Drinking Distilled. Onset, course and treatment of alcohol use disorders in the general population
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Citation for published version (APA):

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Chapter 5

Alcohol consumption and symptoms as predictors for relapse of DSM-5 alcohol use disorder
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ABSTRACT

Background
Alcohol consumption levels and alcohol use disorder (AUD) symptoms may serve as easily quantifiable markers for AUD relapse after remission and might help prevention workers identify at-risk individuals. We investigated the predictive value of alcohol consumption and AUD symptoms on relapse.

Methods
Data are from the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2). We selected 506 people in ≥ 12-month DSM-5 AUD remission at baseline and assessed their status at 3-year follow-up. AUD symptoms and drinking patterns were assessed using the Composite International Diagnostic Interview 3.0. Time since remission was assessed retrospectively at baseline and ranged from 1 to 48 years. Predictors for relapse were examined using Cox regression analysis.

Results
Cumulative AUD relapse rate was 5.6% at 5 years, 9.1% at 10 years and 12.0% at 20 years. Relapse was predicted by both medium (15-28/22-42 drinks weekly for women/men) and high (≥ 29/43) past alcohol intake, ≥ 6 lifetime AUD symptoms, ‘impaired control over use’, and at-risk (≥ 8/15) current intake. The risk of relapse was especially high when medium or high past intake or ≥ 6 lifetime symptoms coincided with current at-risk drinking.

Conclusions
Only a minority of people in DSM-5 AUD remission relapsed, but the risk of relapse increased substantially with the presence of at least one of the risk factors. Moreover, at-risk current drinking coupled with other risk factors substantially increased the likelihood of relapse. Therefore, current drinking may provide an adequate reference point for relapse prevention.

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Published in Drug and Alcohol Dependence (2014) 140: 85-91.
INTRODUCTION

Population-based studies suggest that approximately one in five people meet the criteria for an alcohol use disorder (AUD) in their lifetime [1-3]. The disorder usually presents itself in a mild form: approximately 70% go into remission within three years [4-6] and only a small minority of those in remission experience a relapse [5,7]. Even though relapse rates are low, the high personal and societal costs associated with chronic, recurrent AUD [8,9] warrant the need for relapse prevention measures. The small group at risk of recurrence should be distinguished from those with a high probability of sustained remission. Although information from longitudinal population-based research is limited, there are indications that alcohol consumption level and AUD symptoms could serve as easily quantifiable markers [10] which could help general practitioners and prevention workers to identify people at risk of relapse.

A 30-year prospective study among males observed that higher drinking frequency predicted relapse [11]. Longitudinal epidemiological studies have observed that past alcohol consumption predicted AUD incidence [12,13] and persistence [4,6], but to our knowledge, relapse after AUD remission has not been examined. There is also population-based evidence for the role of the number of AUD symptoms in predicting relapse [7], but the predictive value of specific AUD symptoms on relapse remains under-researched. Such information could be valuable because dependence symptoms and craving, rather than abuse symptoms, have been shown to be important predictors of AUD persistence in a longitudinal population-based study [14]. Specific symptoms may predict a severe course of AUD, including relapse. Moreover, as past alcohol intake and AUD symptoms are related [15], these aspects should be examined in relation to one another in order to determine their predictive value.

Furthermore, at-risk drinking during remission may present an additional risk [7]. Previous research has shown that roughly one-third of those in remission drink considerably (> 7 drinks weekly for women and > 14 drinks weekly for men [6,7]), and are at increased risk of relapse [7,15]. Moreover, at-risk drinking during remission may moderate the relationship between past alcohol intake and number or type of AUD symptoms and relapse. In particular, people with a high past alcohol intake or a high number of lifetime AUD symptoms who drink considerably during remission may have a particularly high risk of relapse.

This article aims to establish the predictive value of past alcohol intake, number and type of lifetime AUD symptoms and alcohol intake during remission on AUD relapse. Data are from a general population survey with 506 people in AUD remission in the 12-months before baseline and their 3-year follow-up. The study examines whether: (i) high past alcohol intake and a high number of lifetime AUD symptoms each predict AUD relapse; (ii) lifetime AUD symptom type predicts relapse independently of past alcohol intake; (iii) at-risk drinking during remission, i.e. current at-risk drinking, predicts relapse and moderates the relationship between lifetime AUD characteristics and relapse.
METHODS

Sample
Data were obtained from the first two waves of the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2); a prospective epidemiologic survey in the general Dutch population. Baseline data were collected between November 2007 and July 2009. A multistage, stratified, random sampling procedure of households was applied with one respondent randomly selected in each household [16]. This resulted in a total sample of 6,646 adults aged 18-64 (response: 65.1%) at baseline.

The Composite International Diagnostic Interview (CIDI) 3.0 was used at baseline (T0) and 3-year follow-up (T1) to identify drinking patterns and AUD diagnoses. Specifically, a lifetime version was administered at T0 and a 3-year version at T1. The CIDI is a fully structured, lay administered, internationally recognized interview developed by the WHO. Clinical reappraisal interviews indicate good validity [17].

Cohort
Using both retrospective and prospective data, we aimed to study the time to relapse for AUD in relation to associated risk factors among respondents in remission. To compile the study sample, respondents with a lifetime AUD diagnosis at T0 (n = 706) were identified. Next, 198 individuals with a current AUD episode at T0 and two individuals with invalid data on ‘age of last AUD episode’ were excluded. Of the remaining 506 subjects at risk of relapse, 421 (83.2% of T0) were interviewed again at 3-year follow-up (T1). Attrition was not associated with demographics (age and sex), past alcohol consumption level, number and type of lifetime AUD symptoms or current at-risk drinking (univariable analyses).

Assessments
Alcohol use disorder and symptoms. The CIDI 3.0 [18] assessed lifetime (T0) and 3-year (T1) presence of all separate DSM-5 AUD symptoms of alcohol abuse, dependence and craving [19]. The CIDI 3.0 assessed recency of the last episode of AUD retrospectively at T0: respondents were asked at what age the previous AUD episode ended. The relapse age was assessed at T1: respondents were asked at what age the first episode of AUD since T0 began. The DSM-5 cluster criterion (≥ 2 symptoms in the same 12-month period) was not included in our diagnosis [6;20;21]. Based on DSM-5 severity levels, the lifetime number of symptoms was categorized as mild (2-3 symptoms), moderate (4-5 symptoms) or severe (≥ 6 symptoms) AUD.

Relapse. Relapse was deemed to have occurred if respondents reported ≥ 2 DSM-5 AUD symptoms between T0 and T1. Time to relapse was assessed using the age of recency reported at T0 and the relapse age collected at T1. For example, if a respondent was 48 at T0 and the previous episode of AUD ended at age 43, the time in remission...
was five years at baseline. If another episode of AUD is reported between T₀ and T₁ at age 49, time to relapse is 6 years.

**Alcohol consumption.** Past alcohol intake was calculated by multiplying answers to two questions: “Think about the years in your life when you drank most. During those years, how often did you usually have at least one drink: every day, nearly every day, 3-4 days a week, 1-2 days a week, 1-3 days a month, or less than once a month?” and “On the days you drank during those years, about how many drinks did you usually have per day?”. Next, a categorical variable was constructed with three levels of past alcohol intake: low-risk drinking with ≤ 14/21 drinks weekly for women/men; medium-risk drinking with 15-28/22-42 drinks weekly for women/men; and high-risk drinking with ≥ 29/43 drinks weekly for women/men. The first cut-off point was drawn from internationally recognized low-risk drinking guidelines [22;23]; the second cut-off point doubled these numbers and was used to identify a high-risk group. Respondents answered two similar questions about alcohol intake in the past 12-months to assess current intake. Current at-risk drinking was set at ≥ 8/15 drinks weekly for women/men, a lower level than that used to assess past intake, in line with previous research [6;7].

**Statistical analyses**

AUD relapse (yes/no) during the 3-year follow-up period was the primary outcome variable. The Kaplan–Meier curve was used to estimate cumulative relapse rates, which are somewhat higher than unadjusted relapse rates, due to a correction for censored data [24]. For each year since remission, a relapse rate is calculated by dividing the number of people who relapsed by the number still at risk, thus without censored data for that point in time (i.e., data from those who already relapsed or those with a more recent remission). Cumulative relapse rates are calculated by multiplying the relapse rates reported up to that point. Thus, all respondents, including those not assessed at follow-up, were included in the analyses (n = 506).

After a check of the proportional hazards assumption (the shape of the survival function must be the same for all levels of a particular risk factor), both univariable and multivariable Cox regression analyses were performed to examine predictors for time to relapse, both separately and in relation to one another. This method corrects for censored data [24]. Finally, whether current at-risk drinking moderated the association between lifetime predictors (past alcohol intake, number of lifetime AUD symptoms, and significant symptom type) and AUD relapse was investigated using an additive model: additive interaction exists if the combined effect of lifetime characteristics and current at-risk drinking on AUD relapse is stronger than the sum of the separate effects. Additive interaction was tested by comparing the hazard ratio (HR) of lifetime characteristics and current at-risk drinking combined with the expected value in the event of no interaction: HR (AB) ≈ HR (A) + HR (B) - 1. If the expected HR is smaller
than the lower threshold of the 95% confidence interval for the HR of the combined effect, additive interaction is assumed [25-28].

Analyses were performed using Stata version 12.0 [29]. The data were weighted to correct for baseline differences in the response rates in different population groups and differences in the probability of respondent selection within households. As previous research suggests that age and sex affect relapse rates [7;30], all analyses were adjusted for age and sex.

RESULTS

Description of the sample

Table 5.1 shows age and sex of the total group and the separate alcohol use disorder characteristics. The majority of the 506 respondents in remission from DSM-5 AUD were male (76.0%) and had a mean age of 40 years (SE = 0.8). At baseline (T₀), time since remission ranged from 1 to 48 years with an average of 11 years (SE = 0.6) (not in table). Between T₀ and T₁, 46 respondents developed two or more DSM-5 AUD symptoms and were thus deemed to have relapsed. The estimated cumulative relapse rate was 1.4% at 1 year, 2.9% at 2 years, 5.6% at 5 years, 9.1% at 10 years and 12.0% at 20 years (Figure 5.1). Thereafter, remission appeared quite stable with a total cumulative relapse rate of 12.8% after 22 years.

Figure 5.1. Kaplan-Meier curve of time to relapse of DSM-5 alcohol use disorder (AUD) in a cohort of respondents in remission from AUD at baseline (n = 506). The risk table presents the number of respondents at risk at the corresponding point in time.
Alcohol use disorder characteristics as predictors of relapse

Respondents had a mean past alcohol consumption level of approximately 50 drinks weekly (SE = 5.6) and reported on average 3.4 lifetime AUD symptoms (SE = 0.1). Notably, the correlation coefficient between past alcohol intake and number of lifetime symptoms was only 0.32. Table 5.1 shows that respondents were equally distributed across the three past alcohol intake categories. Moreover, the majority of the respondents (71.6%) reported lifetime mild AUD (2-3 symptoms), 14.0% reported moderate AUD (4-5 symptoms) and 14.4% reported severe AUD (≥ 6 symptoms). Univariable analyses showed that both medium (15-28/22-42 drinks weekly for women/men) and high (≥ 29/43) alcohol intake predicted relapse, as did lifetime severe AUD, but not lifetime moderate AUD. The multivariable model showed that high alcohol intake did not significantly predict relapse, but medium alcohol consumption and lifetime severe AUD did when adjusted for each others’ effect. Based on these findings, two dichotomous variables were constructed for further analyses, for medium to high alcohol intake (yes/no) and presence of lifetime severe AUD (yes/no).

Prevalence was highest for the lifetime AUD symptoms ‘larger quantities or longer than intended’ and ‘hazardous use’, and lowest for ‘important activities given up or reduced’ and ‘continued use despite physical or psychological harm’ (Table 5.2). In the univariable analyses, risk of relapse was higher for the lifetime AUD symptoms ‘impaired control over use’, ‘use despite social or interpersonal problems’, and ‘craving’. In the first multivariable model, which included symptoms with $p < 0.10$ in the univariable analyses, only ‘impaired control over use’ predicted relapse. The second multivariable model also included past alcohol intake and results showed that both ‘impaired control over use’ and past alcohol intake predicted relapse, independently of one another.

Current at-risk drinking

At baseline, 31.3% (n = 155) of the respondents reported current at-risk drinking, i.e. ≥ 8/15 drinks weekly for women/men during remission. The cumulative relapse rate of respondents with current at-risk drinking (25.3% after 20 years) was twice that of the overall cumulative relapse rate (12.0%). Current at-risk drinking predicted relapse in both univariable (HR = 4.74, 95% CI = 2.09; 10.78) and multivariable analyses [adjusted for significant lifetime characteristics: at least medium alcohol intake, lifetime severe AUD, and ‘impaired control over use’ (HR = 4.92, 95% CI = 2.16; 11.17)]. Moreover, moderation analyses demonstrated that current at-risk drinking exacerbated the effect of medium to high alcohol intake (HR = 9.72, 95% CI = 2.87; 32.94) and lifetime severe AUD (HR = 25.84, 95% CI = 9.05; 73.76) on the risk of relapse, but no significant moderation was observed with the lifetime AUD symptom ‘impaired control over use’ (Table 5.3).
Table 5.1. Past alcohol intake and number of lifetime AUD symptoms as predictors of AUD relapse (n = 46) in individuals with a DSM-5 AUD in diagnostic remission for at least 12 months at baseline (n = 506). Descriptives and results of Cox survival analyses in hazard ratios (HRs) with 95% confidence intervals (95% CI).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Predicting relapse</th>
<th>Cumulative relapse rate</th>
<th>Univariable b</th>
<th>Multivariable b, c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sex %</td>
<td>Age % male</td>
<td>mean (SE)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Total sample</td>
<td>100.0</td>
<td>76.0</td>
<td>40.4 (0.8)</td>
<td>12.0</td>
</tr>
<tr>
<td>Past alcohol intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-risk drinking</td>
<td>32.5</td>
<td>78.8</td>
<td>38.3 (1.3)</td>
<td>4.6</td>
</tr>
<tr>
<td>Medium-risk drinking</td>
<td>33.7</td>
<td>77.3</td>
<td>40.0 (1.5)</td>
<td>16.3</td>
</tr>
<tr>
<td>High-risk drinking</td>
<td>33.8</td>
<td>72.0</td>
<td>42.9 (1.2)</td>
<td>14.2</td>
</tr>
<tr>
<td>Number of lifetime AUD symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild: 2-3 symptoms</td>
<td>71.6</td>
<td>74.3</td>
<td>40.6 (1.0)</td>
<td>9.3</td>
</tr>
<tr>
<td>Moderate: 4-5 symptoms</td>
<td>14.0</td>
<td>76.7</td>
<td>38.3 (1.4)</td>
<td>10.9</td>
</tr>
<tr>
<td>Severe: ≥ 6 symptoms</td>
<td>14.4</td>
<td>83.9</td>
<td>41.5 (2.0)</td>
<td>27.9</td>
</tr>
</tbody>
</table>

Note. * Not calculated; ** p < 0.05; *** p < 0.01. AUD: alcohol use disorder; Low-risk drinking: ≤ 14/21 drinks weekly for women/men; Medium-risk drinking: 15-28/22-42 drinks weekly for women/men; High-risk drinking: ≥ 29/43 drinks weekly for women/men.

* Cumulative relapse rate after 20 years calculated for each predictor; overall cumulative relapse rate after 20 years = 12.0%.

b Analyses were adjusted for sex and age.

¹ Predictors that had p < 0.10 in the univariable analyses were included.
Table 5.2. Lifetime AUD symptoms as predictors of AUD relapse (n = 46) in individuals with a DSM-5 AUD in remission for at least 12 months at baseline (n = 506). Results of Cox survival analyses in hazard ratios (HRs) with 95% confidence intervals (95% CI).

<table>
<thead>
<tr>
<th>Lifetime AUD symptoms</th>
<th>%</th>
<th>Cumulative relapse rate a</th>
<th>Univariable b</th>
<th>Multivariable b, c</th>
<th>Multivariable b, d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Larger quantities or longer than intended</td>
<td>81.3</td>
<td>13.8</td>
<td>2.86 (0.73; 11.20)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Impaired control over use</td>
<td>25.8</td>
<td>27.2</td>
<td>4.74*** (2.07; 10.86)</td>
<td>3.68*** (1.77; 7.64)</td>
<td>3.70*** (1.76; 7.77)</td>
</tr>
<tr>
<td>Great deal of time spent obtaining, using or recovering</td>
<td>20.6</td>
<td>21.6</td>
<td>2.04 (0.86; 4.82)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Failure to fulfill major role obligations</td>
<td>38.2</td>
<td>15.4</td>
<td>1.63 (0.79; 3.38)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Continued use despite social or interpersonal problems</td>
<td>16.9</td>
<td>21.0</td>
<td>2.34* (1.01; 5.39)</td>
<td>1.44 (0.70; 2.97)</td>
<td>1.35 (0.65; 2.79)</td>
</tr>
<tr>
<td>Important activities given up or reduced</td>
<td>11.4</td>
<td>19.7</td>
<td>1.55 (0.66; 3.67)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hazardous use</td>
<td>59.2</td>
<td>10.9</td>
<td>0.73 (0.37; 1.42)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Use despite physical or psychological harm</td>
<td>14.5</td>
<td>23.7</td>
<td>2.46+ (0.99; 6.12)</td>
<td>1.09 (0.45; 2.61)</td>
<td>1.22 (0.49; 3.05)</td>
</tr>
<tr>
<td>Tolerance</td>
<td>27.9</td>
<td>13.9</td>
<td>1.46 (0.66; 2.31)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>15.3</td>
<td>16.7</td>
<td>1.62 (0.74; 3.57)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Craving</td>
<td>25.4</td>
<td>22.6</td>
<td>2.79** (1.35; 5.78)</td>
<td>1.62 (0.89; 2.93)</td>
<td>1.29 (0.67; 2.47)</td>
</tr>
<tr>
<td>Past medium-risk drinking</td>
<td>67.5</td>
<td>15.4</td>
<td>3.84* (1.30; 11.33)</td>
<td>-</td>
<td>3.39* (1.13; 10.16)</td>
</tr>
</tbody>
</table>

Note. - Not calculated; + p < 0.10; * p < 0.05; ** p < 0.01; *** p < 0.001. AUD: alcohol use disorder. Past medium-risk drinking: ≥ 15/22 drinks weekly for women/men.

a Cumulative relapse rate after 20 years calculated for each predictor; overall cumulative relapse rate after 20 years = 12.0%.

b Analyses were adjusted for sex and age.

c All lifetime AUD symptoms that had p < 0.10 in the univariable analyses were included.

d All lifetime AUD symptoms that had p < 0.10 in the univariable analyses and past medium-risk drinking were included.
Table 5.3. Combined effects of lifetime characteristics and current at-risk drinking on relapse (n = 46) in individuals with a DSM-5 AUD in diagnostic remission for at least 12 months at baseline (n = 506). Results of Cox survival analyses in hazard ratios (HRs) with 95% confidence intervals (95% CI).

<table>
<thead>
<tr>
<th>Combined effect of Lifetime severe AUD</th>
<th>Relapse a</th>
<th>Expected HR b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past medium-risk drinking</td>
<td>Current at-risk drinking</td>
<td>HR (95% CI) p</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>1.00 (- -)</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>1.98 (0.45; 8.68)</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>1.48 (0.22; 9.96)</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>9.72 (2.87; 32.94)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combined effect of Impaired control over use</th>
<th>Relapse a</th>
<th>Expected HR b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past medium-risk drinking</td>
<td>Current at-risk drinking</td>
<td>HR (95% CI) p</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>1.00 (- -)</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>4.33 (0.92; 20.44)</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>5.48 (2.44; 12.28)</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>25.84 (9.05; 73.76)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combined effect of Impaired control over use</th>
<th>Relapse a</th>
<th>Expected HR b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past medium-risk drinking</td>
<td>Current at-risk drinking</td>
<td>HR (95% CI) p</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>1.00 (- -)</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>9.11 (2.31; 35.98)</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>8.68 (2.58; 29.20)</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>29.65 (9.80; 89.69)</td>
</tr>
</tbody>
</table>

Note. - Not calculated. In bold means significant at 0.05 for the combined effect. AUD: alcohol use disorder; Current at-risk drinking: ≥ 8/15 drinks weekly for women/men; Past medium-risk drinking: ≥ 15/22 drinks weekly for women/men; Lifetime severe AUD: ≥ 6 lifetime AUD symptoms.

a Analyses were adjusted for sex and age.

b Expected HR in the case of no interaction is the sum of the separate effects of the lifetime characteristic and current at-risk drinking. Additive interaction is assumed if the expected HR lies below the lower limits of the confidence intervals of the combined effect of the lifetime characteristic and current at-risk drinking.

DISCUSSION

Key findings

In this longitudinal population-based study, the cumulative relapse rate of DSM-5 AUD after 20 years was only 12%, with very few new cases of relapse. Past alcohol intake and number of lifetime symptoms were important predictors, each contributing to the risk of relapse, independently. Therefore, both characteristics could be used to target relapse prevention efforts. This was also true for the lifetime AUD symptom ‘impaired control over use’. Special attention should be paid to reducing intake among people in remission: this was a strong independent predictor of relapse and current at-risk drinking exacerbated the effect of past alcohol consumption levels and number of lifetime AUD symptoms on the risk of relapse.
Limitations
When interpreting the findings, the following limitations should be taken into account. First, the DSM-5 clustering criterion (≥ 2 symptoms in the same 12-month period) was not included in our AUD diagnosis [6;20;21]. This may have resulted in some overestimation of the lifetime prevalence of AUD. However, this effect is likely to be small because multiple symptoms have been shown to be associated with poor outcomes, regardless of 12-month clustering [31]. Second, the CIDI 3.0 was designed and validated for the assessment of DSM-IV AUDs [17], not for DSM-5 AUD. Although the criteria used in DSM-IV and DSM-5 are very similar, reliability of the DSM-5 AUD diagnosis based on the CIDI 3.0 is unknown and could be lower than for DSM-IV, which may have resulted in a somewhat higher relapse rate. Third, in line with other population-based surveys, alcohol intake and AUD symptoms and AUD remission were assessed by self-report. Reports on such behavior may be influenced by social stigma. Moreover, people may have difficulties remembering which symptoms were present or the exact time since the last episode of AUD, particularly people in long-term remission. Such biases may have resulted in an underestimation of the predictive value of past drinking levels and lifetime AUD symptoms. Fourth, in prospective studies, the internal validity of findings may be affected by selective attrition [32-34]. Assuming that censoring is noninformative (independent of the study outcome – in this instance AUD relapse), Cox regression deals with censored data. In NEMESIS-2, attrition was not associated with DSM-IV mental disorders after adjusting for sociodemographic characteristics [35] and we observed no association between attrition and relapse predictors in the present study. Therefore, sample attrition is unlikely to have an important effect on our findings. Finally, the present study focused on easily quantifiable markers of AUD relapse. However, a broader set of risk factors, such as comorbid psychopathology and childhood maltreatment, is likely to be relevant for prediction of relapse and should be examined in future research.

Findings
This major longitudinal population-based study shows that only a small minority of people with lifetime AUD experience a relapse [5;7] - the cumulative relapse rate after 20 years was 12.0%. Comparison with previously observed relapse rates is difficult due to methodological differences. For example, a previous prospective general population study in the Netherlands [5] observed a 2-year relapse rate of DSM-IV alcohol abuse and alcohol dependence of 10.0% and 13.6%, respectively. Initially, this seems much higher than our cumulative 2-year relapse rate (2.9%). However, that study only included people in 12-month diagnostic remission [5], thus, no individuals in long-term remission, whereas risk of relapse decreases with time since remission [7]. Post-hoc analyses confirmed that the focus on individuals only recently in remission explains this discrepancy. Specifically, 41 participants in our study had a remission time of only 1 year at baseline and their relapse rate at 3-year follow-up was 14.8%, i.e. comparable to
Predicting alcohol use disorder relapse

The previous study in the Netherlands. Thus, taking into account time since remission has a major impact on the findings and is therefore an essential factor when examining predictors for relapse. Moreover, as this was the first population-based study, which assessed time to relapse, we could observe that the relapse was quite stable at a very low level after 20 years.

The weak correlation coefficient between past alcohol intake and number of lifetime AUD symptoms is in line with previous, cross-sectional, findings from NEMESIS-2. Specifically, limited overlap between excessive drinking and AUDs was observed, suggesting that these factors are indicative of discrete aspects of problematic alcohol use [21]. The current study observed that past alcohol intake and number of lifetime AUD symptoms both predicted relapse, independently of one another. General practitioners could use both aspects to identify people with lifetime AUD at-risk of relapse. In DSM-5, AUD severity is assessed on a scale based on the number of symptoms: mild (2-3 symptoms), moderate (4-5 symptoms) and severe (≥ 6 symptoms). Whereas there were no significant difference in relapse risk between those with mild and those with moderate AUD, the small group of people with severe AUD (14.4%) were at substantially higher risk of relapse. Even though prevention of relapse in the larger group with mild or moderate AUD could prevent more costs at societal level [36], targeting this smaller, but more severe group seems more efficient, given the strong association with relapse. The effect of past alcohol intake was somewhat difficult to ascertain as the risk of relapse was substantially increased in groups with past alcohol intake of just ≥ 15/22 drinks weekly for women/men, including two-thirds of those in AUD remission. This group is much too large for targeted prevention and therefore past alcohol consumption may be better used as a marker for relapse in combination with other risk factors.

Of the specific AUD symptoms, we found that ‘impaired control over use’ (lifetime prevalence: 25.8%) was the strongest predictor of relapse both in univariable analyses and when controlled for the presence of other significant symptoms and past alcohol intake. This specific AUD symptom has also been found to predict other associated phenomena, such as incidence of substance use disorders [37;38] and AUD persistence [14]. The present findings show that even when people with this symptom succeed in controlling their drinking and remit from AUD, risk of relapse remains high, i.e., more than a quarter of them relapsed within 20 years. In the CIDI 3.0, the exact wording of this symptom was: “Were there times when you tried to stop or cut down on your drinking and found that you were not able to do so?”. Notably, this is somewhat stricter than the DSM-5 definition of the symptom (i.e., “persistent desire or unsuccessful efforts to cut down or control use”) and also stricter than the definition of impaired control in the early models of alcoholism, which more generally referred to an “inability to control one’s drinking” [39;40]. Even though the rather strict CIDI definition may have strengthened the role of impaired control in the prediction of relapse, the definition is concrete and can be easily and reliably assessed [17]. Moreover, the early models of
alcoholism already described loss of control as a core aspect of alcoholism and that perspective is supported by the current findings.

Regarding craving, findings in this population-based study only partly confirm previous clinical findings in which craving was identified as an important predictor for relapse [41]. Previous epidemiological research has led to skepticism with regard to the role of craving in the diagnosis of AUD. For example, Keyes et al. observed that with the addition of craving, few new cases were identified and only limited additional information regarding severity of the disorder was obtained [42]. Nevertheless, our findings suggest that lifetime craving might be of some value in identifying people at risk of relapse as more than one-fifth of the individuals with lifetime presence of craving relapsed within 20 years.

In line with previous research [7], we observed that at-risk drinking during remission increased the risk of relapse. This was also the case when adjusted for the effect of other significant lifetime predictors. As current drinking patterns can be easily identified, at-risk drinking may provide an adequate starting point for relapse prevention. Moreover, we observed that an accumulation of risk factors substantially increased the likelihood of relapse. Particularly, at-risk drinking during remission intensified the relationship between medium to high past alcohol intake and relapse, as well as that between lifetime severe AUD and relapse. This suggests that for people with those severe lifetime characteristics of AUD, special attention should be given to drinking habits during remission. Focus on abstinence or very low intake is advisable for this group.

Implications
Our findings suggest that lifetime AUD characteristics may help to detect individuals at risk of chronic, recurrent AUD. Those with higher past alcohol intake or more lifetime AUD symptoms, as well as those with ‘impaired control over use’ seem to have an increased risk of relapse. Careful monitoring and assistance for people with these characteristics may prevent relapse. In addition, special attention should be paid to drinking patterns during remission. Reduced-risk drinking is frequently used in web-based interventions [43;44] and clinical settings [45], but a focus on abstinence or very low intake seems preferable [7].

REFERENCES


