



## Treatment seeking adults with autism or ADHD and co-morbid Substance Use Disorder: Prevalence, risk factors and functional disability

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### ABSTRACT

**Background:** Little is known about Autism Spectrum Disorder (ASD) in adults, especially not about ASD with co-morbid Substance Use Disorder (SUD). We wanted to examine how adults with ASD compare to adults with ADHD on prevalence and risk factors for co-morbid SUD, and on disability levels associated with SUD.

**Methods:** We stratified 123 treatment seeking adults with ASD ( $n=70$ ) or ADHD ( $n=53$ ), into current, former and no history of SUD (SUD+, SUD<sup>^</sup>, and SUD–), and conducted interviews to explore associated risk factors and current levels of disability.

**Results:** Prevalence of co-morbid SUD was higher in ADHD than in ASD in our sample (58% versus 30%,  $p=0.001$ ). There was no statistically significant difference between ASD and ADHD in risk factors or disability scores. Patients with lifetime SUD started regular smoking earlier in life (OR=5.69, CI<sub>95%</sub> 2.3–13.8), reported more adverse family events (OR=2.68; CI<sub>95%</sub> 1.2–6.1), and had more parental SUD (OR=5.36; CI<sub>95%</sub> 1.0–14.5). Disability scores were significantly lower in SUD– and SUD<sup>^</sup> groups compared to the SUD+ group.

**Discussion:** These findings suggest that ASD and ADHD share similar risk factors for SUD. High disability in ASD and ADHD with SUD may normalize after prolonged abstinence. Early onset of SUD was not associated with more severe disability scores than later onset. Results suggest that a subgroup of patients with former SUD may have a higher level of functioning before the onset of SUD in comparison to those without lifetime SUD.

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## 1. Introduction

Autism Spectrum Disorders (ASDs) and Attention Deficit and Hyperactivity Disorder (ADHD) are developmental disorders that often persist into adulthood (Seltzer et al., 2003; Wilens et al., 2004). Current prevalence estimates for ASD and ADHD in adulthood are 0.6% (Kessler et al., 2006) and 4.4% (Frith, 2003), respectively. Both disorders are characterized by their pertinent impact on a person's development, starting at a very young age. In addition, both disorders can present with co-morbid conditions such as Substance Use Disorder (SUD). The objectives of the present

study are to look at SUD prevalence in both ADHD and ASD, the risk factors for SUD, the associated functional disability, and the relationship between age of onset of SUD and functional disability.

Patients with a chronic mental disorder – such as ASD or ADHD – and co-morbid SUD, tend to experience more impairments in functioning and health than those without SUD (Drake et al., 1998; Soyka, 2000). The epidemiological catchment area (ECA) study indicated that the co-occurrence of SUD and mental disorders was 29% for alcohol disorder and 15% for another drug disorder (Regier et al., 1990).

Co-morbidity of SUD in ADHD has been extensively studied, and risk factors for SUD have been described and replicated by different authors (Armstrong and Costello, 2002; Wilens, 2004). The prevalence of SUD among ADHD adults is estimated between 17% and 45% for alcohol dependence or abuse, and 9–30% for drug dependence or abuse (Wilens and Upadhyaya, 2007). In contrast, the interest of the scientific community for adult ASD is relatively new, which could

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explain why we have not been able to find literature on prevalence figures for the co-morbidity of ASD with SUD. The onset of SUD usually occurs during adolescence and is often accompanied by other types of pathology (Armstrong and Costello, 2002; Chambers et al., 2003; Tarter et al., 2003). Moreover, the severity of outcome in the general psychiatric population is reported to be inversely related to the age at which SUD develops (Angold et al., 1999; Costello et al., 1999; Haahes et al., 2002). Whereas the onset of unproblematic substance use is associated with environmental factors (in particular peer influence), the transition from substance use to use of SUD is strongly associated with genetic factors (Dawes et al., 2000; Kendler et al., 2003). Among the known risk factors for SUD in psychiatric populations – and especially in ADHD – are early onset of smoking (Biederman et al., 2006), disruptive behavior in childhood (Compton et al., 2005; Harpold et al., 2007), and a parental history of SUD (Biederman et al., 2008). None of these risk factors have, to our knowledge, been studied for the relationship between ASD and SUD.

The outcome in adulthood for adolescents with ADHD and SUD is reported to be worse than for those without SUD, but it is unknown how the outcome of adults with ASD is affected by co-morbid SUD.

In this cross-sectional study, we explore – for the first time – the prevalence, risk factors and consequences of co-morbid SUD in adults with ASD and compare these to the prevalence, risk factors and consequences of co-morbid SUD in adults with ADHD. We hypothesize (1) that the prevalence of SUD in ASD is lower than in ADHD, but comparable to other psychiatric populations; (2) that known risk factors for co-morbid SUD in ADHD are similar to the risk factors for co-morbid SUD in adults with ASD; (3) that the level of disability is higher in patients with ASD or ADHD with co-morbid SUD compared to those without SUD; that disability levels are lower in ASD and ADHD patients after prolonged remission of SUD; and (4) that early onset of SUD correlates with a high level of adult disability.

## 2. Methods

### 2.1. Subjects

We recruited a consecutive sample of 123 patients between January 2006 and June 2007, from two specialized diagnostic centers for adult patients with possible developmental disorders such as ASD and ADHD. After being diagnosed with ASD or ADHD, 191 patients ( $n = 100$  ASD and  $n = 91$  ADHD) were informed by their own clinicians about the study and asked for permission to be approached by the research team. Exclusion criteria were: history of co-morbid psychotic disorder, bipolar disorder, IQ less than 80, insufficient command of the Dutch language, and uncorrected visual or auditory impairment. Of the 167 patients contacted by our team, 138 agreed to participate and gave informed consent. Of those, 13 withdrew from participation for unaccounted reasons and 2 were excluded due to a total IQ below 80, leaving 123 patients for analyses. The IQ was determined by means of the Dutch Wechsler Adult Intelligence Scale III in 85 patients (Uterwijk, 2000; Wechsler, 1997). For the remainder ( $n = 38$ ) the IQ had already been established elsewhere with valid methods. The DSM-IV diagnoses of ASD and ADHD were based on current and retrospective assessment by experienced clinicians. For a diagnosis of ASD multiple sources of information were used: semi-structured clinical interviews based on the autism diagnostic interview revised (ADI-R) were used (Lord et al., 1994), a DSM-IV checklist, and all available information from schools and child psychiatric services concerning childhood development. The ADHD diagnoses were made according to a national protocol, including a semi-structured developmental history, and a DSM-IV criteria checklist for adult and childhood ADHD symptoms (Kooij et al., 2005).

As part of our study, a blind expert clinician (RvdG) reviewed 10 randomly selected charts and conducted 10 randomly selected clinical interviews, using the Autism Diagnostic Observation Schedule protocol for the diagnosis of ASD (Lord et al., 2000) and a DSM-IV checklist for adults for the diagnosis of ADHD (Kooij et al., 2005). His diagnoses were compared with the diagnoses that were routinely made at the centers. Interrater agreement was high with Cohen's kappas of 0.78 for the chart reviews and 0.81 for the clinical interviews. Seven subjects (5.7%) had been diagnosed with ADHD before being diagnosed with ASD in the centers. Because all ADHD associated symptoms reported by these subjects could – in retrospect – better be explained by ASD, we decided to use only the diagnosis ASD in these patients.

### 2.2. Procedure and assessments

Subjects were tested during two sessions of 3 h each, on different days, as part of a larger overall study on the co-morbidity of ASD and ADHD with SUD (Sizoo et al., 2009). In order to obtain representative results for ADHD, subjects with ADHD were required to cease stimulant medication 2 days prior to assessment. Other regular medications and the use of coffee and nicotine were not interrupted.

Substance Use Disorder (SUD) was diagnosed by the research clinician if the DSM-IV criteria for abuse or dependence were met. The substances that were investigated were alcohol, methadone, sedatives, hypnotics, anxiolytics, cocaine, heroin, amphetamines, cannabis, and combinations of these. Because behavioral addictions, like gambling, seem to share the same neurobiological underpinnings of craving and dependence, gambling was also included in our definition of SUD (Goudriaan et al., 2006; Potenza, 2007). Three of the 123 subjects (2%) presented with co-morbid gambling. Subjects with current abuse or dependence were designated as SUD+ ( $28/123 = 23\%$ ), and those with no lifetime history of SUD as SUD- ( $72/123 = 58\%$ ). Subjects with a former history of SUD, who had been abstinent for at least 6 months prior to participating in the study, were designated as SUD<sup>^</sup> ( $23/128 = 19\%$ ). During the assessments none of the participants were noticed to be under influence of alcohol or illicit drugs, and none admitted having used any of the researched substances in the 24-h period prior to the assessment.

Information on the presence of risk factors for SUD was based on the European version of the Addiction Severity Index, the EuropASI (Hartgers and Kokkevi, 1996). The EuropASI is a semi-structured interview that is widely used in addiction treatment. It elicits eight index severity scores for self-reported problems (current and lifetime) in different areas of functioning (physical health; work, education and income; alcohol; drugs; legal services and police; family and social relations; psycho-emotional complaints; gambling). In the EuropASI, the risk factor 'parental SUD' is defined as having grown up with at least one parent with problematic alcohol or drug use. The risk factor 'early onset of regular smoking' was based on the reported age at which smoking started of at least one cigarette every day for at least 1 year. It was difficult to define the risk factor 'disruptive behavior in childhood' reliably using this retrospective method. We therefore substituted this risk factor by the risk factor 'adverse family history'. This factor was defined as the mean of nine dichotomous ASI items: history of sexual, physical, or emotional abuse in childhood or adolescence (items 1–3), a history of severe and enduring problems with father, mother or siblings (items 4–6), and the absence of a "close, long, and personal relationship" with father, mother, or siblings (items 7–9). The resulting score for 'adverse family history' ranged from 0 (harmonious) to 10 (severe conflicts).

Outcome was measured in terms of social disability using World Health Organization Disability Schedule II (WHODAS II). This is a 32-item self-report generic instrument that measures health-related quality of life and addresses both physical and psychological conditions. The WHODAS II yields a total score and 6 subscale scores for different areas of functioning over the last 30 days: understanding and communication, getting around, self-care, getting along with others, household activities, and participation in society (World Health Organization, 2001). The scores are transformed from raw scores (ranging from 1 = no difficulty, to 5 = extreme difficulty or inability) to standardized total scores for each domain that range from 0 (highest level of functioning) to 100 (lowest level of functioning). The total score is calculated using a syntax provided by the WHO. The WHODAS II has been used in various clinical settings to measure functioning and disability, and has been shown to have good psychometric properties. Four participants (two ASD and two ADHD) did not complete the WHODAS II due to time constraints. In our study the WHODAS II showed good internal consistency (Cronbach's alpha total score = 0.852).

### 2.3. Statistical analysis

**2.3.1. Risk factors for lifetime SUD.** Risk factors for the prediction of lifetime SUD include: age of smoking onset, parental history of SUD, and adverse family history. In accordance with the literature 'early smoking onset' is defined as the start of regular smoking before the age of 16. For the analysis of this risk factor we excluded six patients (four ADHD and two ASD) who reported that SUD preceded regular smoking. Adverse family history, was not normally distributed (mean = 3.82, SD = 2.42, range 0.00–8.90) and was dichotomized; adverse family history was defined as present for scores equal and greater than 5, and absent below 5. Lifetime SUD (LTSUD) was defined as a former or current history of SUD (SUD<sup>^</sup> or SUD+).

For each of the three risk factors we performed a univariate logistic regression analysis with LTSUD as dependent variable and risk factor, diagnosis and the risk factor by diagnosis interaction as independent variables. The latter assesses whether the effect of the risk factor on LTSUD was modified by diagnosis (i.e., different between patients with ASD and patients with ADHD). In case diagnosis did not modify the relation between the risk factor and LTSUD, we removed the interaction term from the model and presented the odds ratio (OR), adjusted for diagnosis. The conditions 'absence of a risk factor' and 'ASD' were assigned as the reference category for the independent variables. In addition we fitted a multiple logistic regression model, in which all three risk factors and diagnosis were entered simultaneously.

**2.3.2. Relationship between disability and SUD status.** To assess whether the relation between level of disability and diagnosis was modified by co-morbid SUD, we performed for each of the seven WHODAS II scores a separate multiple linear regression

**Table 1**  
Comparison of demographic characteristics and risk factors for developing Substance Use Disorder (SUD) in adults with Autism Spectrum Disorder or ADHD.

	ASD (N = 70)			ADHD (N = 53)			Test statistic
	N (pct) <sup>a</sup>	Mean	SD	N (pct)	Mean	SD	
Age		34.44	11.783		32.02	11.322	$t_{(121)} = 1.146, p = .254$
Female	15 (21)			17 (32)			$\chi^2_{(1)} = 1.776, p = 0.183$
Total IQ	56	103.09	13.846	29	104.17	10.468	$t_{(83)} = -0.370, p = 0.713$
Living alone	48 (69)			42 (79)			$\chi^2_{(1)} = 1.751, p = 0.186$
Lifetime SUD	20 (30)			31 (58)			$\chi^2_{(1)} = 11.12, p = 0.001$
Age of onset SUD	20 (29)	19.50	5.434	31 (58)	18.87	5.584	$t_{(49)} = 0.397, p = 0.693$
Age onset smoking	32 (46)	16.63	3.471	42 (79)	14.64	2.739	$t_{(72)} = 2.746, p = 0.008$
Adverse family history <sup>b</sup>		3.9	0.240		3.7	0.245	$t_{(121)} = -0.468, p = 0.640$
Parental SUD <sup>c</sup>	11 (16)			16 (30)			$\chi^2_{(1)} = 3.688, p = 0.055$

<sup>a</sup> Numbers in the N column represent frequency (percentage).

<sup>b</sup> Childhood history of serious problems with family members and/or emotional, physical or sexual abuse (0 = none to 10 = severe).

<sup>c</sup> Number of cases with at least one parent with a history of Substance Use Disorder.

analysis with WHODAS II scores as dependent variables. We introduced two dummy variables to account for the three dichotomous SUD states (SUD<sup>-</sup>, SUD<sup>^</sup>, and SUD<sup>+</sup>), which were entered as a block into the model. SUD status (the dummy variables), diagnosis, and the diagnosis by SUD status interaction were entered as independent variables. The latter assesses whether the relation between level of disability and SUD status is modified by diagnosis.

**2.3.3. Relationship between disability and age of onset SUD.** A bivariate Pearson correlation coefficient was computed between age of SUD onset and total WHODAS II scores and the EuropASI index severity scores for all patients with current SUD, to explore the relationship between disability and the age of onset of SUD.

All statistical analyses were carried out with SPSS 15.0 software, using two-tailed tests with  $\alpha = 0.05$ .

#### 2.4. Ethics and patient protection

Prior approval for the study was obtained from the regional medical ethical committee. Patient protection was guaranteed by assigning a unique numeric code to patient data; the key of which was only known to the principal researcher. After complete description of the study to the subjects, written informed consent was obtained.

### 3. Results

#### 3.1. Sociodemographic characteristics and types of SUD in ASD and ADHD

The 123 subjects enrolled in the present study were adult Caucasian males ( $n = 91$ ) and females ( $n = 32$ ) (Table 1). The ASD group consisted of 70 subjects with a diagnosis Autistic Disorder ( $n = 10$ ), Asperger Disorder ( $n = 31$ ), or Pervasive Developmental Disorder not otherwise specified (PDD-NOS;  $n = 29$ ). The ADHD group consisted of 53 subjects (inattentive subtype:  $n = 10$ , combined subtype:  $n = 43$ ).

Demographic characteristics were very similar for ASD and ADHD, but age of smoking onset was significantly lower in ADHD. The prevalence of SUD was significantly higher in ADHD than in ASD patients (58% versus 30%,  $\chi^2_{(1)} = 11.12, p = 0.001$ ) and this overall difference could be attributed to higher rates of cocaine and cannabis use disorders in ADHD patients. The distribution of the types of SUD (including gambling) in both diagnostic groups is summarized in Table 2.

#### 3.2. Risk factors

Table 3 shows the prevalence of the various risk factors in the ASD and ADHD groups stratified by history of lifetime SUD. Logistic regression analysis revealed that none of the diagnoses by predictor interaction terms were significant, indicating that the relationship between the predictors and lifetime SUD was not modified by diagnostic group (ASD or ADHD). We therefore computed the ORs with the risk factors and the diagnosis as dependent variables to obtain

ORs adjusted for diagnosis. The adjusted OR for early smoking onset was 5.69 ( $p < 0.001, CI_{95\%} = 2.3-13.8$ ), the adjusted OR for an adverse family history was 2.68 ( $p = 0.019, CI_{95\%} = 1.2-6.1$ ), and the adjusted OR for parental SUD was 5.36 ( $p < 0.001, CI_{95\%} = 1.0-14.5$ ). The ORs that were yielded by the multiple logistic regression analysis with all three risk factors as dependent variables, including diagnosis, were significant for early smoking onset, and for parental SUD, but was no longer significant for adverse family history.

#### 3.3. Disability

Table 4 shows the mean disability scores for the SUD<sup>-</sup>, SUD<sup>^</sup> or SUD<sup>+</sup> subgroups, for ASD ( $N = 68$ ) and for ADHD ( $N = 51$ ) patients. Linear regression analysis showed that the (diagnosis by SUD status) interaction terms were not statistically significant for any of the WHODAS II scores. This indicates that the association between disability and SUD status was not modified by diagnostic category (ASD and ADHD). Therefore, linear regression analyses without the interaction term were used with SUD status (dummy variables) as the only independent variable.

The comparisons between the different SUD states for the combined ASD and ADHD patients are summarized in Table 5. The SUD<sup>+</sup> group showed a significantly higher standardized total disability score than the SUD<sup>-</sup> and SUD<sup>^</sup> groups. Unexpectedly, the differences in disability were larger between the SUD<sup>^</sup> and SUD<sup>+</sup> groups, than between the SUD<sup>-</sup> and SUD<sup>+</sup> groups, with statistical significance for the indices "Domestic Housekeeping" and the "Getting Along with Others". For the "Participation in Society" index differences were also statistically significant, but larger between the SUD<sup>+</sup> and SUD<sup>-</sup> group, than between the SUD<sup>+</sup> and the SUD<sup>^</sup> group.

**Table 2**  
Prevalence of Substance Use Disorders (SUDs) in adults with Autism Spectrum Disorder (ASD) or ADHD.

	ASD (N = 70) N (pct)	ADHD (N = 53) N (pct)
No. history of SUD	50 (70)	22 (42)
Alcohol	10 (14)	7 (13)
Methadone	1 (2)	0 (0)
Sedatives, hypnotics, anxiolytics	0 (0)	1 (2)
Cocaine	0 (0)	5 (9)
Amphetamines	1 (2)	2 (4)
Cannabis	5 (7)	9 (17)
Alcohol and drugs	2 (3)	0 (0)
Polydrug	1 (2)	4 (8)
Gambling	0 (0)	3 (5)
	70 (100)	53 (100)

**Table 3**  
Prevalence of risk factors among adults with Autism Spectrum Disorder (ASD) or ADHD, stratified to history of lifetime Substance Use Disorder (LTSUD) and adjusted Odds ratios (ORs).

Risk factor N (%)	ASD (N = 70)		ADHD (N = 53)		LTSUD (N = 20)		LTSUD (N = 31)		Univariate logistic regression model-1 <sup>a</sup>			Multiple logistic regression model-2 <sup>b</sup>		
	No.	LTSUD (N = 50)	No.	LTSUD (N = 22)	No.	LTSUD (N = 20)	No.	LTSUD (N = 31)	Adjusted OR <sup>c</sup>	95% CI	p-Value	Adjusted OR <sup>c</sup>	95% CI	p-Value
Onset smoking ≤15 years	5 (10)	7 (35)	6 (27)	6 (27)	7 (35)	7 (35)	22 (71)	22 (71)	5.69	2.3/13.8	.000	4.30	1.7/10.9	.002
Adverse family history	14 (28)	8 (40)	3 (14)	3 (14)	8 (40)	8 (40)	14 (45)	14 (45)	2.68	1.2/6.1	.019	2.01	.81/5.0	.133
Parental SUD	3 (6)	8 (40)	4 (18)	4 (18)	8 (40)	8 (40)	12 (39)	12 (39)	5.36	1.0/14.5	.001	3.74	1.3/10.8	.015

<sup>a</sup> Univariate logistic regression analysis with LTSUD as dependent variable, and the specific risk factor and diagnosis (ASD or ADHD) as independent variables.

<sup>b</sup> Multiple logistic regression analysis with LTSUD as dependent variable, and all three risk factors and diagnosis (ASD or ADHD) as independent variables.

<sup>c</sup> Adjusted for diagnosis.

### 3.4. Early SUD onset and disability outcome

There was no statistically significant correlation between the total WHODAS disability score and the age of SUD onset. Neither was there a significant correlation between the eight EuropASI index severity scores and the age of SUD onset.

## 4. Discussion

This is the first study examining the prevalence, the risk factors and consequences of SUD in treatment seeking adult patients with ASD, making a comparison with treatment seeking patients with adult ADHD.

In our sample the prevalence of co-morbid SUD in adult ADHD patients is nearly twice that of co-morbid SUD in adult ASD patients (58% versus 30%). Other studies also showed a high prevalence of SUD in adults with ADHD (Biederman et al., 1998, 2008; Kessler et al., 2006) reporting similar percentages as the one found in the current study. To our knowledge, the only estimate of drug and alcohol use in an ASD population is given in a retrospective study by Santosh (2006) where it is suggested that subjects with Pervasive Developmental Disorders (PDDs) report significantly lower drug and alcohol use than psychiatric controls (3% versus 17%). However this figure is based on only two questions in a 55-item clinical questionnaire (Santosh and Mijovic, 2006). To our knowledge, there is no other study on the prevalence of SUD in ASD. The current study shows that the prevalence of SUD among our sample of treatment seeking ASD patients is 30%, which is comparable to that among other psychiatric populations. Nonetheless, it should be kept in mind that our prevalence is based on a sample that was referred to specialized centers for adults with developmental disorders, and cannot be generalized to ASD or ADHD patients in the general population. Furthermore, the availability of addiction treatment facilities in these centers might have lead to a relatively high prevalence of SUD co-morbidity in our sample.

Risk factors for developing SUD in ASD or ADHD were very similar, with the largest odds ratio for early smoking onset (OR = 5.68), followed by parental SUD (OR = 5.36), and adverse family history (OR = 2.67). There was no significant interaction between diagnosis and risk factors in the three univariate logistic regression analyses and the effect of each risk factor is thus not modified by diagnosis. In a multiple logistic regression including all three risk factors for SUD, adverse family history was no longer significantly associated with lifetime SUD. This does not imply that adverse family history is not a risk factor, but it merely indicates that early onset of smoking and parental SUD are strongly related to adverse family history, and may explain why adverse family history is related to lifetime SUD in the univariate analysis. The ADHD adults started regular smoking 2 years earlier than the ASD patients (mean age: 14.6 versus 16.6). Other investigators have reported an early onset of smoking in ADHD compared to youth without ADHD (Biederman et al., 2006; Kollins et al., 2005). The average age of smoking onset in our ASD patients is similar to that of the normal controls in these studies.

Risk factors for SUD in general can be divided into genetic and environmental factors. The three risk factors that were the focus of this study, share genetic and environmental characteristics and are probably not independent. Early onset of smoking has been demonstrated to be a risk factor for SUD in both the general population (e.g. Ilomäki et al., 2008), and in ADHD patients. Our study shows that early onset of smoking is also a risk factor for SUD in ASD patients. Parental SUD is an important risk factor for SUD in the general population with a high heritability ( $h^2 = 0.78$ ; Kendler and Prescott, 1998). Also, in patients with ADHD, a family history of alcohol and/or drug abuse has been shown to be predictive of co-morbid SUD (Faraone et al., 2008). The current study shows

**Table 4**  
WHODAS II scores stratified by diagnosis and Substance Use Disorder (SUD) status.<sup>a</sup>

WHODAS II scores <sup>b</sup>	ASD (N = 68)						ADHD (N = 51)					
	SUD–		SUD <sup>^</sup>		SUD+		SUD–		SUD <sup>^</sup>		SUD+	
	N = 49		N = 6		N = 13		N = 22		N = 17		N = 12	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Standardized total score	23.6	15.92	28.3	16.22	30.6	12.90	24.2	15.58	17.1	13.52	33.8	19.02
Understanding and communicating	25.9	22.81	35.8	18.55	28.1	21.94	34.3	22.38	23.8	17.37	40.0	25.23
Physical mobility	10.8	17.01	13.5	17.86	15.4	14.35	10.8	14.71	5.5	12.28	14.6	29.60
Self-care	6.3	12.02	8.3	9.83	10.8	22.90	6.4	10.49	2.4	6.64	9.2	14.43
Getting along with others	39.3	29.02	34.7	22.00	37.8	25.37	21.2	21.78	10.8	17.12	34.0	28.53
Domestic housekeeping	23.7	25.71	25.0	22.58	35.4	26.65	38.6	25.50	12.9	21.44	46.7	28.39
Participation in society	29.5	20.27	38.2	27.06	45.5	20.52	27.5	21.04	30.4	22.48	46.2	25.65

<sup>a</sup> SUD– = no history of SUD, SUD<sup>^</sup> = prolonged remission of SUD, SUD+ = and current SUD.

<sup>b</sup> WHODAS II scores indicate level of disability (range 0 = no disability to 100 = maximum disability).

that this also applies to patients with ASD. Childhood maltreatment is not only a risk factor for SUD in ADHD and ASD, but also in the general population (e.g. Clark et al., 1997). Finally, it has been frequently suggested that the etiological factors contributing to SUD are both environmental and genetic, and that each factor may augment the other. Although specific figures vary, it is clear that the presence of a psychiatric disorder as such is a risk factor, but that the causal mechanisms are complicated (see Tarter et al., 1999).

The results support the hypothesis that patients with ASD are indeed at risk for developing SUD, whereby the same risk factors apply as those that are known to increase the risk for SUD in ADHD patients. However, the absence of significant differences between ASD and ADHD might be due to a lack of power, because the size of the ASD groups with LTSUD was limited. Therefore, further research is needed to search for risk factors in addition to the ones studied here, and to determine the possible specificity of these risk factors for patients with ASD.

Our second objective was to assess the functional outcome of SUD co-morbidity in ASD and ADHD. Lower functional outcome in the three SUD subgroups is reflected by higher disability scores for different areas of functioning. As predicted, the results indicate that co-morbid SUD is associated with more disability in both ASD and ADHD patients. Noteworthy is that patients with current SUD have more severe disabilities than those with SUD in remission. In clinical practice it is, therefore, important to probe for current SUD bearing in mind the associated functional consequences of SUD. Apparently the domains of functioning that cover domestic housekeeping and participation in society are most affected by SUD. The effect of SUD status on disability is not statistically significant different for ASD and ADHD patients. It is our clinical impression, however, that SUD has more consequences in terms of functional outcome in the ASD group than the ADHD patients. There are large inter-individual differences in our sample. This high variance in combination with the small sample size could explain the lack of statistical significance.

**Table 5**  
Comparison of disability scores<sup>a</sup> between different states in Substance Use Disorder (SUD) in 68 adults with Autism Spectrum Disorders (ASDs) or 51 adults with ADHD.

	SUD– versus SUD+			SUD <sup>^</sup> versus SUD+		
	$\Delta$ WHODAS II <sup>b</sup>	<i>p</i>	95% C.I.	$\Delta$ WHODAS II	<i>p</i>	95% C.I.
Standardized total score	–8.36	0.022	–15.52 to –1.19	–12.09	0.008	–21.00 to –3.19
Understanding and Communicating	–5.28	0.310	–15.52 to 4.69	–6.84	0.289	–19.57 to 5.88
Physical mobility	–4.17	0.303	–12.15 to 3.81	–7.39	0.143	–17.31 to 2.52
Self-care	–3.66	0.223	–9.59 to 2.26	–6.09	0.104	–13.44 to 1.27
Getting along with others	–2.31	0.708	–34.16 to –3.77	–18.97	0.015	–14.54 to 9.91
Domestic housekeeping	–12.49	0.040	–24.40 to –0.58	–24.71	0.001	–39.51 to –9.92
Participation in society	–16.96	0.001	–26.84 to –7.08	–13.41	0.033	–25.68 to –1.13

<sup>a</sup> WHODAS II scores measure levels of disability in different areas (0 = no disability, 100 = maximum disability).

<sup>b</sup>  $\Delta$ WHODAS II = difference in WHODAS II scores between SUD categories.

Bearing in mind the limitations of a cross-sectional design, a conclusion is that patients with ASD, like those with ADHD, experience significant problems in functioning with co-morbid SUD. We can only speculate as to the causal direction of this relationship. However, given the statistically significant differences between the SUD+ and the SUD<sup>^</sup> groups, there is an indication that the functional impairments due to SUD might be reversible in both diagnostic groups. However, an alternative explanation could be that those who managed to stop using substances were those in whom the Substance Use Disorder was less severe. These considerations need to be tested in longitudinal design.

Domestic housekeeping and participation in society are most affected by SUD status. Interestingly, post hoc analyses reveal that, compared to the SUD+ group, there is even less disability in 'getting along with others', and 'domestic housekeeping' in the group with former SUD (SUD<sup>^</sup>) than in the group without any history of SUD (SUD–). This suggests that there is a distinct subgroup of patients with ASD or ADHD and former co-morbid SUD (SUD<sup>^</sup>) that has – or returns to – a higher (premorbid) level of functioning compared to ASD and ADHD patients without any history of SUD. In the literature this is also referred to as the paradox of the dually diagnosed (Penk et al., 2000). The clinical relevance of such a subgroup among psychiatric patients would be that, successful treatment for co-morbid SUD could lead to levels of functioning which are higher than among patients without a history of SUD.

Finally, contrary to reports by others and our last hypothesis, early onset of SUD in the current study is not associated with higher levels of disability in patients with ASD or ADHD, nor with addiction severity. The reason for not finding this association could be due to the fact that all our patients with current SUD already participated in treatment programs, ameliorating their levels of disability.

#### 4.1. Limitations

This study has both strengths and limitations. The main strengths are the relatively large general sample size and the

structured assessment of co-morbid Substance Use Disorders and pathological gambling. The main limitations are the unknown representativeness of the study group for the target population, the clinical diagnostic procedures, the absence of another psychiatric control group, and the relatively small size of some of the diagnostic subgroups. Sex distribution was similar to that of ASD and ADHD patients in the general population, but the number of subjects with ASD exceeded those with ADHD, whereas the prevalence of ADHD in the general population is much higher than that of ASD (Gillberg and Wing, 1999; Murphy and Barkley, 1996). A possible explanation is that the participating expert centers are used more often by referral agencies when autism is suspected than when ADHD is suspected, because ADHD is more readily diagnosed and treated in general psychiatric settings. Another limitation is that clinicians in the expert centers, and not research assistants, carried out the diagnostic procedures. We compensated for this by reviewing and verifying all diagnoses before inclusion. Another possible limitation is that all instruments used were based on self-report meaning that the measures obtained are subjective and not necessarily related to third party data. However, given the nature of this exploratory study, there is enough material for future longitudinal studies.

#### 4.2. Conclusions

Prevalence of SUD in treatment seeking patients with ASD is comparable to other psychiatric patients, but not as high as in patients with ADHD. The risk factors that are known to increase the risk for SUD in psychiatric patients, particularly in those with ADHD, also apply to patients with ASD. Levels of disability are higher in patients with ASD or ADHD with co-morbid SUD, but there is an indication that disability levels may normalize during abstinence in excess of 6 months. Furthermore, a longitudinal follow-up is needed to support the suggestion that there is a subgroup of patients with ASD or ADHD and co-morbid SUD that returns to a higher level of functioning after successful abstinence, than the group with ASD or ADHD without a history of SUD.

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#### Contributors

Authors Sizoo and van Wijngaarden-Cremers designed the study and wrote the protocol. Author Sizoo managed the literature searches and summaries of previous related work. Authors Sizoo, Gorissen van Eenige and Koeter undertook the statistical analysis, and author Sizoo wrote the first draft of the manuscript. Authors van der Gaag and van den Brink supervised the study. All authors contributed substantially to and have approved the final manuscript.

#### Conflict of interest

Prof. Wim van den Brink and Dr. Maarten Koeter report no conflict of interests related to the current manuscript. Prof. Rutger Jan van der Gaag and Dr. Patricia van Wijngaarden-Cremers have received funding for RCTs from Eli Lilly and Jansen Cilag. They are advisors for Eli Lilly and Jansen Cilag, but report no conflict of interests related to the current manuscript. All other authors declare that they have no conflicts of interest.

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