Substance Use Disorders in Adolescents with Attention Deficit Hyperactivity Disorder: A Four-Year Follow-up Study

Annabeth P. Groenman [1, 2], Jaap Oosterlaan [2], Nanda J. Rommelse [2], Barbara Franke [2], Herbert Roeyers [3], Robert D. Oades [4], Joseph A. Sergeant [1], Jan K. Buitelaar [2], Stephen V. Faraone [8]

1 VU University Amsterdam, Department of Clinical Neuropsychology, Amsterdam, The Netherlands;

2 Radboud University Nijmegen Medical Centre, Donders Institute for Brain, Cognition and Behavior, Department of Cognitive Neuroscience, Nijmegen, The Netherlands;

3 Ghent University, Department of Experimental Clinical Health Psychology, Ghent, Belgium;

4 University Clinic for Child and Adolescent Psychiatry, Biopsychology Group, Essen, Germany;

5 SUNY Upstate Medical University, Department of Psychiatry and Behavioral Sciences, Syracuse, USA.

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ABSTRACT

Aim: To examine the relationship between a childhood diagnosis of ADHD with or without ODD/CD and the development of later alcohol/drug use disorder (psychoactive substance use disorder(PSUD)) and nicotine dependence in a large European sample of ADHD probands, their siblings and healthy control subjects.

Participants, Design, Setting: Subjects (n=1017) were part of the Belgian, Dutch and German part of the International Multicenter ADHD Genetics (IMAGE) study. IMAGE families were identified through ADHD probands aged 5-15 years attending outpatient clinics, and control subjects from the same geographic areas. After a follow-up period (m: 4.4 years) this subsample was reassessed at a mean age of 16.4 years.

Measurements: PSUD and nicotine dependence were assessed using the Diagnostic Interview Schedule for Children, Alcohol Use Disorders Identification Test, Drug Abuse Screening Test, and Fagerström test for Nicotine Dependence.

Findings: The ADHD sample was at higher risk of developing (Hazard Ratio (HR) = 1.77, 95%CI= 1.05-3.00) and nicotine dependence (HR = 8.61, 95% CI = 2.44-30.34) than healthy controls. The rates of these disorders were highest for ADHD youth who also had conduct disorder, but could not be accounted for by this comorbidity. We did not find an increased risk of developing PSUD (HR = 1.18, 95% CI = .62-2.27) or nicotine dependence (HR = 1.89, 95% CI = .46-7.77) among unaffected siblings of ADHD youth.

Conclusions: A childhood diagnosis of attention deficit hyperactivity disorder is a risk factor for psychoactive substance use disorder and nicotine dependence in adolescence and comorbid conduct disorder, but not oppositional defiant disorder, further increases the risk of developing psychoactive substance use disorder and nicotine dependence.

Keywords: Age of onset, attention deficit hyperactivity disorder, conduct disorder, familial association, nicotine dependence, oppositional defiant disorder, psychoactive substance use disorder.

Studies of alcohol abusers report the prevalence of ADHD in this population to range between 35 and 71 per cent, while studies of substance dependent populations report the prevalence of ADHD to range between 15 and 25 per cent (1). For example, Schubiner et al. (2) found that 24% of 201 adult inpatients in a substance abuse treatment facility had ADHD. Levin et al. (3) found that 10% of cocaine dependent adults met strict criteria for ADHD. The prevalence rates of ADHD are much lower in the general population (e.g. 5.3% in youth (4) and 3-5% in adulthood (5-7) than in substance-dependent subjects.

Considering the high prevalence of ADHD among substance users, ADHD might be more common among adolescents and young adults who later develop psychoactive substance use disorder (PSUD; alcohol and/or drug use disorder) than among those who will not develop PSUD. This hypothesis is supported by a recent meta-analysis, which showed that adolescents with ADHD are at a 1.35 times increased risk of developing an alcohol use disorder, a 2.36 times increased risk for nicotine use and a 3.48 times increased risk for non-alcohol drug use disorder (for meta-analysis, see 8). Whilst this meta-analysis incorporated studies of North American origin, a very large European population-based study confirmed these results recently [9], showing that symptoms of ADHD are predictive of later substance use.

Several studies have shown that conduct disorder (CD) and oppositional defiant disorder (ODD) play an important role in the later development of PSUD [10–13]. For example, August et al. [13] showed that only subjects with comorbid externalizing disorders (n = 82) had significantly higher rates of PSUD and regular tobacco use compared to both ADHD-only (n = 27) and healthy control subjects (n = 91).While some studies suggest that the increased risk for developing PSUDs that is seen in ADHD could be explained completely by comorbid CD/ODD in this group (for a review, see [14]), other studies could not confirm this [11,15]. Whereas these studies underline the importance of examining the relationship between PSUD and comorbid CD and ODD in ADHD, most studies used a combined measure of CD and ODD. Loeber et al. [16] concluded that CD and ODD are distinct syndromes, which indicates the need to consider these two disorders separately. The one study that made this distinction [11] found that comorbid CD increased the risk for developing PSUD, while ADHD with comorbid ODD did not. This issue therefore deserves further investigation.

Family studies of ADHD document an association between ADHD and PSUD in the family members of children with ADHD. Higher rates of alcoholism were found in the adult siblings of adult ADHD probands compared to the siblings of psychiatric controls [17]. Similar findings have been obtained in two large double-blind family genetic studies of female and male ADHD probands [18, 19], in which higher rates of PSUD in the relatives of ADHD probands were reported compared to relatives of comparison subjects without ADHD. Taken together, these findings suggest that ADHD and PSUD may share familial causes. All these studies, however, included relatives of ADHD probands, regardless of their ADHD status, making it difficult to disentangle common environmental effects from the effects of ADHD.

This study describes a 4-year follow-up of a large sample of western European origin of well-defined childhood

diagnosed probands with ADHD and both their affected and unaffected siblings. This study uses multiple informants for ADHD, PSUD and nicotine dependence diagnoses. The aim of the present study was to assess (i) the prevalence and age of onset of PSUD and nicotine dependence in a large sample of ADHD probands followed-up in early to late adolescence, (ii) the effects of an additional childhood diagnosis of ADHD–comorbid ODD or CD on developing PSUD and nicotine dependence in ADHD probands and (iii) the familial risk of PSUD and nicotine dependence in unaffected siblings of ADHD probands.

Method

Subjects

Subjects participating in this study were part of the Belgian, Dutch and German International Multicenter ADHD Genetics (IMAGE) study [20]. IMAGE families were identified through ADHD probands aged 5–17 years attending out-patient clinics at the data collection sites between 2003 and 2006. For each ADHD proband, at least one available sibling was recruited. Siblings were not required to have ADHD, but a diagnosis of ADHD was not used as an exclusion criterion. Family members were of European Caucasian 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 behaviours that might mimic ADHD. Additional healthy control participants were recruited from primary and high schools from the same geographical regions as the participating ADHD families.

Probands, siblings and healthy control subjects were assessed at baseline and re-invited to participate in a follow-up study 4.4 years [standard deviation (SD) = 0.71] on average after study entry. A total of 1017 (85.3% of original sample) children and adolescents above the age of 12years participated in the follow-up (also see Table 1 at end of article). A total of 63 participants participated at the Belgian site, 36 at the German site and 915 at the Dutch site. At baseline, no significant differences were found between those followed-up successfully and those lost to follow-up on age and gender (all P-values > 0.05). At baseline, no differences were found among ADHD participants followed-up and those lost to follow-up on ADHD severity, CD and ODD (all P-values > 0.05). Ethical approval for the study was obtained from the National Institute of Health registered ethical review boards for each centre. After a complete description of the study, written informed consent was obtained from parents and children.

ADHD , ODD and CD diagnoses

In ADHD families both probands and siblings were screened similarly, using the standard procedures of the IMAGE project, described fully elsewhere [20]. Briefly, baseline measures included the long version of Conners' Parent (CPRS-R:L) and Teacher Rating Scales (CTRS-R:L [21]), used to identify and quantify ADHD symptoms; t-scores ≥ 63 on the Conners' ADHD subscales (L, M and N) were considered clinical. Healthy control subjects were required to not have a clinical score on these measures. A full description of measures and the algorithm used is provided in Box 1.

Follow-up Measures

A parental report of PSUDs was obtained using the SUD module of the Diagnostic Interview Schedule for Children (DISC-IV-P [22]). The DISC-IV-P was administered by telephone and scored with a computer algorithm to derive

Box 1

Detailed description of International Multicenter ADHD Genetics (IMAGE) diagnostic measures and Algorithm

Baseline measures included the Parental Account of Childhood Symptoms (PACS [43]) interview. The PACS is a semi-structured, standardized, investigator-based interview developed to provide an objective measure of child behaviour. A trained interviewer administered the PACS to parents, who were asked for detailed descriptions of their child's typical behaviour in a range of specified situations (for an exact description of the interview procedure, we refer to [20]). These included the long version of Conners' Parent (CPRS-R:L) and Teacher Rating Scale (CTRS-R:L [21]). A standardized algorithm was applied to the PACS to derive each of the 18 DSM-IV attention deficit hyperactive disorder (ADHD) symptoms, providing operational definitions for each behavioural symptom. These were combined with items that were scored 2 (pretty much true) or 3 (very much true) in the teacher-rated Conners ADHD subscales (L, M and N) to generate the total number of hyperactive–impulsive and
inattentive symptoms of the DSM-IV symptom list [44]. A standardized algorithm was applied to combine symptom count on the PACS and CTRS-R: L, both providing operational definitions of each of the 18 behavioural symptoms defined by the DSM-IV. Situational pervasiveness was defined as symptoms occurring within two or more different situations as assessed with the PACS interview, as well as the presence of one or more items that scored 2 or higher, or more, from the ADHD scale of the CTRS-R: L (for a full description of the algorithm procedure also see [45]). The PACS sections dealing with disruptive behaviour [oppositional defiant disorder (ODD) and conduct disorder (CD)] are structured similarly to the ADHD section, except that symptoms are not evaluated across multiple situations. The PACS assesses all DSM-IV [44] ODD and CD symptoms. Symptom ratings were dichotomized with absence of a symptom coded as 0 and presence of symptom as 1, and then summed separately for ODD and CD symptoms. Two categorical measures of disruptive behavior encompassing ODD and CD were defined. The first measure defined ODD according to the DSM-IV criteria based on information from the PACS and the CPRS-R: L. The second measure defined CD according to the DSM-IV criteria using a standardized algorithm applied to the PACS. Subjects with ODD were not allowed to score positive for CD, while subjects with CD were allowed to score positive for ODD. In addition to the interview, rating scales were used to quantify ADHD and ODD severity.

DSM-IV-defined SUD diagnoses. Age of first substance use was also assessed in the interview. A number of questionnaires was completed by participants. The Alcohol Use Disorders Identification Test (AUDIT [23]) was used to identify self-reported alcohol dependence. Scores on the AUDIT may range from 0 to 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 [23]. The Drug Abuse screening Test–20 (DAST; [24]) was used to assess drug use disorders. Scores on this questionnaire may range from 0 to 20. A cut-off of 5 was used to identify possible drug use disorders [24]. The Fagerström test nicotine dependence. Scores on this questionnaire may vary between 0 and 10. A cut-off of 6 was used to identify nicotine dependence [25]. Age of first nicotine use was also assessed in this questionnaire. All participants were provided with a personal return envelope to increase trust, and to ensure confidentiality of sensitive information.

A best-estimate diagnosis of PSUD was considered present if either alcohol or drug use disorder was present in the subject. A best-estimate diagnosis of alcohol use disorder was considered present if either scores on the AUDIT (self-report) or DISC-IV-P alcohol module (parent report) met criteria stated above. A best-estimate diagnosis of drug use disorder was considered present if either the DAST (self-report) or DISC-IV-P marihuana module or other drugs module (parent report) met criteria stated above. Nicotine dependence was considered present if scores on either the FTND (self-report) or the tobacco module of the DISC-IV-P (parent report) met the criteria stated above.

Statistical analyses

All analyses were conducted using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). In the present analyses, probands with ADHD as well as affected siblings were included in the ADHD group. Three groups were used in the analyses: subjects diagnosed with ADHD at baseline, their unaffected siblings and healthy control subjects. Analyses of variance (ANOVAs) were performed to assess whether groups differed on IQ at baseline, age at follow-up, follow-up interval and t-scores on the oppositional scales of the CTRS-R: L. A Kruskal–Wallis test assessed whether groups differed in the proportion of males.

To investigate whether the risk of developing PSUD and nicotine dependence differed between the groups, Cox proportional hazard models were fitted. Correction for clustered (family) data was performed using robust standard errors [26]. The models used age of first substance use as the survival time for the cases and current age as the time of censoring for the non-cases.

When an increased risk of developing PSUD or nicotine dependence was observed, we explored whether or not this was related to ADHD, ODD or CD, using Cox proportional hazard models. The effects of ODD and CD were analysed separately. To assess the effect of childhood ODD and CD on the risk of developing PSUD, the sample was divided into four groups: healthy controls, ADHD subjects without ODD or CD (the ADHD-only group), ADHD subjects with ODD and ADHD subjects with CD. Of 47 of the 511 ADHD subjects, data were missing regarding the presence of absence of ODD/CD and consequently these cases were omitted from the analyses.

Linear regression models were fitted using general estimation equations (GEE [27]) to assess the effects of a childhood diagnosis of ADHD, ODD or CD on age of first substance use. GEE is a method that takes into account clustered data in family studies. Correction for family dependency was performed using family number as repeated measure. We used the Holm sequential Bonferroni method [28] to correct for multiple testing.

RESULTS

Demographics

Table 1 (end of article) describes demographic and clinical features of the three groups [top panel; ADHD (n = 511), unaffected siblings (n = 286) and healthy control subjects (n = 220)]. At baseline, 176 of the ADHD subjects met criteria for ODD and 91 subjects met criteria for CD. Four unaffected siblings were diagnosed with having ODD; none had CD. None of the healthy control subjects met criteria for ODD or CD. There were small but statistically significant group differences in current age, follow-up interval, gender and IQ. The lower panel of Table 1 displays the demographic and clinical features of the ADHD-only, ADHD + ODD, ADHD + CD and healthy control group. These groups did not differ in current age; however, significant group differences were found

in follow-up interval, IQ, ODD severity and gender. All subsequent analyses were adjusted statistically for current age, gender and follow-up interval.

Risk for PSUD and nicotine dependence in ADHD

Adolescents with a childhood ADHD diagnosis were 1.8 times more likely to develop a PSUD and 8.6 times more likely to develop nicotine dependence compared to healthy controls. Interestingly, unaffected siblings were not at increased risk of developing a PSUD or nicotine dependence compared to healthy controls. Unaffected siblings were 2.9 times less likely to develop nicotine dependence compared to their ADHD siblings, while they did not differ in the risk of developing a PSUD (also see Table 2 end of article).

Risk for PSUD and nicotine dependence in ODD and CD

An increased risk of developing a PSUD was found for the group with comorbid ADHD + CD [hazard ratio (HR) = 2.45, 95% confidence interval (CI): 1.17–5.19] and for the ADHD-only group (HR = 2.02, 95% CI: 1.07–3.83) compared to healthy controls. Interestingly, the comorbid ADHD + ODD group was not at increased risk of developing a PSUD compared to healthy control the ADHD-only group, the comorbid ADHD + CD group was not at increased risk of developing PSUD (HR = 1.20, 95% CI: 0.78–2.07), while the comorbid ADHD + ODD group was at decreased risk of developing a PSUD (HR = 0.53, 95% CI: 0.311–0.91); however, this did not remain significant after correction for multiple comparisons (see left panel, Fig. 1 below).

The risk for developing nicotine dependence was increased in the comorbid ADHD + CD group (HR = 13.96, 95% CI: 2.89–67.49), the comorbid ADHD + ODD group (HR = 8.36, 95% CI: 1.78–39.30) and the ADHD-only group compared to healthy controls (HR = 6.58, 95% CI: 1.50–28.96). The comorbid ADHD + ODD group did not have an increased risk for developing nicotine dependence compared to the ADHD-only group (HR = 1.33, 95% CI: 0.68–2.62), while the comorbid ADHD + CD group did have an increased risk (HR = 2.22, 95% CI: 1.09–4.53) (see right panel, Fig. 1 below).

All analyses were re-run with the ADHD-only group and healthy controls to check whether or not increased levels of ODD severity in the ADHD-only group are at the base of the increased risk for PSUD and nicotine dependence that was found. After correction for ODD severity, the ADHD-only group remained at increased risk of developing nicotine dependence (HR = 6.64, 95% CI: 1.40–31.425) but not, however, for developing a PSUD (HR = 1.67, 95% CI: 0.83–3.35).

Age of onset

Participants with a childhood ADHD diagnosis had a younger age of first substance use (B = -0.525, Wald $\chi 2$ = 7.035, P = 0.008) and nicotine use (B = -1.631, Wald $\chi 2$ = 36.768, P < 0.001) compared to healthy controls. Unaffected siblings were younger at commencement of nicotine use (B = -0.762, Wald $\chi 2$ = 6.940, P = 0.008) compared to healthy controls, but not in terms of age of first substance use (B = 0.158, Wald $\chi 2$ = 0.949, P = 0.330).

Analyses that focused on the effect of ODD and CD on the age of first substance use revealed a younger age of first use was found for the comorbid ADHD + CD (B = -0.905, Wald $\chi 2$ = 10.551, P = 0.001) and the ADHD-only group (B = -1.398, Wald $\chi 2$ = 17.453, P < 0.001) compared to healthy controls. The finding of a younger age of first substance use in the comorbid ADHD + ODD group did not

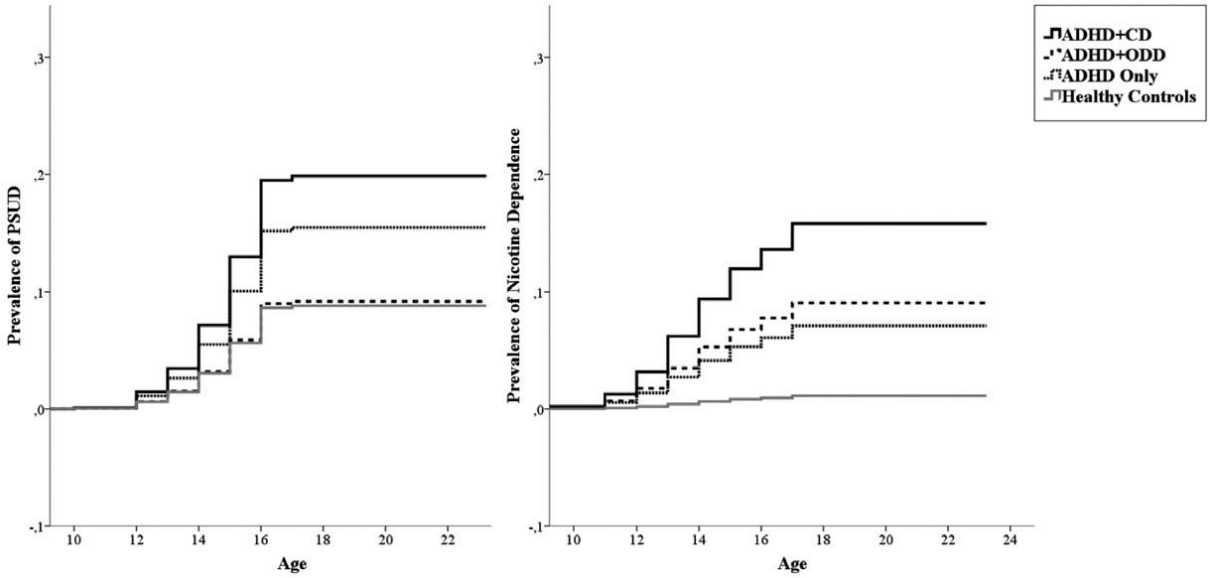

Figure 1 Cumulative life-time risk for any psychoactive substance use disorder and nicotine dependence. All comparisons were corrected for gender and follow-up interval. Unaffected siblings were omitted from the analyses because only four subjects met criteria for oppositional defiant disorder (ODD). ADHD= attention deficit hyperactivity disorder; CD= conduct disorder

survive correction for multiple comparisons (uncorrected: B = -0.473, Wald $\chi 2$ 4.584, P = 0.032). The ADHD + ODD and ADHD + CD groups did not have a younger age of first substance use compared to the ADHD-only group (B = 0.165, Wald $\chi 2$ = 0.630, P = 0.427 and B = -0.432, Wald $\chi 2$ = 2.994, P = 0.084, respectively).

Analyses focusing on the effect of ODD and CD for the age of first nicotine use revealed a younger age of first use in the comorbid ADHD + CD group (B = -2.147, Wald $\chi 2$ = 29.786, P < 0.001), the comorbid ADHD + ODD group (B = -1.398, Wald $\chi 2$ = 17.453, P < 0.001) and the ADHD-only group (B = -1.767, Wald $\chi 2$ = 22.785, P < 0.001) compared to healthy controls. Compared to the ADHD-only group, age of first nicotine use was not different in the comorbid ADHD + CD and the comorbid ADHD + ODD groups (B = -0.380, Wald $\chi 2$ = 0.887, P = 0.346 and B = 0.368, Wald $\chi 2$ = 1.100, P = 0.294, respectively).

DISCUSSION

This 4-year follow-up study of ADHD adolescents confirms previous reports indicating that childhood ADHD is a risk factor for the subsequent development of PSUD and nicotine dependence [8,29]. At a mean age of approximately 16 years our ADHD sample, compared with healthy controls, showed a higher prevalence of PSUD as well as nicotine dependence. We did not find an increased risk for unaffected siblings of developing PSUD or nicotine dependence. Our results do not confirm previous studies suggesting that the increased risk of developing nicotine dependence, which is seen in ADHD, could be accounted for completely by comorbid CD [30]. Interestingly, we observed that subjects with comorbid ADHD + ODD did not demonstrate an increased risk for developing PSUD or nicotine dependence compared to healthy controls, while the ADHD-only group did. The risk of developing either PSUD or nicotine dependence were largest for the comorbid ADHD + CD group.

Several studies have shown that youth who smoke cigarettes have an increased risk for alcohol and drug use disorders

[31]. The high risk of smoking among ADHD youth suggests that our sample is at high risk for future alcohol and drug use disorders. In one study [32], cigarette smokers were more likely to use illegal drugs subsequently, compared with non-smokers. Another study reported that smoking a pack of cigarettes per day increased the risk for illicit drug use by 10–30 times [33]. A recent study found similar results in subjects with ADHD [34]. This suggests that nicotine use can be seen as a gateway to other drugs in typically developing children and in subjects with ADHD.

The existing literature is inconsistent concerning the role of CD in later development of PSUD in adolescents with ADHD. While some studies yield supportive evidence (e.g. [13]), most fail to demonstrate that ADHD without comorbid CD does not increase risk for the development of PSUD and nicotine dependence (e.g. [11]). Our results confirm the latter studies in that, in the absence of CD, youth with ADHD are still at increased risk of PSUD and nicotine dependence compared to healthy control subjects. However, the increased risk for developing PSUD in the ADHD-only group compared to the healthy control group disappeared after correction for ODD severity. In the current study, we demonstrate that subjects with a childhood diagnosis of ADHD with comorbid CD are at much higher risk of developing PSUD and nicotine dependence compared to ADHD subjects without CD. We replicate the findings of Biederman et al. [11], that CD is a risk factor for the development of PSUD in ADHD, although this risk is not observed in this study for ODD. While ADHD subjects with ODD were at increased risk for developing nicotine dependence compared to healthy control subjects, their risk was not increased compared to the ADHD-only subjects. Although ODD is a risk factor for developing CD, some evidence suggests that CD is more likely to persist into adolescence than ODD (10.8 versus 32.5% [35]); possibly, only a current ODD/CD diagnosis is a risk factor for PSUD. Unfortunately, to our knowledge, no studies have examined the effect of persistence of ODD or CD on the later development of PSUD. Consistent with previous research [12,36], we showed that subjects with ADHD and ADHD + CD have an earlier age of first substance use. To our knowledge, this is the first study to show that subjects with a childhood ADHD + ODD diagnosis do not start using substances at a younger age compared to healthy control subjects.

Previous family studies of ADHD have shown that ADHD and PSUD co-aggregate in families [37–39]. In contrast to these findings, we did not find an increased prevalence of PSUD and nicotine dependence among the unaffected siblings of our ADHD probands. The failure to find support for this hypothesis cannot be attributed to a lack of power, because we had a relatively large sample of unaffected siblings (n = 286). The lack of difference may be explained by the selection procedure that was used for unaffected siblings, as previous studies assessed the prevalence of PSUD in siblings regardless of the presence or absence of ADHD [40]. Importantly, this could indicate that ADHD itself, and not shared family environment, are responsible for the increased risk of adolescents with ADHD of developing PSUD or nicotine dependence. However, another possible reason for the failure to replicate elevated risk for siblings is their main age of approximately 17 years, which could mean that many participants in our study did not pass the ages of highest risk for substance use disorders. Indeed, despite the lack of statistically significant differences, it is notable that

for all comparisons (Table 2 end of article), the hazard ratios comparing siblings to healthy controls were greater than 1.0. Future studies should follow-up subjects with childhood diagnosed ADHD at later ages to elucidate this important issue.

Our results should be considered in the context of some methodological limitations. Our sample included only Caucasian youth. Because our ADHD probands were referred for ADHD, and at initial inclusion into the study all had combined-type ADHD, we cannot generalize our findings to community samples of adolescents with ADHD. However, our results—which are based mainly on participants with combined subtype ADHD, show a striking resemblance to the results found in community-based samples—which, typically, include more subjects with the inattentive type of ADHD (e.g. [13]). A possible explanation is that symptoms of inattention are predictive of later PSUD [12, 41, 42]. Furthermore, the current ADHD sample had a much larger proportion of males than the unaffected siblings and healthy control subjects. Although we corrected for gender, the gender composition of our sample might have affected the results. Parent report of age of first psychoactive substance use was used in our analyses, possibly causing an overestimation of age of first substance use. However, a reporting bias between parents of ADHD subjects and controls seems unlikely, and it is not expected that this has affected our results. Finally, we used adult cut-off scores for the self-report questionnaires. Although this approach would not have biased results to finding spurious case–control differences, it may have influenced our estimates of prevalence.

Despite these limitations, we add to current knowledge on three levels. First, we have provided further evidence that ADHD is a risk factor for PSUD and nicotine dependence, and that ADHD accelerates the onset of these disorders. Furthermore, we found that ADHD with comorbid CD, but not ODD, further increases the risk of developing PSUD, but subjects with ADHD without comorbidities are still at increased risk. No evidence was found that this increased risk of developing PSUD and nicotine dependence in participants with ADHD is due to familial risk factors shared by the unaffected siblings, i.e. genes and/or the common environment.

Declarations of interest

J.O. has been on the advisory board of Shire and UCB Pharmaceuticals. He has received an unrestricted grant from Shire. H.R. is a member of an Advisory Board to Shire and has received research funding and conference attendance support from Shire and Eli Lilly. R.D.O. has received research funding and conference attendance support from Shire. J.A.S. is a member of advisory board of Shire and Eli Lilly, has received a research grant from Lilly and speaker fees from Shire, Lilly, Janssen-Cilag and Novartis. In the past 3 years, J.K.B. has been a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly, Bristol-Myer Squibb, Schering Plough, UCB, Shire, Novartis and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents or royalties. In the past year, S.V.F. received consulting income and/or research support from Shire, Otsuka and Alcobra and research support from the National Institutes of Health (NIH). In previous years, he has received consulting fees or was on Advisory Boards or participated in continuing medical education programmes sponsored by: Shire, McNeil, Janssen, Novartis, Pfizer and Eli

Lilly. S.V.F. receives royalties from books published by Guilford Press: Straight Talk about Your Child's Mental Health and Oxford University Press: Schizophrenia: The Facts. A.P.G., N.R. and B.F. have no conflicts of interest to declare.

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References

1. Wilens T. E. AOD use and attention deficit/hyperactivity disorder. Alcohol Health Res World 1998; 22: 127–30.
2. Schubiner H., Tzelepis A., Milberger S., Lockhart N., Kruger M., Kelley B. J. et al. Prevalence of attention-deficit/hyper-activity disorder and conduct disorder among substance abusers. J Clin Psychiatry 2000; 61: 244–51.
3. Levin F. R., Evans S. M., Kleber H. D. Prevalence of adult attention-deficit hyperactivity disorder among cocaine abusers seeking treatment. Drug Alcohol Depend 1998; 52: 15–25.
4. Polanczyk G., de Lima M. S., Horta B. L., Biederman J., Rohde L. A. The worldwide prevalence of ADHD: a systematic review and meta-regression analysis. Am J Psychiatry 2007; 164: 942–8.
5. Faraone S. V., Biederman J. What is the prevalence of adult ADHD? Results of a population screen of 966 adults. J Atten Disord 2005; 9: 384–91.
6. Kessler R. C., Adler L., Barkley R., Biederman J., Conners C. K., Demler O. et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry 2006; 163: 716–23.
7. Fayyad J., De Graaf R., Kessler R., Alonso J., Angermeyer M., Demyttenaere K. et al. Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. Br J Psychiatry 2007; 190: 402–9.
8. Charach A., Yeung E., Climans T., Lillie E. Childhood attention-deficit/hyper-activity disorder and future substance use disorders: comparative meta-analyses. J Am Acad Child Adolesc Psychiatry 2011; 50: 9–21.
9. Sihvola E., Rose R. J., Dick D. M., Korhonen T., Pulkkinen L., Raevuori A. et al. Prospective relationships of ADHD symptoms with developing substance use in a population derived sample. Psychol Med 2011; 41: 1–9.
10. Mannuzza S., Klein R. G., Bessler A., Malloy P., LaPadula M. Adult outcome of hyperactive boys. Educational achievement, occupational rank, and psychiatric status. Arch Gen Psychiatry 1993; 50: 565–76.
11. Biederman J., Wilens T., Mick E., Faraone S. V., Weber W., Curtis S. et al. Is ADHD a risk factor for psychoactive substance use disorders? Findings from a four-year prospective follow-up study. J Am Acad Child Adolesc Psychiatry 1997; 36: 21–9.
12. Molina B. S., Pelham W. E. Jr. Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. J Abnorm Psychol 2003; 112: 497–507.
13. August G. J., Winters K. C., Realmuto G. M., Fahnhorst T., Botzet A., Lee S. Prospective study of adolescent drug use among community samples of ADHD and non-ADHD participants. J Am Acad Child Adolesc Psychiatry 2006; 45: 824–32.
14. Flory K., Lynam D. R. The relation between attention deficit hyperactivity disorder and substance abuse: what role does conduct disorder play? Clin Child Fam Psychol Rev 2003; 6: 1–16.
15. Szobot C. M., Rohde L. A., Bukstein O., Molina B. S., Martins C., Ruaro P. et al.

Is attention-deficit/hyperactivity disorder associated with illicit substance use disorders in male adolescents? A community-based case–control study. Addiction 2007; 102: 1122–30.
16. Loeber R., Burke J. D., Lahey B. B., Winters A., Zera M. Oppositional defiant and conduct disorder: a review of the past 10 years, part I. J Am Acad Child Adolesc Psychiatry 2000; 39: 1468–84.
17. Manshadi M., Lippmann S., O'Daniel R. G., Blackman A. Alcohol abuse and attention deficit disorder. J Clin Psychiatry 1983; 44: 379–80.
18. Faraone S. V., Biederman J., Keenan K., Tsuang M. T. A family-genetic study of girls with DSM-III attention deficit disorder. Am J Psychiatry 1991; 148: 112–7.
19. Faraone S. V., Biederman J., Mick E., Williamson S., Wilens T., Spencer T. et al. Family study of girls with attention deficit hyperactivity disorder. Am J Psychiatry 2000; 157: 1077–83.
20. Brookes K., Xu X., Chen W., Zhou K., Neale B., Lowe N. et al. The analysis of 51 genes in DSM-IV combined type attention deficit hyperactivity disorder: association signals in DRD4, DAT1 and 16 other genes. Mol Psychiatry 2006; 11: 934–53.
21. Conners C. K., Sitarenios G., Parker J. D., Epstein J. N. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. J Abnorm Child Psychol 1998; 26: 257–68.
22. Shaffer D., Fisher P., Lucas C. P., Dulcan M. K., Schwab-Stone M. E. NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. J Am Acad Child Adolesc Psychiatry 2000; 39: 28–38.
23. Saunders J. B., Aasland O. G., Babor T. F., de la Fuente J. R., Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption—II. Addiction 1993; 88: 791–804.
24. Gavin D. R., Ross H. E., Skinner H. A. Diagnostic validity of the drug abuse screening test in the assessment of DSM-III drug disorders. Br J Addict 1989; 84: 301–7.
25. Heatherton T. F., Kozlowski L. T., Frecker R. C., Fagerstrom K. O. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict 1991; 86: 1119–27.
26. Huber P. J. The behavior of maximum likelihood estimates under non-standard conditions. In: Le Cam L. M., Neyman J. editors. Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability. Berkeley, CA: University of California Press; 1967, p. 221–233.
27. Norton E. C., Bieler G. S., Ennett S. T., Zarkin G. A. Analysis of prevention program effectiveness with clustered data using generalized estimating equations. J Consult Clin Psychol 1996; 64: 919–26.
28. Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat 1979; 6: 65–70.
29. Lee S. S., Humphreys K. L., Flor K., Liu R., Glass K. Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. Clin Psychol Rev 2011; 31: 328–341.
30. Brook D. W., Brook J. S., Zhang C., Koppel J. Association between attention-deficit/hyperactivity disorder in adolescence and substance use disorders in adulthood. Arch Pediatr Adolesc Med 2010; 164: 930–4.
31. Merrill J. C., Kleber H. D., Shwartz M., Liu H., Lewis S. R. Cigarettes, alcohol, marijuana, other risk behaviors, and American youth. Drug Alcohol Depend 1999; 56: 205–12.

32. Lai S., Lai H., Page J. B., McCoy C. B. The association between cigarette smoking and drug abuse in the United States. J Addict Dis 2000; 19: 11–24.
33. Torabi M. R., BaileyW. J., Majd-Jabbari M. Cigarette smoking as a predictor of alcohol and other drug use by children and adolescents: evidence of the 'gateway drug effect'. J School Health 1993; 63: 302–6.
34. Biederman J., Petty C. R., Hammerness P., Batchelder H., Faraone S. V. Cigarette smoking as a risk factor for other substance misuse: 10-year study of individuals with and without attention-deficit hyperactivity disorder. Br J Psychiatry 2012; 201: 207–14.
35. Biederman J., Petty C. R., Dolan C., Hughes S., Mick E., Monuteaux M. C. et al. The long-term longitudinal course of oppositional defiant disorder and conduct disorder in ADHD boys: findings from a controlled 10-year prospective longitudinal follow-up study. Psychol Med 2008; 38: 1027–36.
36. Katusic S. K., Barbaresi W. J., Colligan R. C., Weaver A. L., Leibson C. L., Jacobsen S. J. Psychostimulant treatment and risk for substance abuse among young adults with a history of attention-deficit/hyperactivity disorder: a population based birth cohort study. J Child Adolesc Psychopharmacol 2005; 15: 764–76.
37. Morrison J. R., Stewart M. A. A family study of the hyperactive child syndrome. Biol Psychiatry 1971; 3: 189–95.
38. Cantwell D. P. Psychiatric illness in the families of hyperactive children. Arch Gen Psychiatry 1972; 27: 414–7.
39. Faraone S. V., Adamson J. J., Wilens T. E., Monuteaux M. C., Biederman J. Familial transmission of derived phenotypes for molecular genetic studies of substance use disorders. Drug Alcohol Depend 2008; 92: 100–7.
40. Faraone S. V., Biederman J., Monuteaux M. C. Attention deficit disorder and conduct disorder in girls: evidence for a familial subtype. Biol Psychiatry 2000; 48: 21–9.
41. Burke J. D., Loeber R., Lahey B. B. Which aspects of ADHD are associated with tobacco use in early adolescence?, J Child Psychol Psychiatry 2001; 42: 493–502.
42. Pingault J. B., Cote S. M., Galera C., Genolini C., Falissard B., Vitaro F. et al. Childhood trajectories of inattention, hyperactivity and oppositional behavior and prediction of substance abuse/ dependence: a 15-year longitudinal population-based study. Mol Psychiatry 2012; DOI: 10.1038/mp.2012.87.
43. Chen W., Taylor E. Parental Account of Children's Symptoms (PACS), ADHD phenotypes and its application to molecular genetic studies. In: Oades R. D. editor. Attention-Deficit/Hyperactivity Disorder and the Hyperkinetic Syndrome: Current Ideas and Ways Forward. Hauppauge, NY: Nova Science Publishing Inc; 2006, p. 3–20.
44. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.
45. Rommelse N. N. J., Oosterlaan J., Buitelaar J., Faraone S. V., Sergeant J. A. Time reproduction in children with ADHD and their non-affected siblings. J Am Acad Child Adolesc Psychiatry 2007; 46: 582–90.

Table 1 Subject characteristics

	ADHD		*Unaffected siblings*		*Healthy controls*				
	n = 511		*n = 286*		*n = 220*				
	mean	*SD*	*mean*	*SD*	*mean*	*SD*	*F*	*p*	
Age (min–max)	16.4 (12.0–22.6)	2.4	16.9 (12.1–24.4)	3.3	16.4 (12.2–23.2)	2.5	3.4	0.033	U > A = HC
% Male	80.0	–	45.1	–	40.5	–	149.8**a**	<0.001	A > U = HC
Estim. full-scale IQ	100.0	14.1	102.8	13.5	105.6	9.5	13.7	<0.001	A < U = HC
Follow-up interval (ys)	4.58	0.56	4.54	0.49	3.71	0.78	173.96	<0.001	HC < A = U
ADHD diagnosis at baseline									
Inattentive	44		–	–	–	–			
Hyperact./impuls.	18		–	–	–	–			
Combined	446		–	–	–	–			

	ADHD only		*ADHD–ODD*		*ADHD–CD*		*Healthy controls*				
	n = 197		*n = 176*		*n = 91*		*n = 220*				
	mean	*SD*	*mean*	*SD*	*mean*	*SD*	*mean*	*SD*	*F*	*p*	
Age (range)	16.55 (12.1–22.6)	2.50	16.49 (12–22.3)	2.35	16.46 (12.1–22.5)	2.56	16.36 (12.2–23.2)	2.52	0.25	0.87	A = O = CD = HC
% Male	75.6	–	83.0	–	89.0	–	40.0	–	120.76**a**	<0.001	HC < A = O > CD
Estim. full-scale IQ	101.33	14.15	98.73	14.50	99.13	12.32	105.58	9.49	10.69	<0.001	A = O = CD < HC
Follow-up interval (ys)	4.64	0.54	4.59	0.53	4.53	0.59	3.71	0.78	97.81	<0.001	A = O < CD < HC
t-Score oppositional scale CTRS-R:L at baseline	60.56	13.11	61.68	13.30	66.90	13.64	48.72	6.66	73.04	<0.001	HC < A = O < CD

Group comparisons were performed using Tukey's test when variances were equal, otherwise Dunnett's T3 was used. A = attention deficit hyperactivity disorder (ADHD) group; U = unaffected siblings; HC = healthy controls; ODD,
O = oppositional defiant disorder; CD = conduct disorder; SD = standard deviation; CTRS = Conners' Teacher Rating Scale. a = $\chi 2$.

Table 2: Prevalence rates of psychoactive substance use disorder and nicotine dependence in adolescents with attention deficit hyperactivity disorder (ADHD), their unaffected siblings and healthy controls.

	Prevalence rates						*Hazard ratios*					
	ADHD *N = 511*		*Unaffected Siblings* *n = 286*		*Healthy controls* *n = 220*		*ADHD versus healthy controls*		*Unaffected siblings versus ADHD*		*Unaffected siblings versus healthy controls*	
	n	*%*	*n*	*%*	*n*	*%*	*HR*	*95% CI*	*HR*	*95% CI*	*HR*	*95% CI*
Psychoactive substance use disorder	103	20.2	41	14.4	26	11.8	1.77*	1.05–3.00	0.76	0.51–1.15	1.18	0.62–2.27
Nicotine dependence	50	9.8	12	4.2	6	2.7	8.61*	2.44–30.34	0.35*	0.16–0.76	1.89	0.46–7.77

Hazard ratios (HR) were calculated using Cox proportional hazard regression. All comparisons were corrected for gender and follow-up interval in years. 95% CI: 95% confidence interval. *Significant at $P < 0.05$.