurodevelopmental conditions, such as cerebral palsy or epilepsy. Here we demonstrated that the risk of comorbidity decreased remarkably when the associated neurodevelopmental conditions were adjusted, implying a potential moderating effect of these early associated neurodevelopmental conditions on the comorbidity, and a complicated pattern of comorbidity between the psychiatric disorders and neurodevelopmental conditions. These associated conditions may cause additional difficulties with social communication deficits thus increase the risk of developing major psychiatric comorbidities. It warrants clinical attention that associated neurodevelopmental conditions may increase the risk of developing major psychiatric comorbidity later on. Meanwhile, future studies may need to take this into consideration when assessing the risk of comorbidity.

This study had several major limitations. First, during the study year 2001–2012, some comorbidity may not show up yet, such as MDD that the peak risk period for onset of MDD ranged from mid- or late adolescence to early 40s [Kessler & Bromet, 2013]. Second, the sample was from national insurance claims database, ASD individuals seeking medical services may be more serious than those in the community. Factors that influence the accessibility of medical services may limit the generalizability of our findings. Third, we used one-year washout period to exclude prevalent cases with major psychiatric illness. However, patients with remote recurrent cases might not be excluded and misclassify as incident cases. Lastly, this study focused on the incidence rates of major psychiatric comorbidity in individuals with ASD, without information of clinical presentation of these comorbidities. Some clinical syndromes may not distinct from each other or distinguishable from the ASD phenotypes (e.g., anxiety or depression). Although we focused on major psychiatric comorbidities that have more specific symptoms and serious function impairment. Future studies may combine chart review to provide more specific details for observation [Sapmaz, Baykal, & Akbas, 2018] to enhance early detection and timely access to treatment. Nevertheless, owing to the high coverage rate (near 99%) of national health insurance of Taiwan, the affordable medical services, and high referral rate, our findings reflect the incidences of psychiatric comorbidity for ASD individuals who seek medical assessment and

treatment in the real world. We adopted the diagnosis system of ICD-9-CM, though an outdate diagnosis system, which allowed us to look into the subtypes of ASD.

In conclusion, ASD showed higher incidences of major psychiatric disorders including SSD, BD, and MDD. More awareness of comorbidities in the individuals with ASD is recommended in order to improve clinical assessment, detection and quality care, particularly for the subpopulations with higher risk of major psychiatric comorbidities including individuals with non-autism ASD and female gender. The fact that some ASD-associated conditions (e.g., epilepsy and cerebral palsy) may moderate the risk of developing major psychiatric comorbidities is also an important feature of ASD that was disregarded in previous studies. Future research may take this challenge to dissect the intertwining relationship between the ASD-associated early neurodevelopmental conditions and the later psychopathology in ASD adults.

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Conflict of Interest

No potential conflicts of interest relevant to this study were reported.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplementary Table 1. The incidence of major psychiatric comorbidities before and after the diagnosis of autism spectrum disorder

Supplementary Table 2. Annual incidence by autism-spectrum disorder, gender, and age group at cohort entry date