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ORIGINAL ARTICLE

Childhood trajectories of inattention, hyperactivity and oppositional behaviors and prediction of substance abuse/dependence: a 15-year longitudinal population-based study

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Numerous prospective studies have shown that children diagnosed with attention deficit/hyperactivity disorder (ADHD) are at higher risk of long-term substance abuse/dependence. However, there are three important limits to these studies: (a) most did not differentiate the role of hyperactivity and inattention; (b) most did not control for associated behavioral problems; and (c) most did not consider females. Our aim was to clarify the unique and interactive contributions of childhood inattention and hyperactivity symptoms to early adulthood substance abuse/dependence. Behavioral problems of 1803 participants (814 males) in a population-based longitudinal study were assessed yearly between 6 and 12 years by mothers and teachers. The prevalence of substance abuse/dependence at age 21 years was 30.7% for nicotine, 13.4% for alcohol, 9.1% for cannabis and 2.0% for cocaine. The significant predictors of nicotine dependence were inattention (odds ratio (OR): 2.25; 95% confidence interval (CI): 1.63–3.11) and opposition (OR: 1.65; 95%: 1.20–2.28). Only opposition contributed to the prediction of cannabis dependence (OR: 2.33; 95% CI: 1.40–3.87) and cocaine dependence (OR: 2.97; 95% CI: 1.06–8.57). The best behavioral predictor of alcohol abuse/dependence (opposition) was only marginally significant (OR: 1.38; 95% CI: 0.98–1.95). Frequent oppositional behaviors during elementary school were clearly the most pervasive predictors of substance abuse/dependence in early adulthood. The association of childhood ADHD with substance abuse/dependence is largely attributable to its association with opposition problems during childhood. However, inattention remained an important predictor of nicotine dependence, in line with genetic and molecular commonalities between the two phenotypes suggested in the literature.

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INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) has been shown to predict many long-term negative outcomes,[1–5] including substance abuse/dependence.[6,7] However, past research suffers from several shortcomings that limit our understanding of the specific role of ADHD symptoms. Of interest is whether inattention and/or hyperactivity symptoms are responsible for the association between ADHD and substance abuse/dependence, and if this association remains significant after controlling for other behavioral problems. We address these and other questions in a large population-based sample of boys and girls followed between the ages of 6 and 21 years.

In a recent meta-analytic review[6] including 13 prospective studies of participants diagnosed with ADHD in childhood and followed after age 18 years, ADHD children were found to be at higher risk of alcohol, cannabis, nicotine and drug use disorder (non-alcohol). Not all of these results were robust to meta-analysis control procedures (for example, removing one study and re-estimating the effect). In another recent meta-analysis[7] including 27 prospective studies assessing substance disorders in adolescence and adulthood, childhood ADHD prospectively predicted adolescent/adult nicotine, alcohol, cannabis and cocaine use disorders (that is, abuse or dependence). Analyses were more robust to meta-analysis control procedures. Thus, there is solid evidence to demonstrate that children diagnosed with ADHD are at higher risk of long-term substance disorders. However, a number of conceptual and methodological problems in previous studies limit the conclusions that can be drawn about the unique role of inattention and hyperactivity symptoms as predictors of substance abuse/dependence.

First, few studies distinguished between inattention and hyperactivity symptoms.[7,8] This distinction appears essential as the two dimensions of ADHD can make specific contributions depending on the substance outcome.[9,10] For instance, it has been suggested that inattention symptoms play a specific role in the prediction of nicotine dependence. On the basis of the genetic and molecular commonalities between nicotine use and hyperactivity (that is, dopaminergic and nicotinic-acetylcholinergic circuits), some authors hypothesized that nicotine use may help the self-regulation of inattention.[7,10,11] Second, few studies have adequately controlled for other externalizing problems,[7] which have also been found to predict substance abuse/dependence. In

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studies that did control for the co-occurrence of other externalizing problems, the unique predictive contribution of ADHD symptoms was less evident.[7] Consequently, it has been suggested that the role of ADHD symptoms in the prediction of substance abuse/dependence has been overstated.[8] In addition, the few studies accounting for the comorbidity of other externalizing problems mostly considered conduct disorder, overlooking the putative role of opposition. Yet, opposition appears to be an important possible confounder as its prevalence is higher and mostly stable in childhood, in particular for girls.[12] Furthermore, ADHD seems more strongly linked with oppositional than with conduct disorder symptoms.[12] Third, it has also been suggested that ADHD symptoms act as a trigger to early onset of substance abuse,[7,10] and more studies are needed to verify this possibility. Fourth, most studies were conducted with clinically based samples and few included girls. Thus, studies with population-based samples are needed to verify whether the findings hold true in the general population and are similar for boys and girls.[8,11,13] Fifth, there is considerable evidence to show that ADHD symptoms are continuously distributed in the population,[14] the same being true for substance abuse/dependence.[7] Diagnoses, compared to dimensional measures, might lead to underestimate the association between ADHD symptoms and substance abuse/dependence symptoms.[10] Finally, the role of moderators must be considered because they may diminish (for example, anxiety) or exacerbate (for example, opposition) the role of ADHD symptoms in the prediction of substance abuse/dependence.[13,15,16]

Two studies have tackled some of these issues. The Minnesota Twin Family Study followed[13] a population-based sample of 1512 children from 11 to 18 years and showed that hyperactivity/impulsivity symptoms predicted most substance abuse/dependence outcomes. Inattention did not contribute except possibly for nicotine dependence. The Christchurch Health and Development Study[15] followed a cohort of 1265 children from 7 to 25 years and found that attentional problems (including hyperactivity) did not predict most substance abuse/dependence outcomes after adjustment for externalizing behaviors, anxiety and adversity. Therefore, whereas the first study found a prominent role for hyperactivity/impulsivity, this was not the case for the second study. Several aspects of these two studies may explain the discrepant findings. First, in adolescence, rates of substance abuse/dependence have not yet reached their peak,[10] and only the Christchurch study followed the children until adulthood. Furthermore, the Christchurch study controlled for more variables—anxiety, adversity as well as a measure of externalizing behaviors that included opposition. However, the Christchurch study did not distinguish between inattention and hyperactivity symptoms, which may have prevented the detection of associations.

In this study, we followed longitudinally a population-based sample of male and female participants from 6 years to early adulthood to verify: (1) whether inattention and hyperactivity symptoms differentially predict substance abuse/dependence diagnoses; age at onset of first symptom; and a dimensional measure of substance abuse/dependence (that is, count of lifetime symptoms); (2) whether these predictions are independent from oppositional behaviors, anxiety and adversity; and (3) whether these relationships are moderated by sex or levels of oppositional or anxious behaviors.

METHOD

Participants

The 1803 participants (814 males) belonged to a large cohort of kindergarten children in Quebec's French-speaking public schools (Canada) who were first assessed in 1986–1987 (for details, see Zoccolillo *et al.*[17] and Vitaro *et al.*[18]). For this study, we selected 1803 participants who had a valid diagnosis of substance abuse/dependence in early adulthood. To characterize the present sample, we compared it to a sample of 2000 (1001 males) children belonging to the same cohort and who were selected to be representative of kindergarten children Quebec's French-speaking public schools (Canada).[19] Table 1 presents the characteristics of the two samples: no significant difference was found on initial socioeconomic characteristics (for example, income, education, intact families). Children did not differ on several behavioral characteristics (anxiety, teachers' rated inattention). Small significant differences (Cohen $d < 0.20$) were noted for mothers' rated inattention and for hyperactive and oppositional behaviors, more frequent in the study sample. The percentage of male subjects was also lower in this study (45.1%) than in the representative sample (50.1%). Overall, the study sample was highly similar to the representative sample of the initial cohort.

Table 1. Comparison of the study sample and the representative sample

	Study sample (N = *1803*)		*Representative sample* (N = *2000*)		*Cohen d (or Phi)*
	Mean (or %)	*s.d.*	*Mean (or %)*	*s.d.*	
Maternal socioeconomic status	44.25	12.90	43.99	13.00	0.02
Paternal socioeconomic status	44.75	14.63	43.92	14.86	0.05
Maternal education	12.08	2.59	11.95	2.59	0.05
Paternal education	12.27	3.41	12.15	3.44	0.04
Intact family	16.70	—	16.24	—	0.01
Maternal age first child	24.60	3.94	24.58	3.87	0.00
Paternal age first child	26.80	4.11	26.92	4.04	−0.03
Overall family adversity index	0.27	0.25	0.28	0.25	−0.02
Inattention (teacher, 6 years)	1.85	1.31	1.83	1.28	0.01
Hyperactivity (teacher, 6 years)	1.02	1.31	0.91	1.28	0.09*
Opposition (teacher, 6 years)	1.83	2.31	1.41	2.04	0.19**
Anxiety/depressive symptoms (teacher, 6 years)	1.74	2.03	1.75	2.01	0.00
Inattention (mother, 6 years)	2.58	1.34	2.42	1.31	0.12***
Hyperactivity (mother, 6 years)	1.81	1.34	1.64	1.31	0.13**
Opposition (mother, 6 years)	3.45	1.89	3.11	1.81	0.18**
Anxiety/depressive symptoms (mother, 6 years)	3.47	2.01	3.38	2.01	0.04
Sex of the child	45.1	—	50.1	—	0.05*

Note: The table presents a comparison between the study sample and a sample from the same cohort ($N = 2000$), which was selected to be representative of the Kindergarten children in Quebec. Phi coefficients are proposed instead of Cohen *d* for the variables: intact family; sex of the child.
*$P < 0.01$; **$P < 0.001$; ***$P < 0.05$.

Measures

Substance abuse/dependence. To assess abuse/dependence, we used the Diagnostic Interview Schedule, based on the DSM-III-R criteria.[20,21] The interview took place when participants were aged between 19 and 23 years (mean = 20.88; s.d. = 0.85). Regarding diagnosis, the absence of abuse/dependence was coded 0, and the presence of either abuse, mild, moderate or severe dependence was coded 1. The count of lifetime symptoms was also available. Finally, for each diagnosis, participants were asked their age at onset of first symptom.

Behaviors. Children were rated by teachers using the Social Behavior Questionnaire (SBQ)[22] each year between kindergarten and sixth grade, providing seven assessment points from the age of 6–12 years (in Quebec, at this age, a teacher teaches only at one level so that the assessments were made by a different teacher each year). Mothers also rated children with the SBQ each year. The SBQ is based on the Children's Behavior Questionnaire[23] and the Preschool Behavior Questionnaire,[24] which both demonstrated good psychometric properties, which was also true for the SBQ.[22] Each item of the SBQ was rated from 0 to 2 ('never applies' to 'frequently applies'). Four items assessed inattention: (1) weak capacity for concentration; (2) easily distracted; (3) absentmindedness; and (4) gives up easily (Cronbach's α's for the seven assessments ranged between 0.84 and 0.90 for teachers and between 0.71 and 0.81 for mothers). Hyperactivity was assessed with two items: (1) restless, runs about or jumps up and down, does not keep still; and (2) squirmy, fidgety child (α's for the seven assessments ranged between 0.83 and 0.88 for teachers and between 0.76 and 0.79 for mothers). For the past 5 years (8–12 years), three additional items were available to assess hyperactivity/impulsivity, which we used in sensitivity analyses restricted to this period. These additional items were: (3) jumps from one activity to another; (4) shouts to draw attention; and (5) acts without thinking (α's for the five items of hyperactivity/impulsivity ranged between 0.82 and 0.86 for teachers; 0.75 and 0.76 for mothers). Opposition included five items available at all ages: (1) irritable, quick to 'fly off the handle'; (2) is disobedient; (3) doesn't share toys; (4) blames others; and (5) inconsiderate of others (α's between 0.80 and 0.85 for teachers; 0.63 and 0.69 for mothers). Anxiety-depressive symptoms consisted of five items available at all ages: (a) Is worried. Worries about many things; (b) tends to do things on his own, rather solitary; (c) appears miserable, unhappy, tearful or distressed; (d) tends to be fearful or afraid of new things or new situations; and (e) cries easily (α's between 0.72 and 0.76 for teachers; 0.58 and 0.66 for mothers).

Family adversity index. The index was based on information collected at the start of the study when the children were finishing kindergarten. The index was created by averaging the following indices: (1) family structure (intact or not intact); (2) parents' levels of education; (3) parents' occupational status;[25] and (4) parents' age at the birth of the first child. Families at or below the 30th percentile for each of these indices (or a non-intact family) were coded as having 1 adversity point. The family adversity score ranges from 0 to 1.

Data analysis

Trajectories. To take into account the richness of the seven-yearly teachers' and mothers' ratings of behavioral problems, we utilized developmental trajectory analyses. We estimated trajectories of inattention, hyperactivity, opposition and anxiety/depressive symptoms using *k*-means for longitudinal data.[26] In this procedure, participants who are homogeneous in their behavioral evolution are assigned to a given trajectory. In this study, we employed a three-dimensional version of this procedure to estimate joint trajectories that relied on the repeated assessments of both teachers and mothers. This procedure is original as it provides developmental trajectories of each behavior (for example, inattention) relying on two types of informants instead of one; mental health data from multiple informants is considered more valid than data from a single informant.[27]

Prediction of substance abuse/dependence. We utilized a logistic regression to examine the predictive links between the trajectories and diagnoses of abuse/dependence. Survival models (Cox regression[28]) were used to examine the behavioral trajectories as predictors of age at first symptom. We used the diagnosis as the survival binary variable and age at first symptom as the time variable.

Missing data and complementary analyses. All children but five had at least one teacher's and one mother's assessment for each of the four behavioral dimensions and were included in the estimation of the trajectories.[26] The five children were removed. Of the remaining children, 82 (4.6%) had missing data for the family adversity index. We conducted a single imputation of the index missing values by utilizing the constituent variables of the index as well as behavioral characteristics of the child at age 6 years as assessed by teachers and mothers (later behaviors and adult data were not used in the imputation).[29]

To test whether the results were sensitive to the statistical techniques we utilized, we averaged the behavioral scores over 5 years (8–12 years) instead of using trajectories. We conducted these analyses separately with mothers' and teachers' ratings and used assessments of hyperactivity/impulsivity (with the five items available between 8 and 12 years). We estimated two-way interactions between all variables included in the model. Given the number of interactions tested for each substance abuse/dependence model (6 variables, 15 two-ways interactions), we calculated false discovery rates.[30] Finally, we wanted to ascertain whether childhood behaviors were predictive of the severity of substance abuse/dependence. Therefore, we modeled the count of lifetime symptoms using hurdle regression models,[31] which are detailed in the online material.

RESULTS

Behavioral trajectories

Percentages of participants in each trajectory are presented in Table 2 (first column). We provide an online file that allows the reader to explore the three-dimensional trajectories in a dynamic manner (see Supplementary Figure 1). Of interest is the fact that 17.9% of children had high levels of hyperactivity as assessed by both mothers and teachers. However, 30.8% children were rated almost as highly hyperactive by mothers than the previous group, but manifested almost no hyperactivity according to teachers' ratings. This discrepancy in ratings is interesting as it shows that children in this group are found hyperactive only by mothers. A similar group was observed for both oppositional and anxiety/depressive behaviors, whereas it was not the case for inattention.

Prediction of substance abuse/dependence

A total of 30.7% of the participants reported nicotine dependence (mild, moderate or severe); 13.4% of the participants reported alcohol abuse or dependence (mild, moderate or severe). Cannabis abuse or dependence (mild, moderate or severe) affected 9.1% of the participants. Regarding other illicit drug use, only cocaine was used by at least 1% of the participants. Consequently, we restricted the analyses to cocaine abuse/dependence (2.0%).

We report the predictive values of the trajectories in Table 2. Regarding nicotine dependence, inattention was an important predictor. Children in the high (odds ratio (OR): 2.25; 95% confidence interval (CI): 1.63–3.11) and medium (OR: 1.78; 95% CI: 1.37–2.32) trajectories of inattention were at a higher risk of nicotine dependence. Opposition trajectories were, to a smaller extent, also significantly associated with nicotine dependence. Hyperactivity trajectories did not contribute.

For cannabis, only opposition trajectories made a significant contribution (high trajectory, OR: 2.33; 95% CI: 1.40–3.87). Interestingly, children rated as oppositional by mothers only were also at higher risk of cannabis abuse/dependence (OR: 2.01; 95% CI: 1.33–3.05). Regarding cocaine, only the high trajectory of opposition made a significant contribution (OR: 2.97; 95% CI: 1.06–8.57). Finally, for alcohol, only one of the opposition trajectories—children rated

Table 2. Prediction of substance abuse/dependence diagnoses with behavioral trajectories

	Nicotine		*Cannabis*		*Cocaine*		*Alcohol*	
	OR	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Inattention trajectories								
Low[a] (41.4%)[b]								
Medium (33.0%)	1.78*	1.37–2.32	0.84	0.55–1.27	1.18	0.48–3.07	0.91	0.63–1.29
High (25.7%)	2.25*	1.63–3.11	0.72	0.43–1.19	0.80	0.26–2.46	0.93	0.61–1.43
Hyperactivity trajectories								
Low (51.3%)								
High mother only (30.8%)	0.81†	0.63–1.03	0.95	0.64–1.42	1.22	0.51–2.91	0.98	0.70–1.37
High (17.9%)	0.74†	0.53–1.04	1.08	0.64–1.81	1.62	0.57–4.65	0.98	0.62–1.52
Opposition trajectories								
Low (48.0%)								
High mother only (32.3%)	1.33**	1.03–1.71	2.01*	1.33–3.05	1.88	0.75–4.89	1.38†	0.98–1.95
High (19.7%)	1.65***	1.20–2.28	2.33***	1.40–3.87	2.97**	1.06–8.57	1.43	0.93–2.19
Anxiety trajectories								
Low (50.3%)								
High mother only (28.9%)	0.93	0.73–1.19	0.85	0.57–1.25	0.89	0.38–2.04	0.81	0.58–1.13
High (20.8%)	0.76†	0.57–1.01	0.73	0.45–1.17	1.27	0.53–2.96	0.72	0.48–1.06
Adversity	1.66**	1.11–2.49	0.73	0.37–1.4	5.28***	1.60–17.1	1.22	0.70–2.11
Sex	0.77**	0.62–0.96	2.11*	1.49–3.00	0.74	0.36–1.51	2.30*	1.71–3.09

Note: The table presents odds ratios (OR) and 95% confidence intervals (CI) from logistic regressions. Behavioral trajectories relying on mothers' and teachers' assessments were used to predict diagnoses of substance abuse/dependence. Analyses were conducted on the 1798 participants with data for behavioral trajectories and diagnoses.
[a]Low trajectories are the contrast.
[b]The percentages in this column correspond to the number of participants in each trajectory. The sum is 100% for each behavior.
*$P<0.001$; **$P<0.05$; ***$P<0.01$; †$P<0.10$.

high only by mothers—made a contribution that was marginally significant (OR: 1.38; 95% CI: 0.98–1.95). As relative merits of ORs and risk ratios are debated,[32] we also present risk ratios (see online comments and Supplementary Table 1) along with percentages of substance abuse/dependence in each trajectory.

Survival models' results are reported in Table 3. Inattention trajectories were predictive of nicotine dependence. Figure 1 illustrates the adjusted contribution of inattention to age at onset of first symptoms from early adolescence to early adulthood for girls. The contributions of hyperactivity and opposition trajectories were also very similar to their contributions estimated from logistic regressions.

Complementary analyses

Analyses with average means of behaviors instead of trajectories yielded very similar results overall (see online comments and Supplementary Table 2). To summarize, mothers' and teachers' ratings of inattention were still predictive of nicotine dependence. The use of the five items measure of hyperactivity/impulsivity did not change the fact that this dimension was never predictive. Mother-rated opposition significantly predicted most outcomes, whereas teacher-rated opposition was less predictive.

We tested two-way interactions between all variables included in the model, using average means of behaviors. Very few interactions were significant: accepting even only one interaction in each substance abuse/dependence model would have yielded unacceptably high false discovery rate (superior to 0.10 in most models). Furthermore, the few significant interactions between behavioral variables were negative, contrary to the hypothesis of a synergic effect but coherent with results from a previous study.[15] Regarding sex, very few interactions were significant with the exception of a negative interaction with opposition in the prediction of alcohol abuse/dependence, suggesting that opposition was a significant predictor for women and not for men.

Finally, we modeled the count of lifetime symptoms with hurdle models (see comments and Supplementary Tables 3 and 4). To summarize, inattention predicted not only the absence/presence of symptom(s), but also the count of lifetime symptoms, suggesting that inattention predicts the severity of nicotine dependence. In these analyses, opposition appeared as a predictor of the count of symptoms in the case of cannabis and alcohol abuse/dependence. Anxiety/depressive symptoms appeared as a protective factor against the presence of symptom(s) in the case of nicotine, cannabis and alcohol.

DISCUSSION

The aim of this study was to clarify the contributions of inattention and hyperactivity symptoms to early adulthood substance abuse/dependence, net of possible confounders and in combination with possible moderators. In particular, we wanted to verify whether inattention and hyperactivity symptoms played a different role depending on the type of substance; whether that role was maintained when opposition, anxiety and adversity were controlled for; and whether interactive effects with sex, family adversity and with other behavioral dimensions could be detected. We found that oppositional behaviors were the most pervasive predictors of substance abuse/dependence, that is, for nicotine, cannabis, cocaine and alcohol. However, for the latter outcome, the results were less consistent across analyses. Inattention was an important predictor of the diagnosis of nicotine abuse/dependence as well as its severity assessed by the number of lifetime symptoms. Hyperactivity did not predict any outcome nor did it predict age at onset of first symptom. We found no consistent interactive effects.

The results of this study are coherent with studies casting doubt on the real contribution of ADHD symptoms to later substance abuse/dependence when comorbid externalizing behaviors are

Table 3. Survival models of abuse/dependence

	Nicotine		*Cannabis*		*Cocaine*		*Alcohol*	
	HR	*95% CI*	*HR*	*95% CI*	*HR*	*95% CI*	*HR*	*95% CI*
Inattention trajectories								
Medium	1.61*	1.30–2.01	0.85	0.57–1.27	1.18	0.47–2.94	0.90	0.65–1.25
High	1.94*	1.49–2.51	0.74	0.46–1.2	0.82	0.27–2.44	0.92	0.62–1.36
Hyperactivity trajectories								
High mother only	0.83†	0.68–1.02	0.95	0.65–1.39	1.23	0.53–2.86	0.98	0.72–1.34
High	0.81	0.62–1.06	1.07	0.66–1.73	1.60	0.57–4.47	0.97	0.65–1.46
Opposition trajectories								
High mother only	1.24**	1.01–1.52	1.96*	1.32–2.9	1.86	0.74–4.66	1.35†	0.99–1.86
High	1.47***	1.14–1.88	2.21***	1.37–3.57	2.92**	1.05–8.14	1.39	0.94–2.06
Anxiety trajectories								
High mother only	0.94	0.77–1.15	0.86	0.6–1.24	0.90	0.39–2.05	0.82	0.60–1.11
High	0.81†	0.65–1.02	0.74	0.47–1.17	1.25	0.54–2.87	0.73	0.51–1.06
Adversity	1.36†	0.98–1.89	0.72	0.38–1.36	5.1***	1.61–16.17	1.23	0.74–2.02
Sex	0.78***	0.65–0.93	2.01*	1.44–2.8	0.74	0.37–1.50	2.15*	1.63–2.83

Note: The table presents hazard ratios (HR) and 95% confidence interval (CI) from Cox models. The time variable is the age at first symptom for each outcome as reported by the young adult at the time of diagnosis. Analyses were conducted on the 1798 participants with data for behavioral trajectories and diagnosis. *$P<0.001$; **$P<0.05$; ***$P<0.01$; $^{\dagger}P<0.10$.

controlled for.[7,8,15] Fergusson *et al*.[15] and Fergusson and Horwood[33] proposed a dual-pathway model where attentional problems contribute to academic achievement, whereas conduct problems contribute to substance abuse/dependence and criminality. In their model, crossed contributions (for example, contributions of attentional problems to substance abuse) are viewed as a collateral effect of their comorbidity with other externalizing problems and, therefore, spurious. In their model, each of the two childhood behavioral dimension (that is, attentional problems and disruptive behaviors) has its own specific consequences on adult outcomes.[15,19,33,34] Our study partially supports this model as hyperactivity and inattention did not contribute to most substance outcomes when opposition and other control variables were taken into account.

Nevertheless, some studies have reported a contribution of inattention and/or hyperactivity symptoms to substance abuse/dependence even after controlling for conduct disorders. In particular, the Minnesota Twin Family Study,[13] a large population-based prospective study reported that hyperactivity/impulsivity symptoms predicted most substance abuse/dependence outcomes in adolescence even after controlling for conduct disorders. However, the Minnesota Twin Family Study had less control variables (that is, adversity and anxiety) than this study and controlled for conduct disorder, which may represent a less stringent control than opposition because it is less frequent during childhood, in particular for girls.[12] Thus, some significant contributions reported in the literature may have come from insufficient control for comorbid behaviors as well as adversity. Furthermore, even in the Minnesota Twin Family Study, the contribution of hyperactivity/impulsivity symptoms to adult substance-use disorders was smaller than the contribution of conduct disorders. Overall, we are tempted to share Looby's concern that the role of ADHD symptoms in the development of substance-use disorders has been overstated.[8]

Albeit true for most outcomes, the previous statement is not supported in the case of nicotine dependence. Indeed, we found a solid association of inattention symptoms with nicotine dependence. Such an association has been reported in the literature,[7,10,11] and our study offers a confirmation of this association in a 15-year prospective study of a population-based sample of boys and girls followed into early adulthood. Furthermore, we demonstrated that inattention symptoms were associated not only with the presence of nicotine dependence, but also with the severity of this dependence as assessed by the number of lifetime symptoms. People with inattention symptoms may initiate smoking to alleviate symptoms of inattention as well as to improve executive functions and working memory.[10,13,35] This mitigation of impairing symptoms by nicotine could involve dopamine reward processing system and nicotinic-acetylcholinergic circuits, with a possible interaction with ovarian hormones in women.[11,36,37] If this causal pathway between ADHD symptoms and smoking is verified, prevention aiming at diminishing inattention symptoms should reduce the development of nicotine dependence. Furthermore, in people with both smoking dependence and inattention symptoms, treating the inattention symptoms should help in the success of smoking dependence treatment.[11]

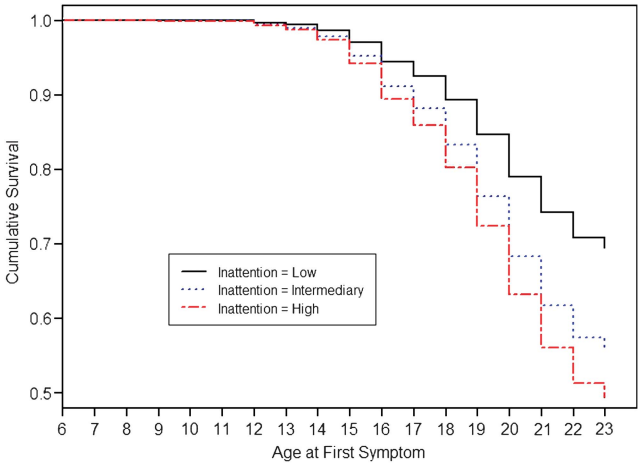

Figure 1. Survival model: Predictive value of female inattention for age at first symptom of nicotine dependence. The adjusted effect of inattention was plotted from a multivariate Cox model. The values for covariates were kept at the mean for the adversity index and at the low trajectory level for behavioral variables other than inattention.

Strengths and limitations

To the best of our knowledge, this study is the first prospective population-based study to assess the contribution of both inattention and hyperactivity symptoms to substance abuse/dependence in early adulthood, while controlling for opposition, anxiety and adversity. Despite its strengths, some limitations need to be acknowledged.

Because of their low prevalence, we were unable to model abuse/dependence to illicit drugs other than cannabis and cocaine. Regarding survival models, we used participants' retrospective recollection of age at first symptom and not repeated diagnoses over the years. In addition, the instrument used to assess childhood externalizing problems was not a diagnostic tool. However, it has proven to be predictive of a range of adult and adolescent outcomes in numerous studies,[18,34,38,39] and our predictive results were based on seven repeated assessments over a 7-year period from mothers and teachers.

Conclusion

We demonstrated in a large prospective sample that childhood inattention made a unique contribution to early adulthood nicotine dependence, and that oppositional behaviors represented a predictor of nicotine, cannabis, cocaine and alcohol abuse/dependence, whereas hyperactivity was not. In terms of theory, these findings argue in favor of specific childhood behavioral predictors for specific substance abuse/dependence outcomes, in particular regarding the link between inattention and nicotine dependence. In terms of practice, the results suggest that prevention or treatment of externalizing problems before the initiation of substance use could reduce the risk for substance-use disorders.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)