Drinking Distilled. Onset, course and treatment of alcohol use disorders in the general population
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Chapter 2

The role of conduct disorder in the association between ADHD and alcohol use (disorder)
Results from the Netherlands Mental Health Survey and Incidence Study-2
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ABSTRACT

Background
Much is unclear about the association between attention-deficit/hyperactivity disorder (ADHD) and alcohol use (disorder). Research on this subject is hindered by the role of conduct disorder (CD). We investigate whether (i) childhood ADHD is associated with higher prevalence and earlier onset of alcohol initiation, regular alcohol use and alcohol use disorder (AUD); (ii) CD mediates or modifies this association.

Methods
Data were derived from the baseline assessment of the Netherlands Mental Health Survey and Incidence Study-2, a general population study. ADHD and CD were assessed among respondents aged 18-44 (n = 3,309). ADHD, CD, and alcohol use (disorder) were assessed using the Composite International Diagnostic Interview 3.0.

Results
Lifetime prevalence was 2.9% for ADHD, 5.6% for CD, 94.3% for alcohol initiation, 85.7% for regular alcohol use and 19.0% for AUD; mean ages of onset were 6.7, 11.5, 14.8, 16.7 and 19.2 years, respectively. After correction for gender and age, ADHD was associated with a higher prevalence of all three stages of alcohol use, but not with earlier onset of these stages. The association between ADHD and prevalence of AUD was fully explained by a mediating role of CD. CD did not modify the associations between ADHD and prevalence and onset of alcohol use (disorder).

Conclusions
The mediating role of CD in the association between ADHD and AUD suggests a developmental pathway from ADHD to CD and subsequent AUD. Early interventions in children with ADHD may prevent CD and subsequent onset of AUD.

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INTRODUCTION

Clinical and epidemiological studies indicate that childhood attention-deficit/hyperactivity disorder (ADHD) is associated with a higher prevalence [1-7] and an earlier onset [6-9] of alcohol use and of alcohol use disorder (AUD). However, results have been inconsistent, especially with regard to the prevalence of alcohol use [2;5;10-12]. Recent meta-analyses on this matter suggest a significant effect of ADHD on the prevalence of AUD [10;13], but not on alcohol use [10]. Lee et al. [10] concluded, however, that the results on which they based their conclusions were somewhat heterogeneous, indicating that other factors might play a role in the association between ADHD and alcohol use (disorder). This is further demonstrated by the finding that conduct disorder (CD) is highly associated with both ADHD [14-16] and alcohol use (disorder) [4;17]. Children with ADHD as well as CD have a higher rate of AUD compared to children with ADHD only [18;19]; thus CD possibly confounds the assumed association between ADHD and AUD. Many studies, however, failed to examine explicitly the role of CD in this association [2-10].

Studies that tried to identify the association between ADHD, CD, and alcohol use (disorder) [1;12;20-23] can be divided into two approaches. The first approach suggests a developmental sequence with ADHD influencing the development of CD, which in turn results in a higher risk of alcohol use (disorder) [20]. This so-called mediating role of CD has been found in prospective studies focusing on the role of CD in the association between ADHD and substance use disorder [15;23-25]. Most of these studies focused on substance use disorder in general, only one [23] explicitly addressed alcohol use (disorder) in young adulthood. Unfortunately, this study measured attention and conduct problems and did not define ADHD and CD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) [26]. Thus, it is still not clear whether there actually is a mediating role of CD in the association between ADHD and alcohol use (disorder). The second approach suggests that children with both ADHD and CD represent a distinct subgroup which has an additionally increased risk of alcohol use (disorder) compared to children with ADHD only or CD only. However, studies on this modifying role of CD have shown conflicting results [1;12;21;22]. Specifically, only one study supported the idea that children with both ADHD and CD have an additionally increased risk of AUD [1]. Other studies [12;21;22] found that children with both ADHD and CD had a higher prevalence of alcohol use (disorder) compared to children with ADHD only or CD only, but the risk of alcohol use (disorder) was not additionally increased in this group of children. Differences in sampling design could play a role in these mixed findings. Knop et al. [1] focused on adults, others on adolescents [12;21] or young adults [22]. The differential results could imply that the modifying role of CD begins to express itself in adulthood. However, further examination of this hypothesis is needed. Thus, research on both approaches with respect to the role of CD in the association between ADHD and prevalence of alcohol use (disorder) has
been inconclusive. To our knowledge, research on both approaches with respect to the age of onset of alcohol use (disorder) is lacking.

Whether CD plays a mediating or modifying role is of great importance for clinical practice. A mediating role would imply that early interventions among children with ADHD are needed to prevent progress from ADHD into CD and subsequent alcohol use (disorder) whereas a modifying role would suggest early diagnosis and intensive treatment of those at highest risk of alcohol use (disorder), being children with both ADHD and CD.

Using data from the baseline assessment of the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2), we will address two questions in particular: (i) whether childhood ADHD is associated with a higher lifetime prevalence and an earlier onset of three stages of alcohol use: alcohol initiation, regular alcohol use, and AUD; and (ii) whether CD mediates or modifies this association. The present study will increase the existing knowledge in four ways. First, to our knowledge, this study is the first to examine the association between ADHD and both prevalence and age of onset of three different stages of alcohol use. Second, both the mediating and modifying role of CD in the association between ADHD and alcohol use (disorder) will be examined. Third, using data of a general population study enables us to examine associations which are applicable to the population at large. Moreover, the use of an adult sample enables us to associate childhood ADHD with AUD at a much later age than most other studies in which the association between ADHD, CD, and alcohol use (disorder) was examined [12,21-23]. This provides us the opportunity to study processes that emerge in adulthood. Fourth, not symptom counts but DSM-IV diagnoses of ADHD, CD, and AUD will be used.

METHODS

Sample and assessment procedures
Data were derived from the baseline assessment of NEMESIS-2. Methods have been reported elsewhere [27]. Briefly, NEMESIS-2 is based on a multistage, stratified, random sampling of households, with one respondent randomly selected in each household (response: 65.1%). The Composite International Diagnostic Interview (CIDI) version 3.0 was used to determine the presence of ADHD, CD, and AUD according to DSM-IV criteria. The CIDI is a fully structured, lay administered interview developed by the World Health Organization. The CIDI is used worldwide, and has been shown to be a reliable and valid instrument [28]. To increase accuracy of retrospective recall, ADHD and CD were only assessed among respondents aged 18-44, conform [29]. This resulted in a total sample of 3,309 respondents.

ADHD and CD. Respondents who answered positively to one of the screener questions for ADHD or for CD entered the relevant CIDI sections. In these sections symptoms
of the disorder, impairment due to these symptoms, and age of onset were assessed. Computerized CIDI algorithms were used to generate diagnoses according to full DSM-IV criteria.

**Alcohol use (disorder).** All participants entered the alcohol section which started with a question to measure alcohol initiation: “How old were you the very first time you ever drank an alcoholic beverage?”. Only participants who reported ever-use continued with the alcohol section, the next question assessed regular drinking: “How old were you when you first started drinking at least 12 drinks per year?”. Only participants who reported regular drinking continued with the next part of the alcohol module assessing symptoms of alcohol abuse and dependence, impairment due to these symptoms, and age of onset.

**Analyses**

Analyses were performed using Stata version 11.1 which enabled us to control for the complex sampling and recruitment procedure of the study. We first established unweighted counts, and then calculated weighted prevalence rates and weighted means to provide characteristics of the sample and summary statistics of ADHD, CD, and alcohol use (disorder). The data were weighted to ensure they were representative of the national population.

The association between ADHD, CD, and prevalence of alcohol use (disorder). Cox regression analyses, which generate hazard ratios (HR), were conducted to test whether ADHD was associated with a higher prevalence rate of alcohol use (disorder) in a univariable model. Cox regression takes both the age of the respondents and the age of onset of alcohol use (disorder) into account. Before conducting these analyses, the proportional hazards assumption was checked; the assumption was not violated in the univariable models.

Next, stepwise Cox regression analyses were conducted. These analyses were adjusted for gender to account for the higher prevalence rates of ADHD and alcohol use (disorder) in males [30;31]. In analyses with alcohol initiation and regular alcohol use, gender was stratified to suffice the proportional hazards assumption [32], stratification was not needed in analyses with AUD. In the first step, we examined whether ADHD was associated with all stages of alcohol use. In the second step, we added CD as a covariate to these models in order to investigate its mediating role. The Sobel test was used to test for significance of mediation [33] after correction for the dichotomous nature of the mediator and outcome variable [34].

In the third step it was investigated whether CD modified the association between ADHD and alcohol use (disorder) using an additive model. Additive interaction exists if the combined effect of ADHD and CD on alcohol use (disorder) is stronger than the sum of the separate effects. Additive interaction was tested by comparing the HR of ADHD and CD combined with the expected value in case of no interaction, namely
$HR(AB) = HR(A) + HR(B) - 1$. If the expected HR is smaller than the lower boundary of the 95% confidence interval of the HR of the combined effect, additive interaction is assumed [35;36].

**The association between ADHD, CD, and age of onset of alcohol use (disorder).** We conducted linear regression analyses, which generate unstandardized coefficients (Bs), to determine whether ADHD was associated with an earlier age of onset of alcohol use in a univariable model. Next, stepwise linear regression analyses, adjusted for age and gender, were used to test the association between ADHD, CD, and onset of alcohol use (disorder). In the first step, we examined whether ADHD was still associated with the onset of alcohol use. In the second step, we added CD to the model in order to test whether CD mediated this association. Again, significance of mediation was checked with the Sobel test. The interaction-term of ADHD and CD was included in the third step in order to examine whether CD modified the association between ADHD and onset of alcohol use (disorder) in an additive model. Level of significance was set at 0.05.

**RESULTS**
Table 2.1 provides characteristics of the sample and summary statistics of ADHD, CD, and alcohol use (disorder) as unweighted counts, weighted percentages and weighted means. Mean age of the 3,309 respondents was 32.0 and 50.4% was male.

Childhood ADHD was present in 2.9% ($n = 74$) of the respondents. Respondents with ADHD were significantly younger than respondents without ADHD (28.9 vs. 32.1; $t(3,307) = -2.81; p = 0.01$) and they were more often male (74.8% vs. 49.6%; OR = 3.0; $p < 0.001$). CD was present in 5.6% ($n = 127$) of the respondents. As expected, childhood CD was much more prevalent in respondents with ADHD than in respondents without ADHD (40.0% vs. 4.5%; OR = 14.0; $p < 0.001$). Mean age of onset of ADHD was substantially lower than that of CD (6.7 vs. 11.5). More specific, 83.7% of the respondents fulfilling criteria for both disorders reported that symptoms of ADHD were present before or at the same time as symptoms of CD.

Most respondents initiated alcohol use (94.3%; mean age 14.8) and regular alcohol use (85.7%; mean age 16.7). Alcohol abuse and dependence were prevalent in respectively 16.6% ($n = 472$) and 2.4% ($n = 54$) of respondents. Given the small number of respondents with alcohol dependence, both diagnoses were combined (AUD; 19.0%, $n = 526$; mean age of onset 19.2) in the analyses. Symptoms of ADHD were present before or at the same time as alcohol initiation, regular alcohol use, and AUD in respectively 93.1%, 95.4%, and 100.0% of the respondents with both ADHD and the corresponding stage of alcohol use. Symptoms of CD were somewhat less present before or at the same time as the three stages of alcohol use, namely in 75.4%, 89.3%, and 94.7% of the respondents with both CD and the corresponding stage of alcohol use.
Table 2.1. Characteristics of the total sample and of respondents with or without attention-deficit/hyperactivity disorder (ADHD). Lifetime prevalence and mean ages of onset (AOO) of ADHD, conduct disorder (CD), and alcohol use (disorder). Results of summary statistics in unweighted counts, weighted column percentages, and weighted means with 95% confidence intervals (95% CI).

<table>
<thead>
<tr>
<th>Sample characteristics</th>
<th>Total sample</th>
<th>Respondents with ADHD</th>
<th>Respondents without ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>Mean age (95% CI)</td>
</tr>
<tr>
<td>Total</td>
<td>3,309</td>
<td>100.0</td>
<td>32.0 (31.6; 32.4)</td>
</tr>
<tr>
<td>Males</td>
<td>1,450</td>
<td>50.4</td>
<td>32.1 (31.6; 32.6)</td>
</tr>
<tr>
<td>Females</td>
<td>1,859</td>
<td>49.6</td>
<td>31.9 (31.4; 32.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample characteristics</th>
<th>Total sample</th>
<th>Respondents with ADHD</th>
<th>Respondents without ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>Mean AOO (95% CI)</td>
</tr>
<tr>
<td>ADHD</td>
<td>74</td>
<td>2.9</td>
<td>6.7 (5.4; 8.0)</td>
</tr>
<tr>
<td>CD</td>
<td>127</td>
<td>5.6</td>
<td>11.5 (10.6; 12.4)</td>
</tr>
<tr>
<td>Alcohol initiation</td>
<td>3,143</td>
<td>94.3</td>
<td>14.8 (14.7; 14.9)</td>
</tr>
<tr>
<td>Regular alcohol use</td>
<td>2,846</td>
<td>85.7</td>
<td>16.7 (16.5; 16.8)</td>
</tr>
<tr>
<td>Alcohol use disorder</td>
<td>526</td>
<td>19.0</td>
<td>19.2 (18.7; 19.7)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>472</td>
<td>16.6</td>
<td>19.3 (18.8; 19.8)</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>54</td>
<td>2.4</td>
<td>19.6 (18.1; 21.2)</td>
</tr>
</tbody>
</table>
The association between ADHD, CD, and prevalence of alcohol use (disorder)

All stages of alcohol use were significantly more prevalent in respondents with ADHD than in respondents without ADHD (Table 2.1). The results of the univariable Cox regression analyses (Table 2.2) support this observation: ADHD was associated with a 54% higher risk of alcohol initiation and a 59% higher risk of regular alcohol use. ADHD almost tripled the risk of developing AUD. Step 1 of Table 2.2 shows that these risks slightly decreased, but remained significant, when gender was added to the model.

After adjustment for CD, respondents with ADHD were still more likely to initiate alcohol use (p = 0.05) and to start regular drinking (p = 0.03). However, ADHD and AUD were no longer significantly associated after adjustment for CD (p = 0.33), indicating a mediating role of CD.

To further investigate whether the association between ADHD and one of the stages of alcohol use operates also via CD as the mediating variable, we compared the HRs of ADHD in Step 1 and Step 2 of Table 2.2. The HR for alcohol initiation slightly declined from 1.42 (Step 1) to 1.37 (Step 2) when CD was added to the model (a non-significant reduction of 3.6%, ((1.42 / 1.37) - 1) * 100; Sobel test: Z = 0.80; p = 0.42). The HR for regular alcohol use declined from 1.42 (Step 1) to 1.34 (Step 2) (a non-significant reduction of 6.0%, ((1.42 / 1.34) - 1) * 100; Sobel test: Z = 1.13; p = 0.26). Thus, the association between ADHD and alcohol initiation as well as the association between ADHD and regular alcohol use were not significantly mediated by CD. However, the HR for AUD sharply declined from 2.29 (Step 1) to 1.39 (Step 2) (a significant reduction of 64.7%, ((2.29 / 1.39) - 1) * 100; Sobel test: Z = 4.93; p < 0.001), indicating that ADHD affected the prevalence of AUD via mediation by CD. Additional analyses demonstrated that this conclusion holds after exclusion of those individuals with CD predating ADHD (16.3%).

The final part of Table 2.2 indicates that CD did not modify the association between ADHD and presence of alcohol use (disorder). This is shown by the fact that the combined effect of ADHD and CD on alcohol use (disorder) is not stronger than the sum of the separate effects.

The association between ADHD, CD, and age of onset of alcohol use (disorder)

Respondents with ADHD had an earlier age of onset of alcohol initiation and regular alcohol use than respondents without ADHD (Table 2.1). The univariable linear regression analyses also show that ADHD was associated with an earlier onset of alcohol initiation and regular alcohol use, but not of AUD (Table 2.3). When age and gender were added to the model the differences in onset disappeared (Step 1). Further analyses demonstrated neither a mediating (Step 2) nor a modifying (Step 3) role of CD in the association between ADHD and onset of alcohol use (disorder). However, CD was significantly associated with an earlier onset of AUD.
Table 2.2. The mediating and modifying role of conduct disorder (CD) in the association between attention-deficit/hyperactivity disorder (ADHD) and the prevalence of different stages of alcohol use. Results of Cox regression analyses generating hazard ratios (HR) and adjusted hazard ratios (adj. HR), with 95% confidence intervals (95% CI).

<table>
<thead>
<tr>
<th></th>
<th>Alcohol initiation</th>
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<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p</td>
<td>HR (95% CI)</td>
<td>p</td>
<td>HR (95% CI)</td>
<td>p</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>1.54 (1.15; 2.05)</td>
<td>0.004</td>
<td>1.59 (1.26; 2.00)</td>
<td>&lt;0.001</td>
<td>2.90 (1.76; 4.77)</td>
<td>&lt;0.001</td>
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<table>
<thead>
<tr>
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<th>Regular alcohol use</th>
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<th>Alcohol use disorder</th>
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<tbody>
<tr>
<td></td>
<td>Adj. HR (95% CI) a</td>
<td>p</td>
<td>Adj. HR (95% CI) a</td>
<td>p</td>
<td>Adj. HR (95% CI) b</td>
<td>p</td>
</tr>
<tr>
<td>Step 1</td>
<td>ADHD</td>
<td>1.42 (1.05; 1.92)</td>
<td>0.02</td>
<td>1.42 (1.12; 1.79)</td>
<td>0.004</td>
<td>2.29 (1.37; 3.81)</td>
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<tr>
<td></td>
<td>CD</td>
<td>1.12 (0.85; 1.46)</td>
<td>0.42</td>
<td>1.16 (0.90; 1.51)</td>
<td>0.25</td>
<td>3.40 (2.33; 4.96)</td>
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<tr>
<td>Step 2</td>
<td>ADHD</td>
<td>1.37 (1.00; 1.87)</td>
<td>0.05</td>
<td>1.34 (1.04; 1.74)</td>
<td>0.03</td>
<td>1.39 (0.72; 2.69)</td>
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<tr>
<td></td>
<td>CD</td>
<td>1.12 (0.82; 1.55)</td>
<td>0.45</td>
<td>1.17 (0.86; 1.60)</td>
<td>0.32</td>
<td>3.96 (2.80; 5.60)</td>
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</table>

<table>
<thead>
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<th>ADHDCD</th>
<th>Alcohol initiation</th>
<th>Regular alcohol use</th>
<th>Alcohol use disorder</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Adj. HR (95% CI) a</td>
<td>Expected HR c</td>
<td>Adj. HR (95% CI) b</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>1.40 (0.97; 2.02)</td>
<td>0.08</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>1.13 (0.82; 1.55)</td>
<td>0.45</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>1.47 (0.91; 2.38)</td>
<td>0.11 1.53</td>
</tr>
</tbody>
</table>

a Analyses were stratified by gender.
b Analyses were controlled for gender.
c Expected HR in the case of no interaction is the sum of the separate effects of ADHD and CD. Additive interaction is assumed if the expected HR lays below the lower limits of the confidence intervals of the combined effect of ADHD and CD.
Table 2.3. The mediating and modifying role of conduct disorder (CD) in the association between attention-deficit/hyperactivity disorder (ADHD) and the age of onset of different stages of alcohol use. Results of linear regression analyses in unstandardized coefficients (B) and adjusted B (adj. B) with 95% confidence intervals (95% CI).

<table>
<thead>
<tr>
<th></th>
<th>Alcohol initiation</th>
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<tbody>
<tr>
<td></td>
<td>B</td>
<td>(95% CI)</td>
<td>p</td>
<td>B</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>ADHD</td>
<td>-1.07</td>
<td>(-1.99; -0.15)</td>
<td>0.02</td>
<td>-1.12</td>
<td>(-1.82; -0.41)</td>
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<tr>
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<tr>
<td>Multivariable model</td>
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<td></td>
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<tr>
<td>Step 1</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>-0.71</td>
<td>(-1.55; 0.13)</td>
<td>0.10</td>
<td>-0.56</td>
<td>(-1.19; 0.06)</td>
</tr>
<tr>
<td>CD</td>
<td>-0.51</td>
<td>(-1.17; 0.14)</td>
<td>0.13</td>
<td>-0.51</td>
<td>(-1.21; 0.13)</td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>-0.54</td>
<td>(-1.39; 0.31)</td>
<td>0.22</td>
<td>-0.38</td>
<td>(-1.14; 0.38)</td>
</tr>
<tr>
<td>CD</td>
<td>-0.51</td>
<td>(-1.17; 0.14)</td>
<td>0.13</td>
<td>-0.54</td>
<td>(-1.21; 0.13)</td>
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<tr>
<td>Step 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD &amp; CD</td>
<td>0.44</td>
<td>(-1.51; 2.38)</td>
<td>0.66</td>
<td>1.17</td>
<td>(-0.43; 2.77)</td>
</tr>
</tbody>
</table>

* Analyses were controlled for age and gender.
DISCUSSION

To our knowledge, the present study is the first to examine the association between ADHD and (onset of) different stages of alcohol use, while taking into account the mediating and modifying role of CD, in a representative sample of the general adult population. The NEMESIS-2 prevalence rates of ADHD (2.9%), CD (5.6%), and AUD (19.0%) are somewhat lower than in the US National Comorbidity Survey Replication [37], but they are within the range of rates that are observed worldwide [38;39].

The association between ADHD, CD, and prevalence of alcohol use (disorder)

A summary of the results with regard to the prevalence of alcohol use (disorder) is given in Figure 2.1a. ADHD was associated with alcohol initiation and regular alcohol use, but not with AUD, when CD was taken into account. These results are in accordance with one [5], but not with other [12;23], prospective studies. Neither the association between ADHD and alcohol initiation nor the association between ADHD and regular alcohol use was mediated by CD. CD did mediate the association between ADHD and AUD. As in other research [20], it was observed that diagnoses of ADHD predated diagnoses of CD, and both diagnoses predated diagnoses of AUD. This strongly suggests that the role of CD as a covariate in the multivariable models represents a mediator and not just some unspecified form of confounding. This finding is in agreement with some prospective studies that examined the mediating role of CD in the association between ADHD and substance use [15;23-25].

It should be noted that initiation of (regular) alcohol use is very common and that regular alcohol use belongs to the normal range of accepted behaviors in Western societies, and therefore these behaviors cannot be interpreted as an indication of a behavioral abnormality related to the presence of ADHD (even though these behaviors occur more often in people with ADHD). The differential role of CD in the association between ADHD and the three stages of alcohol use suggests that the mediating role of CD becomes stronger over time and is associated with more pathological aspects of alcohol use. Notably, this externalizing pathway could be influenced by other factors as well, such as parenting style and peer factors [40;41]. Nevertheless, the maintained developmental pathway stresses the importance of early interventions among children with ADHD to prevent progress from ADHD into CD and subsequent AUD.

Previous studies [1;12;21;22] have reported conflicting findings with regard to the idea that children with ADHD and CD constitute a distinct group that is at extra risk of AUD. We found no evidence for this proposition in an adult sample: the combination of ADHD and CD did not result in a higher risk of alcohol use (disorder) as compared to the sum of the separate effects of ADHD and CD. The small number of individuals with both ADHD and CD (n = 21) may have complicated these findings. However, neither large confidence intervals nor trends in the hypothesized direction were observed, which supports our conclusion that CD is not very likely to play a modifying role.
a) Association between attention-deficit/hyperactivity disorder (ADHD) and the prevalence of different stages of alcohol use without and with the role of conduct disorder (CD)

![Diagram of alcohol initiation, regular alcohol use, and alcohol use disorder with ADHD and CD connections]

b) Association between ADHD and age of onset of different stages of alcohol use without and with the role of CD

![Diagram of alcohol initiation, regular alcohol use, and alcohol use disorder with ADHD and CD connections]

Figure 2.1. Summary of results adjusted for gender and age. Dashed lines indicate no significant association, solid lines indicate significant associations.
The association between ADHD, CD, and age of onset of alcohol use (disorder)

In accordance with previous research [6;9], we found that ADHD was associated with an earlier age of alcohol initiation and of regular alcohol use. However, in contrast to other studies [7;8], our results showed no association between ADHD and onset of AUD. Notably, the association between ADHD and onset of alcohol initiation and regular alcohol use was no longer present when age and gender were added to the model. It thus seems that previous studies, in which no correction for age and gender was made, mistakenly concluded that ADHD was associated with an earlier age of alcohol use.

Neither a mediating nor modifying role of CD was found with regard to the association between ADHD and onset of alcohol use (disorder). However, CD was associated with an earlier onset of AUD. A summary of the results with regard to the onset of alcohol use (disorder) is given in Figure 2.1b.

Limitations

A few cautionary remarks should be made with regard to the current findings. A restriction of this study concerns the relatively small number of individuals with a diagnosis of ADHD, CD or AUD, which may have caused a lack of statistical power. However, the present study used a large population based sample. This enabled us to compare relatively small numbers of diagnosed individuals with large numbers of undiagnosed individuals. The many significant associations as well as the generally narrow confidence intervals suggest that statistical power was sufficient.

Previous research among adolescents showed that the three ADHD subtypes (i.e. inattentive, hyperactive, and combined) had different associations with AUD [5;42]. However, due to the small amount of respondents with ADHD in present study we were not able to assess the possible differential contribution of the three ADHD subtypes. Also, we were unable to conduct separate analyses for alcohol abuse and dependence. Only a small group of respondents developed alcohol dependence, which is characterized by different symptoms as well as a higher symptom count than alcohol abuse (number of criteria occurring within a 12-month period ≥ 3 in dependence vs. ≥ 1 in abuse). The associations with ADHD and CD could thus be different for both AUDs. Previous research suggested, however, that this is not the case [23].

Diagnoses of ADHD, CD, and AUD were based on retrospective reports, as is often the case in population studies. Retrospective assessment could have resulted in recall bias. However, it is unclear how this would affect the presented associations. In accordance with earlier research [29], we choose to restrict our sample to respondents aged 18-44 to minimize problems with recall bias.

Approaches using multi-informant information could have resulted in other prevalence rates of ADHD as compared to the self-reports that were used in present research. However, an earlier comparison between adult self-reports and informant
reports of childhood and adult ADHD showed fairly strong associations between the two [43]. The use of self-reports in present research seems therefore justified.

**Implications**

Notwithstanding the potential limitations, this study helps to understand how ADHD is associated with alcohol use (disorder), and how CD affects this association. Replication of the current findings is needed, preferably in longitudinal design, so that the progression from ADHD to CD and subsequent to AUD can be further examined.

The current paper treated ADHD, CD, and AUD as separate disorders. However, some studies have suggested that these disorders reflect a general dimension of externalizing behavior [44;45]. Future research should study this dimension and the possibility that current findings of mediation represent a phenotypic phased expression of this partially genetically determined [45-47] and partially non-genetically determined [48] externalizing factor. It should be noted that AUDs are more prevalent than CD and that CD is more prevalent than ADHD. Therefore, the development of AUDs cannot be fully explained by this specific (externalizing) pathway, so other pathways must be operating as well, either as some non-ADHD or non-CD like expression of the underlying externalizing vulnerability or along some internalizing vulnerability factor with AUDs more likely to be a consequence of self-medication for existing anxiety or mood disorders [49-52].

Also, important clinical implications can be derived from the current results. The mediating role of CD in the association between ADHD and AUD indicates that treatment of children with ADHD must comprise prevention measures of both CD and AUD. Specifically, ADHD usually precedes the other two disorders and children with ADHD are often still young when they come into treatment. This creates opportunities to deal with early disruptive behavior [53;54] and to prevent CD and AUD to develop. It thus seems essential that adequate prevention measures are devised and examined for children with ADHD so that adverse outcomes can be avoided.

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