I, William B Brinkman M.D., hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research.

It is entitled:
Association Between Substance Use and Current Attention-Deficit/Hyperactivity Disorder Symptoms in a National Sample of Adolescents

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Committee chair: Paul Succop, PhD

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Association Between Substance Use and Current Attention-Deficit/Hyperactivity Disorder Symptoms in a National Sample of Adolescents

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by

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Abstract

Objective: To evaluate the relation between the number of attention-deficit/hyperactivity disorder (ADHD) symptoms and lifetime use of alcohol, tobacco, and drugs in an adolescent sample representative of the United States population.

Design: Cross-sectional survey.


Participants: Twelve- to 15-year-old adolescents (N=2517) in the National Health and Nutrition Examination Survey.

Main Outcome Measure: The National Health and Nutrition Examination Survey Audio Computer Assisted Self Interview of adolescents was used to ascertain lifetime use of alcohol, tobacco, and drugs.

Primary Predictor Measure: The National Institute of Mental Health Diagnostic Interview Schedule for Children (caregiver module) was used to ascertain the presence of ADHD symptoms in the past year.

Results: There was a strong linear relationship between the number of current ADHD symptoms and the likelihood of substance use after controlling for diagnosis of conduct disorder, age, gender, race/ethnicity, poverty status, and household smoke for tobacco use outcome. This relationship was most robust for inattentive symptoms than for total ADHD symptoms or hyperactive-impulsive symptoms along. For every inattentive
symptom, there was a nine to fourteen percent increase in the likelihood of substance use.

**Conclusions:** There is a significant linear relationship between ADHD symptoms and likelihood of lifetime use of alcohol, tobacco, and drug among adolescents in the U.S. The number of ADHD symptoms confers risk of substance use even at symptoms levels below the clinical threshold for diagnosis of ADHD.
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INTRODUCTION

Higher rates of alcohol, tobacco, and drug use have been noted among adolescents diagnosed with attention-deficit/hyperactivity disorder (ADHD) during childhood compared to those without ADHD. For example, longitudinal follow-up from the large multisite Multimodal Treatment Study of ADHD (MTA) found increased rates of alcohol, tobacco, and marijuana use when comparing adolescents with childhood diagnosis of ADHD to their former classmates without ADHD.\(^1,2\) Unfortunately, the 8% of children who meet full diagnostic criteria for ADHD\(^3\) may be the tip of the iceberg. Nearly twice that number present with ADHD symptoms below diagnostic thresholds\(^4\) and these children also appear to be at increased risk, though lesser risk than those with an ADHD diagnosis, for a variety of functional impairments\(^5\) and novelty seeking behaviors.\(^6\) However, less is known about the impact of ADHD symptoms at subthreshold levels on lifetime risk of alcohol, tobacco, or drug use in the general population. Some, but not all,\(^7\) studies have shown that the number of ADHD symptoms are related to substance dependence in older adolescents\(^8\) and young adults.\(^9\) However, these studies have been regionally based rather than nationally representative\(^8\) or have focused on use of a single substance (e.g., tobacco).\(^9\) The objective of our study was to evaluate the relation between the number of symptoms across the two ADHD symptom domains and alcohol, tobacco, and drug use in an adolescent sample representative of the United States population. We hypothesized that, after controlling for covariates, as the number of current ADHD symptoms increased, so would the likelihood of substance use.
METHODS

SAMPLE

The National Health and Nutrition Examination Survey (NHANES) is an annual multistage probability sample survey of the US population. In 2000-2004, a total of 2517 adolescents aged 12 to 15 years participated in NHANES (Table 1). Parent-reported ADHD and conduct disorder (CD) symptoms and adolescent-reported alcohol, tobacco, and drug use were collected. Complete data regarding adolescent ADHD and CD symptoms and each substance use behavior was available as follows: alcohol use for 2311 adolescents (91.8% of total), tobacco use for 2374 adolescents (94.3% of total), and drug use for 2380 adolescents (94.6% of total). Adolescents with (n=2517) and without (n=522) data available to assess parent reported symptoms and adolescent reported substance use did not differ on age, gender, or race. Adolescents from lower income families were less likely to contribute data (p=0.01).

OUTCOMES

Our primary outcomes were adolescent-report of any use of alcohol, tobacco, or drugs. These outcomes were derived from the NHANES Audio Computer Assisted Self Interview (ACASI) which was conducted in English or Spanish. Alcohol use was assessed by asking adolescents, “How old were you when you had your first drink of alcohol, other than a few sips?” Any response other than “I have never had a drink of alcohol other than a few sips,” constituted alcohol use. Tobacco use was assessed by asking adolescents, “Have you ever tried cigarette smoking, even 1 or 2 puffs?” A “Yes” response constituted tobacco use. Drug use was assessed by asking adolescents,
“Have you ever tried marijuana?” and “Have you ever tried any form of cocaine, including crack or freebase?” A “Yes” response to either question constituted drug use. Substance use has been assessed in a similar manner in other epidemiological studies and has been shown to have acceptable reliability and validity among children and adolescents.10

**PRIMARY PREDICTORS**

Primary predictors of substance use were counts of ADHD symptoms. These predictors were based on parent responses to the National Institute of Mental Health Diagnostic Interview Schedule for Children (DISC). The DISC is a structured diagnostic interview instrument designed for use in epidemiological and clinical studies, with reliable versions available in English11 and Spanish.12,13 Caregivers completed the DISC module providing information about the child’s ADHD and CD symptoms, the age of onset, symptom pervasiveness, and related impairments in the previous 12 months. Symptom counts were based on standardized DISC algorithms for ADHD and ranged from 0 to 23.11 Several ADHD symptoms were assessed using multiple questions. Consistent with other reports,14 each question stem was included in the symptom count resulting in 11 inattentive symptoms and 12 hyperactive-impulsive symptoms.

**ADDITIONAL PREDICTORS**

A range of additional predictors to be examined as covariates and potential confounders were selected on the basis of their association with risk taking behavior in previous studies. These included child age,15 child race/ethnicity,7,15 child gender1,15, household income,16 living with a smoker,17 and diagnosis of CD.2,4,7-9
Child race/ethnicity was designated by caregivers and included the categories of ‘non-Hispanic black’, ‘Mexican American’, ‘other Hispanic’, ‘non-Hispanic white’, and ‘other (including multiracial)’. Because of relatively small numbers of subjects in the ‘other Hispanic’ and ‘other (including multiracial)’ groups, the groups were combined into a single other race/ethnicity category which constituted a weighted prevalence of 12.6% in the sample. Household income/poverty line ratio, that is the ratio of the reported household income to the poverty threshold appropriate for the household size, was categorized into quartiles. The ‘living with a smoker’ variable was defined by parent response to the question “Does anyone smoke at home?” Diagnosis of CD was based on meeting Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria from standardized DISC algorithms.11

ANALYSIS

The Cincinnati Children’s Hospital Medical Center institutional review board determined this study to be exempt from review. Because of the complex differential probabilities of selection to achieve oversampling of selected groups in the NHANES cohort, sample weights were applied according to National Center for Health Statistics guidelines for generation of all estimates. Analyses were performed by using SUDAAN 9 (Research Triangle Institute, Research Triangle Park, NC) procedures for analysis of complex surveys. Descriptive statistics on the weighted national prevalence rates of any use of alcohol, tobacco, and drugs are presented across sociodemographic characteristics. We truncated symptom count ranges to avoid small numbers of adolescents at the upper end of each range. Logistic regression analyses were used to
analyze the associations between the primary predictors and any use of alcohol, tobacco, and drugs controlling for covariates.
RESULTS

Among 12- to 15-year old participants, 29.7% engaged in alcohol use, 28.3% engaged in tobacco use, and 10.8% engaged in drug use (Table 1). In unadjusted analyses, prevalence of use increased with age for every outcome. Prevalence of use did not differ by gender or race/ethnicity for any outcome. Prevalence of tobacco use was higher among adolescents from low income households. Differences across income categories were not significant for alcohol or drug use.

Total number of ADHD symptoms (combined number of inattentive and hyperactive/impulsive symptoms) was associated with an increased likelihood of ever trying alcohol, tobacco, and drugs after controlling for the diagnosis of CD, age, gender, race/ethnicity, poverty status, and household smoke for tobacco use outcome (Table 2). Similar analyses also separately examined the relationship between inattentive symptoms and hyperactive/impulsive symptoms and outcomes. Inattentive symptoms were significantly related to all outcomes while hyperactive/impulsive symptoms were significantly related to tobacco use but not alcohol or drug use. The magnitude of effect for the number of inattentive symptoms appeared more robust than for either number of total symptoms or hyperactive-impulsive symptoms alone. For every one symptom increase in inattentive symptoms, there was a nine to fourteen percent increase in the likelihood of substance use (Table 2, Figure 1).
DISCUSSION

In a national sample of adolescents in the United States, we found a strong linear relationship between the number of current ADHD symptoms and the likelihood of substance use after controlling for diagnosis of CD, age, gender, race/ethnicity, poverty status, and household smoke for tobacco use outcome. This relationship was most robust for inattentive symptoms. For every inattentive symptom, there was a nine to fourteen percent increase in the likelihood of substance use.

Our analysis of current adolescent ADHD symptoms as a continuous variable allows us to examine how symptom levels below diagnostic thresholds can impact lifetime risk of substance use in the general population. Congruent with our findings, current ADHD symptoms were significantly related to recent alcohol use, recent smoking, and lifetime drug use in a population-based study in Iceland, which did not control for CD. Given the suggestion that the relationship between ADHD and increased likelihood of substance use may be confounded by comorbid disruptive behavior disorders, our adjustment for CD substantially strengthens our findings. Our report differs from that of a community-based sample in Virginia that found no significant relationship between a continuous measure of ADHD symptoms and lifetime tobacco use. This difference may reflect age differences between the samples. Our study included adolescents age 12-15 years while the Virginia study was limited to 10th graders (e.g. typically 15-year-olds). The overall rate of lifetime tobacco use was much lower in our sample compared to the Virginia study (i.e. 28% vs. 43%) because lifetime tobacco use increases with age. Therefore, our finding of a relationship between ADHD symptoms and lifetime tobacco use may be explained by adolescents with ADHD.
symptoms trying tobacco at relatively younger ages. This hypothesis is consistent with studies that have found earlier onset of smoking among adolescents with a childhood diagnosis of ADHD compared to those without ADHD.\textsuperscript{21,22}

Our observation that the relationship between number of ADHD symptoms and lifetime risk of substance use may be driven primarily by inattentive symptoms is consistent with some prior studies.\textsuperscript{23} However, in other studies, hyperactive-impulsive symptoms appear to more consistently relate to lifetime risk of substance use. Most of these studies approached the ADHD symptoms domains not as continuous measures, but applied a categorical or threshold approach.\textsuperscript{8,24,25} It is well established that the natural history of ADHD is for inattention symptoms to persist at higher levels during adolescence while hyperactivity-impulsivity wanes.\textsuperscript{26} It is possible that applying a threshold measure to hyperactive-impulsive symptoms as a dimension leads to selection of a group of adolescents with more significant problems that have persisted, thereby inflating the influence of hyperactive-impulsive symptoms on lifetime risk of substance use.

Our study has important limitations. First, our study cannot determine causality because of its cross-sectional design. Past longitudinal studies that followed children initially diagnosed with ADHD +/- CD into adolescence clearly document persistent symptoms that preceded substance use.\textsuperscript{2,22,27} However, it is possible for some adolescents in our study that emergence of symptoms occurred after initiating substance use. Second, parents were the only reporters of ADHD symptoms. Given the differences that have been noted between parent and teacher report of ADHD symptoms,\textsuperscript{28} it is possible that our results would differ if teacher reports were available
for analysis. Third, adolescents were the only reporters of substance use. While such reports have been shown to have acceptable reliability and validity in other epidemiological studies, it is possible that the precision of substance use estimates would be enhanced if additional data sources were available for analysis.

Finally, it is beyond the scope of this cross-sectional study to determine the effect ADHD medication use has on substance use. The NHANES DISC collected parent report about use of “medicine for being overactive, being hyperactive, or having trouble paying attention” in the past 12 months and whether medication was taken “most of the time during the last year” (i.e. consistent medication treatment), but there is no measure of lifetime medication treatment which potentially could have affected some outcomes.

Our finding that even low levels of ADHD symptoms increase risk of substance use may have important implications for prevention efforts. Interventions that promote symptom reduction in the general population may help reduce or delay onset of substance use. This notion is supported by a randomized controlled trial of a universal school-based behavioral intervention to prevent disruptive behaviors in mainstream classrooms in The Netherlands in which reductions in ADHD symptoms over the ages of 7-9 years mediated decreases in the probability of tobacco use at age 10-11 years.
CONCLUSIONS

There is a significant linear relationship between ADHD symptoms and likelihood of lifetime use of alcohol, tobacco, and drug among adolescents in the U.S. The number of ADHD symptoms confers risk of substance use even at symptoms levels below the clinical threshold for diagnosis of ADHD.


Table 1. Prevalence of any Alcohol Use, Tobacco Use, and Drug Use by Sociodemographic Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Alcohol Use (N=2311)</th>
<th>Tobacco Use (N=2374)</th>
<th>Drug Use (N=2380)</th>
<th>p value</th>
<th>p value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>N=754</td>
<td>N=682</td>
<td>N=310</td>
<td>29.7</td>
<td>28.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>94</td>
<td>69</td>
<td>13</td>
<td>14.6</td>
<td>13.5</td>
<td>2.2</td>
</tr>
<tr>
<td>13</td>
<td>164</td>
<td>146</td>
<td>51</td>
<td>25.8</td>
<td>22.9</td>
<td>6.5</td>
</tr>
<tr>
<td>14</td>
<td>232</td>
<td>196</td>
<td>97</td>
<td>33.7</td>
<td>30.2</td>
<td>13.1</td>
</tr>
<tr>
<td>15</td>
<td>264</td>
<td>271</td>
<td>149</td>
<td>46.4</td>
<td>49.1</td>
<td>23.0</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>381</td>
<td>340</td>
<td>171</td>
<td>29.2</td>
<td>28.9</td>
<td>11.5</td>
</tr>
<tr>
<td>Male</td>
<td>373</td>
<td>342</td>
<td>139</td>
<td>30.1</td>
<td>27.7</td>
<td>10.1</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>220</td>
<td>210</td>
<td>101</td>
<td>27.8</td>
<td>25.2</td>
<td>12.1</td>
</tr>
<tr>
<td>Mexican American</td>
<td>285</td>
<td>226</td>
<td>114</td>
<td>35.4</td>
<td>28.1</td>
<td>14.1</td>
</tr>
<tr>
<td>Other race/ethnicity</td>
<td>55</td>
<td>52</td>
<td>23</td>
<td>31.6</td>
<td>27.2</td>
<td>10.7</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>194</td>
<td>194</td>
<td>72</td>
<td>28.7</td>
<td>29.3</td>
<td>10.0</td>
</tr>
<tr>
<td>Income to Poverty Ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.00</td>
<td>192</td>
<td>224</td>
<td>100</td>
<td>29.4</td>
<td>38.0</td>
<td>14.9</td>
</tr>
<tr>
<td>1.00-1.85</td>
<td>201</td>
<td>161</td>
<td>86</td>
<td>35.2</td>
<td>34.1</td>
<td>12.6</td>
</tr>
<tr>
<td>&gt;1.85-3.00</td>
<td>146</td>
<td>122</td>
<td>51</td>
<td>30.4</td>
<td>28.1</td>
<td>9.8</td>
</tr>
<tr>
<td>&gt;3.00</td>
<td>185</td>
<td>145</td>
<td>61</td>
<td>27.6</td>
<td>21.7</td>
<td>8.9</td>
</tr>
</tbody>
</table>

*N reflects actual sample size, % is weighted to reflect national prevalence estimates
Table 2. Adjusted odds ratios for ever trying alcohol, tobacco, or drugs by number of ADHD symptoms

<table>
<thead>
<tr>
<th></th>
<th>Alcohol Use</th>
<th></th>
<th></th>
<th>Tobacco Use</th>
<th></th>
<th></th>
<th>Drug Use</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>p value</td>
<td>OR</td>
<td>95% CI</td>
<td>p value</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Total symptoms</td>
<td>1.05</td>
<td>(1.02, 1.08)</td>
<td>0.004</td>
<td>1.09</td>
<td>(1.05, 1.12)</td>
<td>&lt;0.001</td>
<td>1.06</td>
<td>(1.02, 1.10)</td>
</tr>
<tr>
<td>(inattentive &amp; hyperactive impulsive)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattentive symptoms</td>
<td>1.09</td>
<td>(1.04, 1.14)</td>
<td>0.001</td>
<td>1.14</td>
<td>(1.08, 1.20)</td>
<td>&lt;0.001</td>
<td>1.10</td>
<td>(1.04, 1.16)</td>
</tr>
<tr>
<td>Hyperactive/impulsive symptoms</td>
<td>1.06</td>
<td>(0.99, 1.13)</td>
<td>0.08</td>
<td>1.13</td>
<td>(1.05, 1.20)</td>
<td>0.001</td>
<td>1.08</td>
<td>(0.98, 1.18)</td>
</tr>
</tbody>
</table>

Adjusted for age, gender, race/ethnicity, poverty status, household smoke (tobacco outcome), and conduct disorder (yes/no)
Figure 1: Odds ratios for ever trying alcohol, tobacco, or drugs by number of ADHD symptoms

<table>
<thead>
<tr>
<th>Alcohol Use</th>
<th>Tobacco Use</th>
<th>Drug Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
<td><img src="image3" alt="Graph" /></td>
</tr>
</tbody>
</table>

Adjusted for age, gender, race/ethnicity, poverty status, household smoke (tobacco outcome), and conduct disorder (yes/no)

- Total symptoms (12-23 reported symptoms are combined)
- Inattentive symptoms (10-11 reported symptoms are combined)
- Hyperactive/impulsive symptoms (7-12 reported symptoms are combined)