Stimulant treatment for ADHD reduces risk for developing Substance Use Disorder

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Abstract

Background: Attention-Deficit Hyperactivity Disorder (ADHD) is linked to increased risk for substance use disorders (SUDs) and nicotine dependence.

Aim: To examine the effects of stimulant treatment on subsequent risk for SUD and nicotine dependence in a prospective longitudinal ADHD case-control study.

Method: ADHD, conduct disorder (CD) and oppositional defiant disorder (ODD) were assessed at baseline. SUDs, nicotine dependence and stimulant treatment were assessed retrospectively after a mean follow-up of 4.4 years, at a mean age of 16.4 years.

Results: Stimulant treatment of ADHD was linked to a reduced risk for SUDs compared to no stimulant treatment, even after controlling for CD and ODD (HR=1.91; 95%CI=1.10-3.36), but not to nicotine dependence (HR=1.12; 95%CI=.45-2.96). Within the stimulant-treated group, a protective effect of age of first stimulant use on SUDs development was found, which diminished with age, and seemed to reverse around the age of 18.

Conclusions: Stimulant treatment appears to lower the risk for developing SUDs and does not impact the development of nicotine dependence in adolescents with ADHD.

Numerous studies have shown an increased risk to develop substance use disorders (SUDs) and nicotine dependence in patients with Attention-Deficit Hyperactivity Disorder (ADHD). A recent meta-analysis showed that a childhood diagnosis of ADHD increased the risk of developing SUDs and nicotine use (1). While some studies suggest that the increased risk of developing SUDs in ADHD is completely dependent on the presence of comorbid Conduct Disorder (CD)/Oppositional Defiant Disorder (ODD) (2-3), other studies found that ADHD remains a risk factor after adjustment for CD/ODD (4-6). The risks described are substantial and emphasize the need for early intervention to prevent these negative outcomes of a childhood diagnosis of ADHD. Stimulant therapy is the first choice medication treatment in participants with ADHD (7). Since stimulants have the potential to be addictive drugs, concerns have been raised regarding the effects of stimulant treatment on the later development of SUDs in ADHD (8). These concerns are mainly based on the sensitization hypothesis. This theory states that exposure to stimulants alters the dopamine system in such a way that an increased sensitivity is established to the reinforcing effects of previously experienced drugs. This, in turn, may result in an increased risk of developing SUDs and nicotine dependence. Interestingly, all evidence for this hypothesis comes from animal studies (9). So far, the harmful effect predicted by the sensitization hypothesis on the development of SUDs has only been reported by a single study in humans (10). It should be noted that the results of that study may have been confounded by a larger number of participants with comorbid CD in the stimulant-exposed group as compared to the stimulant-naïve group. An alternative hypothesis to the sensitization hypothesis posits that stimulant treatment protects against SUDs and nicotine dependence by decreasing the core symptoms of ADHD (e.g. impulsivity and poor planning) and associated problems (e.g. poor self-esteem, school failure, academic or occupational failure) that lead to drug, alcohol, and nicotine use (11). This hypothesis is supported by several studies (e.g., 12, 13) and a meta-analysis (11) that showed

protective effects of stimulant treatment on the later development of nicotine use and SUDs. Interestingly, some studies, that evaluated participants at a higher mean age, did not find any effect of stimulant treatment on the development of SUDs and nicotine dependence (14-16). Meta-analytic evidence suggests that the protective effect of stimulant treatment is indeed much larger in adolescence (OR: 5.8), than in early adulthood (OR: 1.4) (11). Several other factors might influence the effects of stimulant treatment on SUDs. One study found that stimulant therapy only influences the development of substance abuse in boys, but not girls (12). However, a different study also found this effect in girls (17). Furthermore, an earlier age of stimulant initiation (18) and a longer duration of stimulant use (16) have been reported to have a protective effect on the development of SUDs; however, another study did not replicate these findings (13, 19).

To our present knowledge we are the first prospective, longitudinal study of European origin investigating the effect of stimulant medication on the development of SUD and nicotine dependence in ADHD. The current study describes a four-year follow-up of a large sample of well-defined probands with combined type ADHD, their affected siblings and healthy controls. Our aim was to assess the effects of stimulant treatment on the development of SUDs and nicotine dependence. We also sought to assess the effects of specific characteristics and moderators of stimulant treatment (e.g. age of treatment initiation, duration of treatment, cumulative dose) on the development of SUDs and nicotine dependence.

Method

Individuals participating in this study were recruited as part of the Belgian (n=41), Dutch (n=537) and German (n=21) International Multicenter ADHD Genetics (IMAGE) study (20). ADHD probands aged 5 to 17 years had been recruited from outpatient clinics at the data collection sites between 2003 and 2006. Participants had to be Caucasians of European descent. Exclusion criteria applying to both probands and siblings included autism, epilepsy, IQ < 70, brain disorders, and any genetic or medical disorder associated with externalizing behaviors that might mimic ADHD. In addition, healthy control-participants were recruited from primary and high schools from the same geographical regions as the participating ADHD-families.

In 2008 and 2009 participants were re-invited to participate in the current follow-up study, on average 4.4 years (s.d.=.7) after study entry. A total of 505 participants with a baseline diagnosis ADHD (both probands and affected siblings) and 223 healthy control participants above the age of 12 participated in the follow-up. For 599/728 (82.3%) of these children, information on medication use history were available (i.e. rating of medication use (yes or no) was available). Ethical approval for the study was obtained from the National Institute of Health registered ethical review boards for each center. After a complete description of the study, written informed consent was obtained from both parents and children.

Assessment of ADHD, ODD, and CD at baseline

Baseline measures included the Long Version of Conners' Parent (CPRS-R:L), and Teacher Rating Scale (CTRS-R:L; 21), which were used to quantify ADHD symptoms. Parents and teacher were asked to describe the child's behavior in a medication-free period when filling out the questionnaire. For a full account of the measures used in IMAGE, please see Müller et al (22). T-scores ≥ 63 on the Conners ADHD subscales (L, M and N) were

considered clinical. The CPRS-R:L also assesses symptoms related to ODD (e.g. angry and resentful, argues with adults, loses temper, irritable, temper outbursts) on a 4-point ordinal scale.

The Parental Account of Childhood Symptoms (PACS; 23) interview was administered if scores on the Conners ADHD rating scales were considered clinical. The PACS is a semi-structured, standardized, investigator-based interview developed to provide an objective measure of child behavior. A trained interviewer administered the PACS to the parents, who were asked for detailed descriptions of the child's typical behavior in a range of specified situations. Among others, the PACS covers the Diagnostic and Statistical Manual of mental disorders (DSM-IV; 24)) symptoms of ADHD, CD and ODD (for an exact description of the interview procedure, we refer to 20).

Categorical measures of ADHD, ODD, and CD were created. ADHD was defined using a standardized algorithm applied to combine symptom counts on the PACS and CTRS-R:L, both providing operational definitions of each of the 18 behavioral ADHD symptoms defined by the DSM-IV (24). ADHD symptom count was used as a measure of ADHD-severity. Situational pervasiveness of ADHD was defined as at least two symptoms being present in two or more different situations as assessed with the PACS interview, as well as the presence of one or more items scored as 2 or 3 or more from the ADHD scale of the CTRS-R:L. ODD and CD were defined according to the DSM-IV (24) criteria based on information from the PACS.

Follow-up Measures

A parental report of SUDs was obtained using the Substance use disorder module of the Diagnostic Interview Schedule for Children (DISC-IV-P; 25). The DISC-IV-P was administered by telephone interview, and scored with a computer-based algorithm to derive DSM-IV-defined SUD diagnoses. Age of first substance use was assessed in the interview.

Participants above the age of 12 completed a number of questionnaires. The Alcohol Use Disorders Identification Test (AUDIT; 26) was completed by participants. This questionnaire was used to identify self-reported alcohol dependence. Scores on the AUDIT may range from 0-40. A score of 9 or higher was used to define alcohol abuse, and a score of 13 or more in girls and 15 or more in boys was used as a cut-off to define alcohol dependence (26). The Drug Abuse Screening Test–20 (DAST; 27) was used to assess drug use disorders. Scores on this questionnaire may range from 0 – 20. A cut-off of 5 was used to identify possible drug use disorders (27). The Fagerström test for Nicotine Dependence (FTND; 28) was used to assess nicotine dependence. Scores on this questionnaire may vary between 0 and 10. A cut-off of 6 was used to identify nicotine dependence (28). Age of first nicotine use was also assessed in this questionnaire.

To create best estimate diagnoses of SUDs, these were considered present if scores on *either* self- or parent-report measures met criteria as stated above. We created summary diagnostic groups to aggregate diagnostic information across instruments and informants. For Alcohol Use Disorder (AUD), the AUDIT and alcohol module of the DISC-IV-P were used, for Drug Use Disorder (DUD), the DAST and the marihuana and other drugs module of the DISC-IV-P were used. AUD and DUD were collapsed into one category to form an overall measure of SUDs, to increase reliability of the measure and reduce the number of statistical tests. For nicotine dependence the FTND and the tobacco module of the DISC-IV-P were used. Two main dependent variables were used: an overall measure of SUDs and one measure of nicotine dependence.

Medication history was assessed using parental report of medication use combined with pharmacy records. Predictors derived from this information are previous and/or current stimulant use (yes/no), current use of stimulants (currently on medication yes/no), age at stimulant treatment initiation, age-adjusted duration of stimulant use (defined as the

percentage of time treated with stimulants since the onset of ADHD), and age-adjusted cumulative dosage of stimulants (defined as dosage corrected for number of days since the onset of ADHD).

Statistical analyses

All analyses were conducted using SPSS (IBM SPSS Statistics version 20). Differences between groups in gender, age, IQ, ADHD-severity, and ODD/CD comorbidity were examined using analysis of variance and chi-square tests. Differences between subjects successfully followed- up and those lost to follow-up in gender, age ADHD-severity, and ODD/CD comorbidity were examined using t-test and chi-square tests.

The possible effects of stimulant treatment on the development of drug and alcohol-related SUDs and nicotine dependence were studied using, cox-proportional hazard models . The models used age of first substance use as the survival time for the cases (classified as having an SUD and/or nicotine dependence) and current age as the time of censoring for the non-cases. Correction for clustered (family) data was done using robust standard errors (29). Three groups were included in this analysis: participants with a childhood diagnosis of ADHD who were stimulant-naïve (n = 30) and participants with a short or inconsistent history of stimulant medication never exceeding 12 months (n = 31; n=61 no-stimulant treatment group); participants with childhood diagnoses of ADHD with a history of stimulant medication longer than 12 months (n=327; stimulant treatment group), and healthy control participants (n=211).

Differences in the number of SUD and nicotine dependence between the subjects from Germany (n= 21), Belgium (n= 41), and the Netherlands (n = 537) were examined using generalized estimated equations (GEE;30), robust estimators and exchangeable structure for working correlation matrices.

Within-group analyses were performed to evaluate the potential subtle effects of stimulant medication had on the development of SUDs and nicotine dependence. A logistic regression model was fitted using GEE (30), robust estimators and exchangeable structure for working correlation matrices. All participants with a childhood diagnosis of ADHD and any history of stimulant medication were included in these analyses (n= 358). Any SUD or nicotine dependence were used as the dependent measure. Our data-analytic approach was similar to that suggested by Hosmer and Lemeshow (31). In short, several steps were taken to identify potential predictors of SUDs and nicotine dependence: i) initially, all possible predictor and possible confounding variables (i.e. current use of stimulants, age at stimulant treatment initiation, age-adjusted duration of stimulant use and age-adjusted cumulative dosage of stimulants, ADHD, ODD and CD symptom count at baseline, gender and age at follow-up) were analyzed using a univariate approach. Correlations between predictor variables were calculated to assess whether the assumption of multicollinearity (r>.80) was violated; ii) all predictors with a p-value <.20 and variables with known clinical importance were included in a multivariate model; iii) predictors with p-values>.05 were dropped from the model if this positively influenced the overall fit of the model. To assess the fit of the model the quasi-likelihood under independence model criterion (QIC) was used (32). We will refer to this model as the *initial main effects' model*; iv) we checked whether any meaningful interactions among the main effects improved the fit of the model.

Results

Attrition and Demographics Characteristics

At baseline, among ADHD and control participants, there were no significant differences between those successfully followed up and those lost to follow-up on age (t= .196, p=.845) and gender (χ^2= 3.412, p=.065). At baseline, no differences were found among ADHD participants followed up and those lost to follow-up on ADHD-severity (t= 1.533, p=.126), and presence of CD (χ^2=114, p=.735) and ODD (χ^2= .089, p=.766). No differences were found in the number of SUD and nicotine dependence between the subjects from Germany , Belgium, and the Netherlands (respectively Wald χ^2= 3.379, p= .337 and Wald χ^2= 3.677, p= .299). Table 1 describes demographic and clinical features of the three groups (healthy controls, no-stimulant treatment and stimulant treatment group). The stimulant and no-stimulant groups did not differ in the number of participants who met criteria for ODD or CD, none of the healthy control participants were assessed for ODD or CD. The three groups did not differ in current age. Controls had a significantly higher IQ than the stimulant ADHD group. Furthermore, the stimulant and no-stimulant groups differed in ADHD severity, in that the no-stimulant group had lower ADHD symptom counts. ADHD symptom count was assessed over a medication-free period. Finally, stimulant treated ADHD participants were more likely to be male. In the subsequent Cox proportional hazard models we therefore statistically adjusted for gender and current age. Although no difference was found between the ADHD groups in the prevalence of ODD and CD, separate models, including the no-stimulant and stimulant treatment groups, were built that corrected for ODD, CD and ADHD-severity, to completely rule out their effects.

***********insert table 1 about here*********

Overall effect of stimulant medication

Table 2 displays prevalence rates and hazard ratios for SUDs and nicotine dependence for the healthy control, no-stimulant treatment and stimulant groups. The no-stimulant treatment group had a 2.6 times higher risk of developing an SUD when compared to healthy control participants, and had a 2 times higher risk of developing an SUD than the stimulant treatment group. No significant differences were found between the stimulant treatment and the healthy control group (also see left panel Fig.1). Both the stimulant treatment (HR = 3.56) and the no-stimulant treatment group (HR= 3.83) had an increased risk of developing nicotine dependence compared to healthy control participants. No differences were found between the no-stimulant treatment and stimulant treatment group in their risk for nicotine dependence (also see right panel Fig. 1).

***********insert table 2 about here********************

Analyses between the stimulant treatment and the no-stimulant treatment group were rerun including ODD, CD, and ADHD severity at baseline as covariates, to rule out any role of these measures on the observed protective effect of stimulant treatment on the development of SUDs. The control group was not included in these analyses because the PACS was not administered if scores on the CPRS-R;L and CTRS-R;L were not considered clinical (for an exact description of the interview procedure, we refer to 20). Results remained essentially unchanged: the protective effect of stimulant treatment on the development of SUDs proved not to be dependent on ODD, CD, or ADHD severity (no- vs. stimulant treatment; HR=1.91; 95% CI =1.10-3.36), neither did results concerning nicotine dependence (no- vs. stimulant treatment (HR=1.12; 95% CI =.45-2.96).

**********insert Figure1 about here**********

Predictors of SUDs and Nicotine Dependence in Stimulant-treated Participants

Correlations and results of the univariate analyses are displayed in Table 3. In the *initial main effects' model* for SUDs, seven main effects were retained, namely: current age, age of first stimulant use, treatment delay, current use of stimulants, ODD, CD and gender. Because treatment delay and age of first stimulant use were highly correlated (r=.83), two models were built including all main effects and *either* age of first stimulant use or treatment delay. The main effects' model with the best fit indicated by QIC was the model including age of first stimulant use, ODD and current age. Evaluation of this model showed that including ODD, age of first stimulant use, current age, the interaction between age of first stimulant use and current age led to the most parsimonious model (QIC= 217.79). The protective effect of earlier age of first stimulant use on the development of an SUD was found to decrease with increasing age (OR=.95, Wald χ^2 =13.78, p<.001), see Fig.2.

**********insert Figure2 about here**********

The *initial main effects' model* for nicotine dependence retained 5 possible predictors: current age, age of first stimulant use, age-adjusted duration of stimulant use, current use and symptom count at baseline. It appeared that including current age and age-adjusted duration of stimulant use led to the most parsimonious model (QIC= 163.66). Higher current age was significantly related to an increased risk of developing nicotine dependence (OR=1.17, Wald χ^2 =10.89, p=.001), while percentage of time treated was not significantly associated with risk of developing nicotine dependence (OR=.99, Wald χ^2 =3.77, p=.052).

Discussion

The current study investigated the effects of stimulant medication on the development of alcohol- and drug-related SUDs and nicotine dependence in ADHD. A protective effect of stimulant therapy on the development of the SUDs was found. No difference was found in the risk of developing SUD between the stimulant therapy group and the healthy controls, suggesting normalization. In contrast, no difference in the risk of developing nicotine dependence was found between participants not treated with stimulants and participants who were treated. Specific moderators were investigated in order to further unravel the mechanisms through which stimulant use influences the later development of SUDs. It was found that children who start stimulant medication at a younger age are better protected against the later development of SUDs. However, the effect of age of first stimulant use on SUD development diminished with age, and seemed to reverse around the age of 18.

Our results argue against the sensitization hypothesis. This hypothesis states that stimulant therapy would increase the risk of developing SUDs and nicotine dependence in ADHD, by increasing the sensitivity to substances, through alterations in the dopamine system. Rather, our results support previous findings that stimulant therapy has a protective effect on the development of SUDs (11-13). The protective effect of stimulant treatment on the development of SUD could not be explained in terms of the impact of comorbid ODD or CD symptoms and ADHD-severity, as findings remained essentially unchanged when adjusting for these possible confounds. Furthermore, we found that the stimulant treatment group did not significantly differ in the risk of developing SUDs compared to healthy control participants, while the no-stimulant treatment group did. This suggests normalization of the risk of developing SUDs in the stimulant treatment group, but not in the no-stimulant group. As outlined above, possibly, stimulant treatment may protect against SUDs by decreasing the core symptoms of ADHD (e.g. impulsivity) and associated problems (e.g. poor self-esteem,

school failure, academic or occupational failure) that may lead to drug and alcohol use (11). Although our results show a less robust protective effect of stimulant therapy on the development of SUDs (HR: 2.12) than indicated by an earlier meta-analysis by Wilens et al (33) (HR: 5.8), our findings are of great clinical significance. The present study shows that stimulant-treated participants are twice less likely to develop SUDs than participants that did not receive stimulant treatment.

Interestingly, previous studies have shown that the protective effect of stimulant treatment on the development of SUDs is much stronger in adolescence (4, 12-13) than in adulthood (14-15). This might mean that SUD development is delayed rather than being altered by stimulant treatment. The present study reports on an adolescent sample (mean age=16.4), and we can therefore not draw firm conclusions about the effect of stimulant therapy on SUDs in adulthood. We did find, however, that the protective effect of age of first stimulant use was only true for children up to 18, and that the risk of developing SUDs may even reverse around the age of 18 (Fig.2). Apart from the direct effect of stimulant medication on the development of SUDs, an alternative explanation of our findings is possible. Participants who start stimulant medication early might have greater parental support, however, this parental support may diminish once the individual reaches adulthood. Indeed, parental support has been found to be inversely related to substance use in a large sample of high school students (34). Clearly, future studies are warranted to assess whether parental support mediates the protective effect of stimulant therapy on the development of SUDs.

While we did find a protective effect of stimulant use on the development of SUDs, such a protective effect was not found on the development of nicotine dependence. This is in accordance with another study that also failed to find a protective effect of stimulant use on nicotine dependence, but did find a protective effect on SUDs (35). Other studies did find protective effects on smoking initiation and regular smoking (e.g., 13, 17, 36), but these

studies did not look at nicotine dependence. These findings suggest that stimulant therapy does have a protective effect on the early stages (initiating and regular smoking) of nicotine dependence, while there is no effect on later stage of full onset nicotine dependence. However, due to the relatively low number of subjects with nicotine dependence in our sample (7%), caution should be taken when interpreting the null findings concerning nicotine dependence. Overall, the relationships between ADHD and related externalizing disorder, and nicotine dependence and substance use appear to be complex. ADHD is associated with earlier initiation of smoking and higher rate of regular smoking, and longitudinal twin modeling indicates that the covariance between ADHD and smoking is foremost due to common environmental risk factors (37). Covariance between smoking and substance use was due to both additive genetic and common environmental influences. Further, about half of the covariance between externalizing disorders and substance use was due to shared genetic and half due to shared environmental factors (37). According to the gateway theory, smoking precedes use of substances in many cases (38). However, in a minority of cases, evidence for a reverse gateway is found in that marihuana users had a higher risk for subsequent tobacco use (38). Future prospective studies on the specific trajectories from first nicotine use to nicotine dependency, in ADHD medication treated and medication naïve patients, are warranted to further elucidate the effects of stimulant treatment on the development of nicotine dependence.

Our findings should be viewed in the light of some limitations. First of all, our study design is naturalistic and non-randomized. This makes it impossible to control for all possible confounding factors. The best method of determining the effect of stimulant medication on the development of SUDs and nicotine dependence would be a randomized controlled trial. However, due to practical and ethical issues such studies are not feasible. The current study design makes it difficult to draw conclusions on causality and one should be cautious in

interpreting the results. Second, participating participants were of Caucasian descent, which limits the possibility to generalize our results to other ethnicities. Furthermore, we did not have clinicians make diagnostic judgments but used multiple measures and multiple informants to assess substance and nicotine use and abuse. This approach might have influenced our estimates of the prevalence. Finally and importantly, our no-stimulant treated ADHD group was relatively small compared to the stimulant-treated group, which may have reduced the power of our analyses or the generalizability of our results.

Despite these limitations, our large sample of well-defined participants with ADHD provided us with a unique opportunity to examine the relationship between treatment with stimulant medication and SUDs and nicotine dependence in a large European sample. This study adds two important insights to the available literature. First, we found that the elevated risk of drug- and alcohol-related SUDs and nicotine dependence in ADHD could not be attributed to the use of stimulant medication. Stimulant treatment has a protective effect on the development of drug- and alcohol-related SUDs. Furthermore, we showed that early age of stimulant treatment initiation had a protective effect on the development of SUDs, but that this effect appears to reverse after the age of 18.

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Table 1. Subject characteristics.

	No ADHD	ADHD				
	Healthy Controls (*n*= 211)	No-Stimulant Treatment (*n*= 61)	Stimulant Treatment (*n*= 327)	Test-value	*p*-Value	Contrasts
Gender (n males (%))	90 (41.50)	36 (58.06)	278 (85.00)	X^2=113.03	<.001	H<N<S
Age	16.31 (2.49)	16.57 (2.78)	16.42 (2.34)	*F*=.30	.74	H=N=S
IQ	105.55 (9.60)	101.85 (16.03)	100.02 (13.68)	*F*=11.84	<.001	H=N, N=S, H>S
ADHD Symptom Count	-	14.58 (3.27)	15.88 (2.00)	*F*=15.67	<.001	N<S
ODD (%)	-	15 (30.60)	120 (40)	χ^2=1.57	.21	N=S
CD (%)	-	7 (14.30)	64(21.40)	χ^2=1.31	.25	N=S

Note. N = No Stimulant Treatment, S = Stimulant Treatment, H = Healthy controls, IQ= Intelligence Quotient.

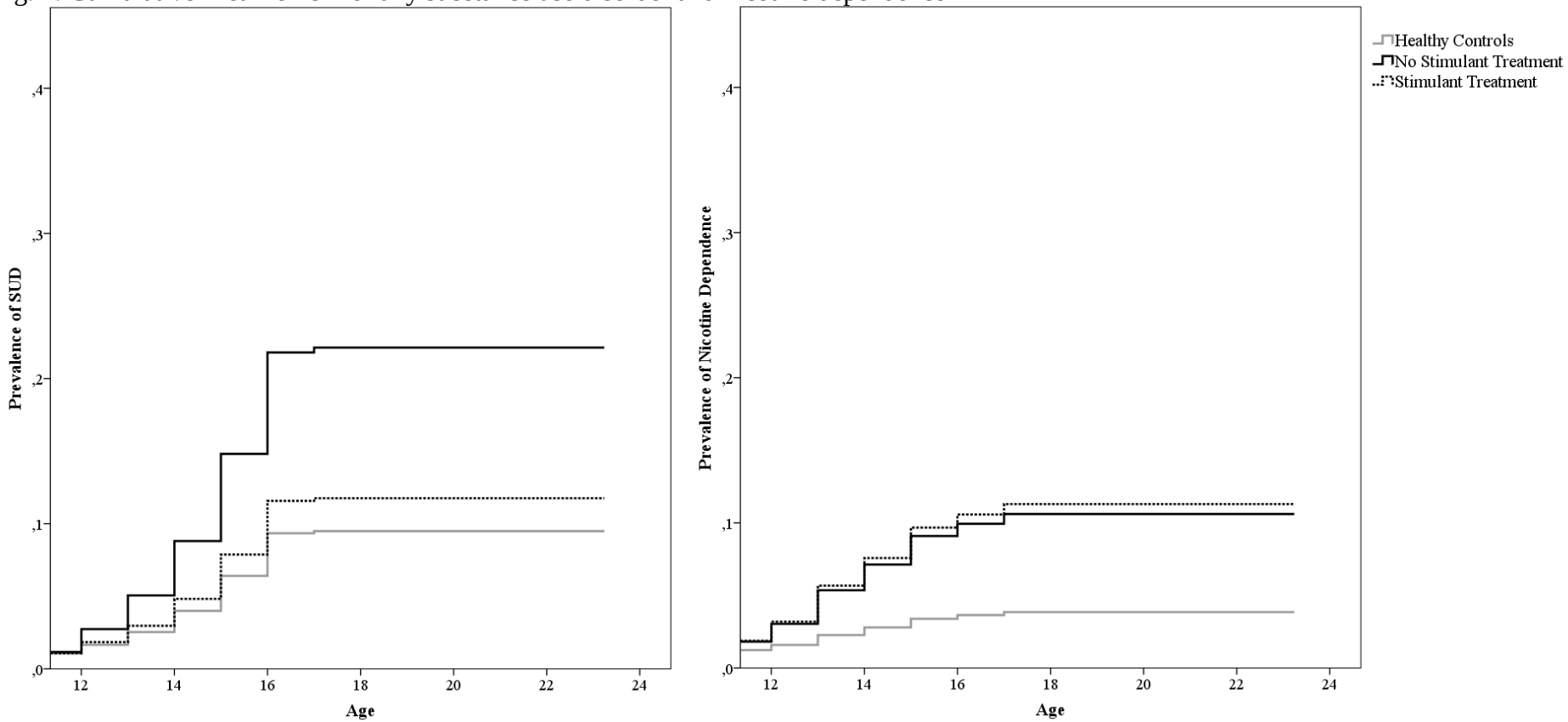
Table 2. Prevalence rates of substance use disorders and nicotine dependence in participants with ADHD with and without a history of stimulant therapy, and healthy controls.

	Prevalence Rates					
	Healthy Controls (*n* = 211)		No-Stimulant Treatment (*n* = 61)		Stimulant Treatment (*n* = 327)	
	n	%	*n*	%	*n*	%
Substance Use Disorders	26	12.3	17	27.9	65	19.9
Nicotine Dependence	6	2.8	6	9.8	30	9.2

	Hazard Ratios					
	No-Stimulant Treatment v. Healthy Controls		No-Stimulant Treatment v. Stimulant Treatment		Stimulant Treatment v. Healthy Controls	
	HR	95% CI	HR	95% CI	HR	95% CI
Substance Use Disorder	2.60*	1.35-4.99	2.00*	1.11-3.63	1.30	.76-2.22
Nicotine Dependence	3.83*	1.11-13.28	1.07	.44-2.61	3.56*	1.28-9.88

Note: Hazard Ratios were calculated using Cox proportional hazard regression. All comparisons were corrected for gender and current age. HR: Hazard Ratio. 95% CI: Confidence Interval.
* Significant at p<.05

Fig. 1: Cumulative lifetime risk for any substance use disorder and nicotine dependence



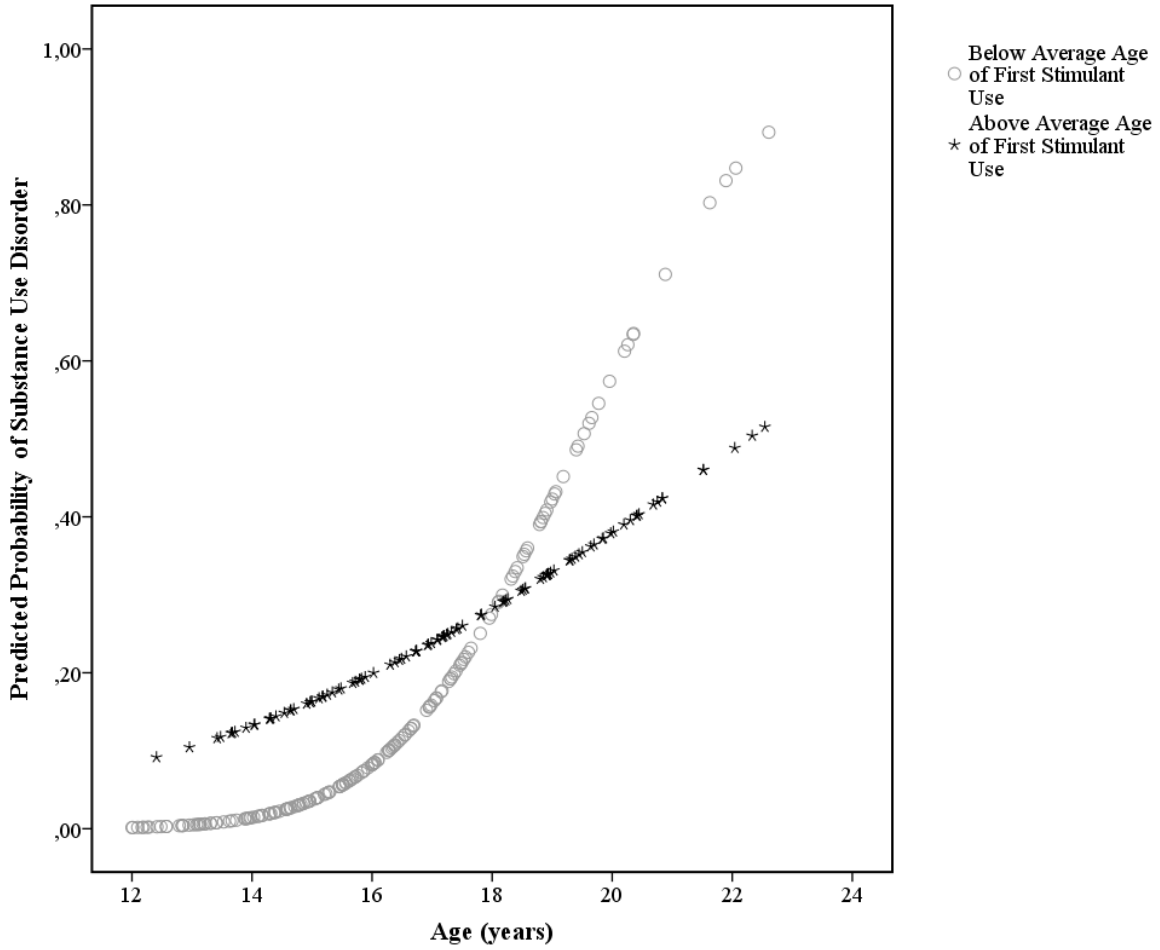
Note; Survival curves were calculated using Cox proportional hazard regression. All comparisons were corrected for gender and current age.
SUD: Substance use disorder

Table 3. Bivariate correlations and univariate outcomes of possible predictors for substance use disorder and nicotine dependence

	Current Age	Age First Stimulant	Current Use	ODD$_a$	Gender$_a$	CD$_a$	Treatment Delay	Age-Adjusted Duration	Age-Adjusted Cumulative Dosage	ADHD Symptom count	SUD		Nicotine Dependence	
											Wald χ^2	*p*-value	Wald χ^2	*p*-value
Current Age	1	.40*	.17*	-0.01	-.01	-0.03	.35*	14*	-.12*	-.19*	57.19	<.001	15.88	<.001
Age First Stimulant		1	.14*	0.01	.11	-0.04	.83*	60*	-.37*	-.22*	7.49	.006	10.07	0.002
Current Use			1	0.06	-.13*	.16*	.14*	52*	-.03	0.04	5.45	0.02	3.37	0.07
ODD$_a$				1	-.04	-.38*	0.07	08	-.03	0.01	4.78	0.03	0.15	0.70
Gender$_a$					1	-.12*	0.09	14	-.24*	-.23*	2.82	0.09	0.07	0.79
CD$_a$						1	-0.05	.02	0.01	-.23*	1.57	0.21	0.53	0.47
Treatment Delay							1	64*	-.42*	-.07	7.07	0.008	11.90	.001
Age-Adjusted Duration									.68*	.17*	.83	0.31	5.67	0.02
Age-Adjusted Cumulative Dosage									1	.19*	.14	0.70	0.27	0.61
ADHD Symptom count										1	0.14	0.74	0.86	0.35

Note. Correlations were calculated using Pearson correlation coefficient except for: $_a$Correlations calculated using Spearman Rank Correlation
* Significant at p<.05

Fig.2. Predicted probability of substance use disorders within stimulant-treated participants with ADHD



Note; Predicted probability of substance use disorder according to GEE model, that included age, gender, and age of first stimulant use age*age of first stimulant use. Below average age of first stimulant use; participants started before age 8.1 years, above average age of first stimulant use; participants started after age 8.1 years.