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Risk of Substance Use Disorder and Its Associations With Comorbidities and Psychotropic Agents in Patients With Autism

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IMPORTANCE The risk of substance use disorder (SUD) in patients with autism spectrum disorder (ASD) remains unclear.

OBJECTIVE To investigate the risk of SUD in patients with ASD and its associations with comorbidities, psychotropic agents (PAs), and mortality.

DESIGN, SETTING, AND PARTICIPANTS This retrospective, population-based, cohort study of 1 936 512 participants used data from the Taiwan National Health Insurance Research Database and was conducted from January 1, 2000, to December 31, 2015. Included participants attended at least 3 outpatient visits within the 1-year study period for symptomatic ASD as determined by the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnostic codes. Individuals diagnosed with ASD before 2000, those diagnosed with SUD before the first visit for ASD, and those with missing data were excluded from the analysis. Patients with ASD and non-ASD controls were matched 1:4 by age, sex, and index date.

EXPOSURES Symptomatic ASD evaluated for at least 3 outpatient visits within the 1-year study period.

MAIN OUTCOMES AND MEASURES Adjusted hazard ratios (aHRs) with 95% CIs for SUD, including alcohol use disorder (AUD) and drug use disorder (DUD), and the risk of mortality were calculated. Data were analyzed from March 1 to July 13, 2020.

RESULTS A total of 6599 individuals with ASD (mean [SD] age, 11.9 [5.1] years; 5094 boys [77.2%]; mean [SD] follow-up period, 8.1 [8.3] years; median follow-up period, 4.3 [interquartile range [IQR], 2.3-5.3] years) and 26 396 controls (mean [SD] age, 12.1 [5.8] years; 20 376 boys [77.2%]; mean [SD] follow-up period, 8.6 [8.9] years; median follow-up period, 4.4 [IQR, 2.4-5.4] years) were enrolled in the study. According to multivariable-adjusted analysis, the aHRs for SUD (2.33; 95% CI, 1.89-2.87), AUD (2.07; 95% CI, 1.60-2.63), and DUD (3.00; 95% CI, 2.15-4.58) were significantly higher in the ASD group than in the non-ASD controls. The aHRs for SUD in the ASD subgroups with 1 PA (0.60; 95% CI, 0.43-0.66) and with multiple PAs (0.37; 95% CI, 0.28-0.49) were significantly lower than those in the ASD subgroup with no PAs. Comparisons between patients with ASD and non-ASD controls with the same comorbidities showed higher aHRs for SUD among patients with ASD (range, 1.17-2.55); moreover, the ASD subgroup not receiving any PAs had an aHR of 6.39 (95% CI, 5.11-7.87) for SUD when they had comorbid tic disorder and aHRs of 5.48 (95% CI, 5.12-5.70) for AUD and 5.42 (95% CI, 5.12-5.80) for DUD when they had comorbid impulse control disorder. The mortality risk was significantly higher in patients with ASD and concomitant SUD than in non-ASD controls without SUD (aHR, 3.17; 95% CI, 2.69-3.89).

CONCLUSIONS AND RELEVANCE These findings suggest that patients with ASD are vulnerable to the development of SUD. Comorbid ASD and SUD were associated with an increase in mortality risk.

Supplemental content

Editorial

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Autism spectrum disorder (ASD) is a highly heritable and heterogeneous neurodevelopmental disorder characterized by impairments in communication, reciprocal social interaction, and restricted and repetitive behaviors or interests.[1,2] Several environmental risk factors (eg, advanced parental age and maternal overweight)[2,3] and more than 100 genes and genomic regions have been found to be associated with ASD; most of these genes contribute to synaptic structure and function or chromatic modification.[2] Patients with ASD often present with a wide range of developmental, psychiatric, physical, and neurologic comorbidities that can influence their functional status, treatment strategies, and childhood development.[4] A multisite surveillance program in the United States reported that only 15% of children aged 8 years with ASD did not have any comorbidities.[1]

Substance use disorder (SUD) is a serious persistent condition that can negatively affect the health of an individual (even leading to death) and the economy, productivity, and social aspects of communities.[5,6] The most common comorbid neurodevelopmental disorder with SUD is attention-deficit/hyperactivity disorder (ADHD).[7] Attention-deficit/hyperactivity disorder and SUD share several neurobiologic mechanisms, such as deficits in anterior cingulate activation and the frontosubcortical systems and blunted striatal dopamine release after challenge with methylphenidate.[7] Recent studies have indicated overlapping neural circuits and molecular signaling pathways between ASD and SUD,[8] some of which are also implicated in the pathophysiology of ADHD, such as structural and functional synaptic changes in medium spiny neurons.[8,9] Additionally, one of the mechanisms contributing to social dysfunction in patients with ASD is motor cognition dysfunction, which is also a key factor mediating the pathophysiology of drug-seeking and drug-taking behaviors in patients with SUD.[10] To date and to our knowledge, little attention has been paid to the association between ASD and SUD.

A review article including 18 small studies (sample sizes ranging from 14 to 414 patients) suggested that relatively few patients with ASD develop SUD.[11] However, this finding was limited by the small sample sizes and differences in the study samples in the included studies. To our knowledge, only 1 population-based study has investigated the risk of SUD in patients with ASD.[12] This study suggested that patients with ASD had 5.9 times higher odds of having an SUD than non-ASD controls; moreover, patients with ASD comorbid with ADHD had the highest risk. However, 2 important questions remain unanswered: (1) whether psychotropic treatment for ASD is associated with a decrease in the risk of SUD and (2) whether the risk of SUD is higher in patients with ASD and comorbidities than in non-ASD controls with the same comorbidities.

In this study, we used a population-based database to investigate the risk of SUD among patients with ASD compared with non-ASD controls. In addition, we explored the associations of comorbidities and psychotropic agents (PAs) with SUD and the mortality risk among patients with comorbid ASD and SUD.

Key Points

Question Do patients with autism have a higher risk of substance use disorder than the general population, and is this risk associated with psychotropic treatment, comorbidities, or mortality?

Findings In this cohort study of 6599 individuals with autism spectrum disorder (ASD) and 26 396 controls without ASD, a diagnosis of autism was associated with an increased risk of substance use disorder, and the risk was much higher in those who had behavioral comorbidities and those who did not receive psychotropic agents. The mortality risk was higher in patients with autism and co-occurring substance use disorder than in non-ASD controls with or without substance use disorder.

Meaning These findings suggest that patients with ASD are vulnerable to the development of substance use disorder, and the use of psychotropic agents for autism is associated with a decreased risk of substance use disorder.

Methods

Data Source

Taiwan initiated the National Health Insurance program on March 1, 1995. Over 23 million (99.9% of Taiwan's population) people had been enrolled by 2018.[13] The Taiwan National Health Insurance Research Database (NHIRD) has provided complete data sources for several epidemiologic studies.[14-17] This cohort study analyzed data derived from the NHIRD. Encrypted personal data, including sex, date of birth, patient identification number, demographic characteristics, dates of clinical visits, levels of care, diagnoses, medical interventions, durations of hospitalizations, the names of the medical institutions providing the services, *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnostic and procedure codes, and outcome at hospital discharge, were obtained from the NHIRD. The Taipei Veterans General Hospital institutional review board approved this study (2018-07-016AC) and exempted informed consent because these databases were anonymized. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (eTable 7 in the Supplement).

Study Design and Participants

This study had a matched cohort design and included data from the outpatient and inpatient Longitudinal Health Insurance Database of the NHIRD. In the Longitudinal Health Insurance Database, 8323 individuals with ASD were identified between January 1, 2000, and December 31, 2015, according to *ICD-9-CM* code 299. Each included patient with ASD attended at least 3 outpatient visits within the 1-year study period for symptomatic ASD according to the *ICD-9-CM* codes and catastrophic illness card. In Taiwan, patients with several mental disorders (*ICD-9-CM* codes 290 and 293 through 297) may be issued a catastrophic illness card in order to reduce their financial burden. We excluded individuals diagnosed with ASD before 2000, those diagnosed with SUD (*ICD-9-CM* codes 291,

292, 303, 304, or 305) before the first visit for ASD, and those with missing data. After exclusions, controls without a diagnosis of ASD were randomly selected and matched by sex, age, and index date. A 1:4 ratio of patients with ASD to non-ASD controls was established to increase the statistical power and to ensure an adequate number of SUD cases for stratified analyses. Alcohol use disorder (AUD) (*ICD-9-CM* codes 291, 303.0, 303.9, and 305.0) and drug use disorder (DUD) (*ICD-9-CM* codes 292, 304, and 305 except 305.0) were classified as SUD subgroups. Eight psychiatric comorbidities that often co-occur with ASD were examined,[1,4,18] namely, intellectual disability, ADHD, obsessive-compulsive disorder, epilepsy, tic disorder, mood disorder, anxiety disorder, and impulse control disorder.

Information regarding prescribed drugs (according to the World Health Organization Anatomical Therapeutic Chemical classification system), drug dosage, days of drug supply, and number of dispensed pills was extracted from the Longitudinal Health Insurance Database. The defined daily dose (DDD) recommended by the World Health Organization is a widely applied international metric that transforms the prescribed amount of a drug into a standard unit of measure.[19] We focused on common PAs for ASD or its psychiatric comorbidities (eTable 1 in the Supplement), including antidepressants, second-generation antipsychotics, and mood stabilizers (lithium and valproate).[20,21] We calculated the sum of the dispensed DDD (cumulative DDD [cDDD]) of the pharmacotherapeutic agents during the follow-up period. The dose of pharmacotherapeutic agents during follow-up was classified into 4 categories: less than 30 cDDD, 30 to 120 cDDD, 121 to 365 cDDD, and greater than 365 cDDD.

Covariates

The covariates included behavioral psychotherapy (eTable 1 in the Supplement), sex, age, years of education (<12 years, ≥12 years), marital status, psychiatric comorbidities, Charlson Comorbidity Index (CCI) score,[22] season of diagnosis, levels of care at medical centers and regional and local hospitals, frequency of psychiatric and nonpsychiatric hospitalizations, length of admission,[22] urbanicity of residence, monthly income-related insured amount (for the individual or from the parents), and follow-up period. A CCI score of 0 indicates that no comorbidities occurred, and higher scores indicate a greater number of comorbidities and a higher mortality risk.[23]

Statistical Analysis

We used Pearson χ^2 tests and *t* tests to generate summary statistics. A time-to-event analysis was used to compare the risk of SUD between the ASD and non-ASD groups, measuring the risk from the time at which the patients received their first ASD diagnosis until the relevant event or end of follow-up (whichever came first). The cumulative incidence of SUD was analyzed using the Kaplan-Meier method, and the log-rank test was used to compare the cumulative incidence curves between the ASD and non-ASD groups. Hazard ratios (HRs) with 95% CIs for the risk of SUD and mortality were calculated using multivariable Cox proportional hazards regression analysis, with observation time since first ASD diagnosis as the time scale. The adjusted HR (aHR) was calculated, with adjustments for behavioral psychotherapy, sex, age, years of education, marital status, psychiatric comorbidities, CCI score, season of diagnosis, levels of care, frequency of psychiatric and nonpsychiatric hospitalizations, length of admission, urbanicity of residence, monthly income-related insured amount, and follow-up period. We also compared the risk of SUD between patients with ASD and comorbidities and non-ASD controls with the same comorbidities. A 2-tailed $P < .05$ indicated statistical significance. All statistical analyses were performed from March 1 to July 13, 2020, using SPSS, version 22 software (SPSS Inc).

Results

A total of 6599 individuals with ASD (mean [SD] age, 11.9 [5.1] years; 5094 boys [77.2%] and 1505 girls [22.8%]; mean [SD] follow-up period, 8.1 [8.3] years; median follow-up period, 4.3 [interquartile range (IQR), 2.3-5.3] years) and 26 396 age-, sex-, and index date–matched controls (mean [SD] age, 12.1 [5.8] years; 20 376 boys [77.2%]; mean [SD] follow-up period, 8.6 [8.9] years; median follow-up period, 4.4 [IQR, 2.4-5.4]) without a diagnosis of ASD were enrolled in the study (**Table 1**). There were no significant differences between the 2 groups in terms of years of education (≥12 years of education, 1025 of 6599 with ASD [15.5%] vs 4126 of 26 396 without ASD [15.6%]; $P = .84$), monthly income-related insured amount (18 000-34 999 Taiwanese new dollars [US $629-$923], 1075 of 6599 with ASD [16.3%] vs 4185 of 26 396 without ASD [15.9%]; $P = .07$), and season of diagnosis (spring season, 1628 of 6599 with ASD [24.7%] vs 6512 of 26 396 without ASD [24.7%]; $P > .99$). Compared with the control group, the ASD group had a lower proportion of married participants (109 of 6599 [1.7%] vs 572 of 26 396 [2.2%]; $P = .008$), a higher CCI score (mean [SD], 0.08 [0.09] vs 0.05 [0.06]; $P < .001$), a higher level of urbanization (level-1 urbanicity, 3025 of 6599 with ASD [45.8%] vs 7864 of 26 396 without ASD [29.8%] $P < .001$), and a higher proportion of participants who had been treated in hospital centers (3026 of 6599 [45.9%] vs 8315 of 26 396 [31.5%]; $P < .001$). The rates of all psychiatric comorbidities, including intellectual disability (1465 of 6599 [22.2%] vs 236 of 26 396 [0.9%]; $P < .001$), ADHD (1524 of 6599 [23.1%] vs 275 of 26 396 [1.0%]; $P < .001$), tic disorder (1112 of 6599 [16.9%] vs 211 of 26 396 [0.8%]; $P < .001$), epilepsy (648 of 6599 [9.8%] vs 198 of 26 396 [0.8%]; $P < .001$), obsessive-compulsive disorder (207 of 6599 [3.1%] vs 55 of 26 396 [0.2%]; $P < .001$), mood disorder (1592 of 6599 [24.1%] vs 375 of 26 396 [1.4%]; $P < .001$), anxiety disorder (1998 of 6599 [30.3%] vs 1342 of 26 396 [5.1%]; $P < .001$), and impulse control disorder (226 of 6599 [3.4%] vs 121 of 26 396 [0.5%]; $P < .001$), were significantly higher in the ASD group than in the control group (eTable 2 in the Supplement).

The Kaplan-Meier curves (eFigure in the Supplement) demonstrated a clear difference in the cumulative incidence of SUD between the ASD and non-ASD groups (723 vs 350 per 100 000 person-years; log-rank test, $P < .001$). The aHRs (95% CI) for SUD (2.33; 95% CI, 1.89-2.87), AUD (2.07; 95% CI, 1.60-2.63),

Table 1. Characteristics of the Study Cohort With and Without ASD, 2000-2015

Variable	No. (%)[a]		*P* value
	With ASD (n = 6599)	Without ASD (n = 26 396)	
Female	1505 (22.8)	6020 (22.8)	>.99
Age, mean (SD), y	11.9 (5.1)	12.1 (5.8)	.10
<6	4232 (64.1)	16 928 (64.1)	>.99
6-11	1117 (16.9)	4468 (16.9)	
12-18	994 (15.1)	3976 (15.1)	
>18	256 (3.9)	1024 (3.9)	
Years of education, ≥12	1025 (15.5)	4126 (15.6)	.84
Marital status, married	109 (1.7)	572 (2.2)	.008
Level of care			
Hospital center	3026 (45.9)	8315 (31.5)	<.001
Regional hospital	3131 (47.5)	9264 (31.5)	
Local hospital	442 (6.7)	8817 (31.5)	
CCI, mean (SD)	0.08 (0.09)	0.05 (0.06)	<.001
CCI			
0	6169 (93.5)	25 121 (95.2)	<.001
1	403 (6.1)	1216 (4.6)	
≥2	27 (0.4)	59 (0.2)	
Urbanicity of residence			
1 (Highest urbanicity level)	3025 (45.8)	7864 (29.8)	<.001
2	2645 (40.1)	12 110 (45.9)	
3	886 (13.4)	2364 (9.0)	
4	43 (0.7)	4058 (15.4)	
Season of diagnosis			
Spring (March-May)	1628 (24.7)	6512 (24.7)	>.99
Summer (June-August)	1825 (27.7)	7300 (27.7)	
Autumn (September-November)	1642 (24.9)	6568 (24.9)	
Winter (December-February)	1504 (22.8)	6016 (22.8)	
Monthly income-related insured amount, Taiwanese new dollars[b]			
<18 000	4865 (73.7)	19 785 (75.0)	.07
18 000-34 999	1075 (16.3)	4185 (15.9)	
≥35 000	659 (10.0)	2426 (9.2)	
Follow-up period, y			
Mean (SD)	8.1 (8.3)	8.6 (8.9)	<.001
Median (IQR)	4.3 (2.3-5.3)	4.4 (2.4-5.4)	.04

Abbreviations: ASD, autism spectrum disorder; CCI, Charlson Comorbidity Index; IQR, interquartile range.

[a] Values are listed as No. (%) unless otherwise specified.

[b] 1.00 Taiwanese new dollar = US$0.035.

Table 2. Hazard Ratios (95% CI) for Substance Use Disorder in the Study Cohort With and Without ASD[a]

Outcome	With ASD (n = 6599)			Without ASD (n = 26 396)			Hazard ratio (95% CI)
	Persons at risk, No.	Event, No.	Crude incidence per 100 000 person-years	Persons at risk, No.	Event, No.	Crude incidence per 100 000 person-years	
Substance use disorder	6599	128	723	26 396	410	350	2.33 (1.89-2.87)
Alcohol use disorder	6599	84	474	26 396	299	256	2.07 (1.60-2.63)
Drug use disorder	6599	44	248	26 396	111	95	3.00 (2.15-4.58)

Abbreviations: ASD, autism spectrum disorder; CCI, Charlson Comorbidity Index.

[a] Adjusted for behavioral psychotherapy, sex, age, years of education, marital status, psychiatric comorbidities, CCI score, season of diagnosis, levels of care, frequency of psychiatric and nonpsychiatric hospitalizations, length of admission, urbanicity of residence, monthly income, and follow-up period.

and DUD (3.00; 95% CI, 2.15-4.58) were significantly higher in the ASD group than in the non-ASD controls (**Table 2**).

The subgroup analyses showed that the aHRs for SUD in the ASD subgroups with 1 PA (0.60; 95% CI, 0.43-0.66) and with multiple PAs (0.37; 95% CI, 0.28-0.49) were lower than those in the ASD subgroup with no PAs (**Table 3**). Moreover, the ASD subgroups with 1 and multiple PAs showed negative dose-response relationships between the cDDD and the risk of SUD;

Table 3. Hazard Ratios for Substance Use Disorder Among Patients With ASD Receiving and Not Receiving Psychotropic Agents[a]

Outcome	ASD subgroup	Persons at risk, No.	Event, No.	Crude incidence per 10 000 person-years	Hazard ratio (95% CI)
Substance use disorder	With no psychotropic agents	759	25	1247	1 [Reference]
	With 1 psychotropic agent	2582	59	834	0.60 (0.43-0.66)
	<30 cDDD	599	15	1130	0.83 (0.78-0.89)
	30-120 cDDD	604	16	865	0.65 (0.55-0.71)
	121-365 cDDD	667	15	789	0.51 (0.38-0.59)
	>365 cDDD	712	13	651	0.49 (0.38-0.52)
	With multiple psychotropic agents	3258	44	510	0.37 (0.28-0.49)
	<30 cDDD	681	12	623	0.46 (0.37-0.51)
	30-120 cDDD	784	11	546	0.37 (0.27-0.48)
	121-365 cDDD	813	11	497	0.37 (0.27-0.43)
	>365 cDDD	980	10	403	0.28 (0.21-0.40)
Alcohol use disorder	With no psychotropic agents	759	17	848	1 [Reference]
	With 1 psychotropic agent	2582	38	537	0.66 (0.60-0.73)
	<30 cDDD	599	10	753	0.90 (0.56-0.96)
	30-120 cDDD	604	11	595	0.72 (0.62-0.80)
	121-365 cDDD	667	9	473	0.57 (0.51-0.70)
	>365 cDDD	712	8	400	0.50 (0.40-0.54)
	With multiple psychotropic agents	3258	29	336	0.40 (0.30-0.50)
	<30 cDDD	681	8	415	0.51 (0.44-0.62)
	30-120 cDDD	784	7	348	0.43 (0.30-0.52)
	121-365 cDDD	813	7	316	0.38 (0.28-0.49)
	>365 cDDD	980	7	282	0.33 (0.21-0.45)
Drug use disorder	With no psychotropic agents	759	7	349	1 [Reference]
	With 1 psychotropic agent	2582	19	269	0.79 (0.61-0.90)
	<30 cDDD	599	4	301	0.80 (0.63-0.95)
	30-120 cDDD	604	5	270	0.85 (0.68-0.98)
	121-365 cDDD	667	5	263	0.73 (0.57-0.83)
	>365 cDDD	712	5	250	0.48 (0.38-0.58)
	With multiple psychotropic agents	3258	15	174	0.45 (0.30-0.52)
	<30 cDDD	681	4	208	0.56 (0.43-0.67)
	30-120 cDDD	784	4	199	0.53 (0.40-0.65)
	121-365 cDDD	813	4	181	0.46 (0.31-0.54)
	>365 cDDD	980	3	121	0.41 (0.23-0.50)

Abbreviations: ASD, autism spectrum disorder; CCI, Charlson Comorbidity Index; cDDD, cumulative defined daily dose.

[a] Adjusted for behavioral psychotherapy, sex, age, years of education, marital status, psychiatric comorbidities, CCI score, season of diagnosis, levels of care, frequency of psychiatric and nonpsychiatric hospitalizations, length of admission, urbanicity of residence, monthly income, and follow-up period.

that is, a higher cDDD resulted in a lower aHR for SUD. The findings for AUD and DUD were similar to those for SUD.

Eight psychiatric comorbidities often co-occur with ASD (eTable 3 in the Supplement). Among all enrolled participants, the presence of the 8 psychiatric comorbidities was associated with an increase in aHRs for SUD, AUD, and DUD compared with the absence of those psychiatric comorbidities, particularly for intellectual disability (aHR, 2.33 [95% CI, 2.01-2.80], 2.30 [95% CI, 1.96-2.71], and 2.54 [95% CI, 2.09-2.87], respectively), ADHD (aHR, 2.50 [95% CI, 2.30-2.90], 2.10 [95% CI, 2.21-2.80], and 2.66 [95% CI, 2.31-2.89], respectively), and anxiety disorder (aHR, 2.97 [95% CI, 2.01-3.20], 3.10 [95% CI, 2.09-3.30], and 2.93 [95% CI, 1.90-3.12], respectively). We further compared the risk of SUD between patients with ASD and psychiatric comorbidities and non-ASD controls with the same psychiatric comorbidities (eg, patients with ASD and ADHD vs non-ASD controls with ADHD) (**Table 4**). We found that the aHRs for SUD, AUD, and DUD were substantially higher in patients with ASD and impulse control disorder (aHR, 2.55 [95% CI, 2.41-2.80], 2.28 [95% CI, 2.03-2.40], and 2.85 [95% CI, 2.73-2.97], respectively) or anxiety disorder (aHR, 2.23 [95% CI, 1.50-2.97], 2.34 [95% CI, 1.62-3.00], and 2.00 [95% CI, 1.98-2.28], respectively) compared with non-ASD controls with the same comorbidities. Comparisons between the ASD subgroups with comorbidities who did not receive any PAs and

Table 4. Comparisons of Risks of Substance Use Disorder Between Patients With ASD and Non-ASD Controls With the Same Comorbidities[a,b]

Outcome	Comorbidity	With ASD, No.			Without ASD, No.			Hazard ratio (95% CI)
		Person	Event	Incidence	Person	Event	Incidence	
SUD	ID	1465	19	628	236	4	507	1.24 (1.05-1.40)
	ADHD	1524	15	330	275	2	295	1.19 (1.01-1.50)
	OCD	207	16	268	55	3	248	1.17 (1.01-1.38)
	Epilepsy	648	9	495	198	2	401	1.24 (1.14-1.48)
	Tic disorder	1112	10	279	211	1	166	1.68 (1.40-1.85)
	Anxiety disorder	1998	25	57	1342	13	33	2.23 (1.50-2.97)
	Mood disorder	1592	28	119	375	3	99	1.64 (1.20-2.11)
	ICD	226	9	1325	121	2	516	2.55 (2.41-2.80)
AUD	ID	1465	10	330	236	2	253	1.30 (1.11-1.49)
	ADHD	1524	8	176	275	1	147	1.20 (1.02-1.50)
	OCD	207	9	151	55	2	165	1.10 (0.85-1.50)
	Epilepsy	648	4	220	198	1	201	1.10 (1.00-1.39)
	Tic disorder	1112	6	168	211	1	166	1.07 (1.01-1.24)
	Anxiety disorder	1998	12	28	1342	6	15	2.34 (1.62-3.00)
	Mood disorder	1592	18	77	375	2	66	1.65 (1.10-2.10)
	ICD	226	4	589	121	1	258	2.28 (2.03-2.40)
DUD	ID	1465	9	297	236	2	253	1.15 (1.01-1.34)
	ADHD	1524	7	154	275	1	148	1.05 (1.03-1.31)
	OCD	207	4	67	55	1	83	0.86 (0.67-1.34)
	Epilepsy	648	5	275	198	1	201	1.37 (1.11-1.59)
	Tic disorder	1112	4	112	211	0	0	NA
	Anxiety disorder	1998	11	25	1342	6	15	2.00 (1.98-2.28)
	Mood disorder	1592	7	30	375	1	33	1.14 (0.92-2.01)
	ICD	226	5	736	121	1	258	2.85 (2.73-2.97)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; AUD, alcohol use disorder; CCI, Charlson Comorbidity Index; DUD, drug use disorder; ICD, impulsive control disorder; ID, intellectual disability; NA, not available; OCD, obsessive-compulsive disorder; SUD, substance use disorder.

[a] Adjusted for behavioral psychotherapy, sex, age, years of education, marital status, psychiatric comorbidities, CCI score, season of diagnosis, levels of care, frequency of psychiatric and nonpsychiatric hospitalizations, length of admission, urbanicity of residence, monthly income, and follow-up period.

[b] Incidence is a crude incidence rate per 10 000 person-years.

Table 5. Mortality Risk in Patients With ASD and Non-ASD Controls With and Without Substance Use Disorder[a]

Variable	Person at risk, No.	Event, No.	Incidence per 10^5 person-years	Hazard ratio (95% CI)
Non-ASD controls				
Without SUD	25 986	297	256	1 [Reference]
With SUD	410	4	328	1.32 (0.84-1.60)
Patients with ASD				
Without SUD	6471	116	669	2.42 (1.89-2.78)
With SUD	128	3	790	3.17 (2.69-3.89)

Abbreviations: ASD, autism spectrum disorder; CCI, Charlson Comorbidity Index; SUD, substance use disorder.

[a] Adjusted for behavioral psychotherapy, sex, age, years of education, marital status, psychiatric comorbidities, CCI score, season of diagnosis, levels of care, frequency of psychiatric and nonpsychiatric hospitalizations, length of admission, urbanicity of residence, monthly income, and follow-up period.

non-ASD controls with the same comorbidities showed that the risk of SUD was substantially higher in those with tic disorder (aHR, 6.39; 95% CI, 5.11-7.87), and the risks of AUD (aHR, 5.48; 95% CI, 5.12-5.70) and DUD (aHR, 5.42; 95% CI, 5.12-5.80) were substantially higher in those with impulse control disorder. Moreover, the subgroup analyses showed that among patients with ASD and the same psychiatric comorbidities, the ASD subgroups taking 1 or multiple PAs had lower risks of SUD, AUD, and DUD than the ASD subgroup not receiving any PAs (eTables 4, 5, and 6 in the Supplement).

Table 5 presents the mortality risks in patients with ASD and non-ASD controls. Compared with non-ASD controls without SUD, patients with ASD and SUD had the highest mortality risk (aHR, 3.17; 95% CI, 2.69-3.89), followed by patients with ASD but without SUD (aHR, 2.42; 95% CI, 1.89-2.78), and then non-ASD controls with SUD (aHR, 1.32; 95% CI, 0.84-1.60).

Discussion

Autism spectrum disorder has long been associated with high rates of comorbid psychiatric and behavioral disorders. The association between ASD and SUD has received little clinical attention in the past. The findings of this study suggest that those diagnosed with ASD had a higher risk of comorbid SUD than the general population. Moreover, compared with non-ASD controls without SUD, patients with ASD and comorbid SUD had an aHR of 3.17 for mortality. The average age in the ASD group was 11.9 years, and the median follow-up duration was 4.3 years. This suggests that adolescents with ASD were vulnerable to developing SUD. However, compared with the ASD subgroup not receiving any PAs, the ASD subgroup receiving PAs had a reduced risk of developing SUD.

The sample sizes of the 18 studies included in a previous systematic review ranged from 14 to 414 patients with ASD.[11] Our study included a relatively large sample size (6599 patients with ASD) and followed the participants for 16 years. Our study found a higher risk of SUD in patients with ASD than in non-ASD controls, which was similar to the findings of a Swedish population-based study.[12] Moreover, the findings of the current study add to the findings of that previous Swedish study. We found that the ASD subgroup receiving PAs had a reduced risk of SUD compared with the ASD subgroup not receiving any PAs. Moreover, among the non-ASD controls and patients with ASD who had the same comorbidities, the patients with ASD had a higher risk of SUD than the non-ASD controls.

The association between SUD and ASD could be explained by neurobiologic mechanisms and behavioral neuroscience. From the perspective of neurobiologic mechanisms, ASD and SUD share several neural circuits and molecular signaling pathways.[8] The neuromodulatory systems in the striatum and basal ganglia play important roles in addiction and reward, and the neuromodulators implicated in the pathogenesis of ASD include opioids, oxytocin, dopamine, and endocannabinoids.[8] For example, striatal opioid systems contribute to the rewarding properties of drug use.[8] Disrupted μ opioid receptor signaling has been shown to trigger a comprehensive autistic syndrome,[24] such as deficits in maternal attachment in mouse pups,[25] reduced interest in a socially rewarding environment in juvenile mice,[26] and blunted response to female ultrasonic vocalizations in male mice.[27] In addition, several molecules, such as methyl CpG-binding protein-2 and fragile X mental retardation protein (FMRP), have been found to contribute to the pathogenesis of ASD and have recently been shown to regulate behavioral and neurobiologic responses in SUD.[8] For example, a variant of the *FMRP1* gene causes the most common inherited form of human ASD.[28] An animal study found that the FMRP protein regulates dendritic pruning and synapse elimination after cocaine exposure, contributing to the development of multiple cocaine-induced behaviors.[29]

From the perspective of behavioral science, the pathophysiology of drug-seeking and drug-taking behaviors in patients with SUD may also mediate syndromic ASD.[10] Motor cognition is used to express, to understand, and to shape behaviors in a motor-based way, and it can be an indicator of the functioning of cortical motor areas. The cortical motor system can be further divided into understanding (motor action and intention understanding) and shaping human behavior (automatized and compulsive behaviors). The cortical motor system functions abnormally in understanding actions in ASD and abnormally in shaping actions in addictive disorders.[30-33] Therefore, abnormalities in the cortical motor system may explain motor cognition commonalities in ASD and SUD, suggesting an association between ASD and SUD.[10]

In a previous population-based study, patients with ASD and comorbid ADHD had a higher risk of SUD than non-ASD controls.[12] In the current study, we found that the ASD subgroups with comorbid impulse control disorder or tic disorder who did not receive any PAs had higher risks of SUD than the non-ASD individuals with the same comorbidities. Both impulse control disorder and tic disorder are behavioral disorders associated with dysfunction of the basal ganglia.[34] Abnormal volumes of the basal ganglia play a role in impulse control disorder and tic disorder.[34] Animal studies also indicated that basal ganglia dysfunction is involved in the pathogenesis of impulse control disorder and tic disorder.[35-37] Because the neuromodulatory systems in the basal ganglia mediate both addictive and autistic behaviors, basal ganglia dysfunction in impulse control disorder and tic disorder may increase the potential for the development of SUD in patients with ASD.

In this study, we found that the ASD subgroups receiving 1 or multiple PAs had lower risks of SUD than the ASD subgroup not receiving any PAs. Moreover, the cDDD of PAs showed a negative association with the risk of SUD (the higher cDDD was, the lower the risk). These findings suggested that PAs may be associated with a reduction in the risk of SUD in the ASD population. In other words, the risk of SUD could be reduced if patients with ASD maintain a stable condition. This finding should remind psychiatrists and the families of patients with ASD of the importance of ASD treatment.

Our study findings raise several important unanswered questions. First, our study suggests an association between ASD and SUD, but the mechanisms remain unexplored. Second, because ASD is a condition with repetitive and restricted behaviors, the risk of behavioral addiction, such as internet addiction, is an important area for future study. Third, although we found an association between PAs and the risk of SUD, the association of nonpharmacotherapies, such as behavioral therapy, family therapy, and psychotherapy, with the risk of SUD requires further investigation. Fourth, in addition to an increased risk of mortality, other psychosocial outcomes of patients with ASD and comorbid SUD constitute an important issue for further research.

Limitations

Several limitations should be taken into account when interpreting the study findings. First, the NHIRD did not include the severity of ASD; therefore, we could not examine the association of ASD severity with the risk of SUD. Second, although we screened a sample of 1 936 512 people with 16 years of follow-up, only 6599 people with ASD were enrolled in the

analysis. The number of enrolled patients was relatively small. Third, we only identified 4 cases of tobacco use disorder in our database. Therefore, the associated outcomes for tobacco use disorder had limited statistical power.

Conclusions

To date and to our knowledge, scant attention has been paid to the risk of SUD in patients with ASD in recent decades. Preliminary data from several small studies reported that few patients with ASD develop SUD. In this study, we found that patients with ASD constituted a population vulnerable to the development of SUD, particularly those who did not receive PAs and have comorbid behavioral disorders, such as impulse control disorder and tic disorder. Moreover, there was a higher associated mortality risk in patients with ASD and comorbid SUD than in non-ASD controls with or without SUD. Future studies are encouraged to examine the mechanisms mediating the association between ASD and SUD.

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