Drinking Distilled. Onset, course and treatment of alcohol use disorders in the general population
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Chapter 1

General introduction
BACKGROUND

Alcohol is the most frequently used drug in Western countries: about 85% of the adults in Europe drank alcohol in the past year [1] and according to Statistics Netherlands, Dutch drinkers consume on average one alcoholic drink every day [2]. The strong embedding of alcohol in society is marked by the central role of alcohol use in social interactions [3]. Common motives to drink are: to relax, to get a good or pleasant feeling, because it is fun or sociable, or because it is part of a celebration [4]. These positive aspects aside, important downsides of alcohol use should not be ignored: excessive alcohol use is probably more harmful for the individual and society than the use of most illicit drugs [5-7]. Although drinking is often considered a social convention, maladaptive drinking patterns can interfere substantially with social functioning, as well as with family life, career, school and with mental and physical health [8-10]. This interference may be indicative of the presence of an alcohol use disorder (see Tables 1.1 and 1.2). In the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), two alcohol use disorders are distinguished based on number and type of criteria: alcohol abuse (≥ 1 of 4 criteria) and dependence (≥ 3 of 7 criteria) [11]. The recently introduced fifth edition of the DSM defines a single alcohol use disorder based on a combination of DSM-IV abuse and dependence criteria (≥ 2 of 11 criteria) with different levels of severity depending on the number of criteria that are met (mild: 2-3 criteria; moderate: 4-5 criteria; severe: ≥ 6 criteria) [12].

Alcohol use disorders affect approximately 76 million people worldwide [13] and about half a million people in the Netherlands [14]. Particularly alcohol dependence is associated with a high disease burden [10;15] and with mortality [16]: about two-thirds of all alcohol-related mortality is caused by the 4% of alcohol users with a diagnosis of alcohol dependence [17]. Therefore, prevention and treatment of, especially severe, alcohol use disorders should be considered a public health priority. In order to plan prevention and treatment, information is needed about alcohol use disorders, their course and their risk indicators in the general population. However, current knowledge is strongly skewed because of the emphasis of research on alcohol use disorders in clinical samples, i.e. the subgroup of people who entered treatment and often have very severe alcohol use disorders and serious comorbidity. However, most people with an alcohol use disorder do not enter treatment [18]. Although longitudinal population-based research is costly and complex, it is crucial to increase our understanding of demographic and clinical characteristics of alcohol use disorders in the general population, such as age, sex, chronicity of the disorder, level of impairment, consumption level and comorbid psychopathology. This information is needed to efficiently target prevention and treatment to those cases in greatest need for help.

Notably, the few existing community studies suggest that alcohol use disorders in the general population are generally milder than in clinical samples and that valid notions in clinical samples may not be true in the general population (e.g. an alcohol
use disorder is inherently related to excessive drinking; an alcohol use disorder is a chronic illness; all people with an alcohol use disorder need treatment) [19-22]. Hence, besides identification of those groups in the general population that are more likely to develop alcohol problems, examination of the disorder itself in the general population is crucial. Among others, these studies should investigate the following questions: to which degree are alcohol use disorders related to the level of alcohol intake, what determines whether individuals reach (stable) remission while others do not, and is treatment seeking related to the level of drinking or the severity of the alcohol use disorder? Therefore, this thesis maps the onset, course and treatment of alcohol use disorders in the general population. It examines potential risk indicators of a severe or persistent disorder with specific consideration for possible effects of the level of alcohol intake. These issues are examined using data from the second Netherlands Mental Health Survey and Incidence Study (NEMESIS-2), a longitudinal population-based study among Dutch adults aged 18-64.

Table 1.1. Definitions of alcohol use disorder according to the two versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM): DSM-IV and DSM-5.

A maladaptive pattern of alcohol use, leading to clinically significant impairment or distress...

**DSM-IV: Alcohol Abuse**

...as manifested by at least 1 (or more) of the following, occurring within a 12-month period:

1. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
2. Recurrent alcohol use in situations in which it is physically hazardous.
3. Recurrent alcohol-related legal problems.
4. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.

**DSM-IV: Alcohol Dependence**

...as manifested by 3 (or more) of the following, occurring at any time in the same 12-month period:

1. Tolerance, as defined by either of the following:
   a. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
   b. A markedly diminished effect with continued use of the same amount of alcohol.
2. Withdrawal, as manifested by either of the following:
   a. The characteristic withdrawal syndrome for alcohol.
   b. Alcohol is taken to relieve or avoid withdrawal symptoms.
3. Alcohol is often taken in larger amounts or over a longer period than was intended.
4. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
5. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
6. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
7. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.

**DSM-5: Alcohol use disorder**

...as manifested by at least 2 of the following, occurring at any time in the same 12-month period:

Craving, or a strong desire or urge to use alcohol.

2-11. All abuse and dependence criteria indicated above, except abuse criterion 3 (‘legal problems’).
Onset of drinking and of alcohol use disorders

Previous research has shown that environmental factors, including parental and school influences [19], play an important role in initiation of alcohol use, but that their effect on the development of problem drinking and the onset of alcohol use disorders is relatively small [20]. However, specific influences, such as childhood psychopathology and traumatic experiences, are important to identify who is at risk of problem drinking or the onset of an alcohol use disorder [20;21]. This thesis specifically focuses on one such influence: the presence of attention-deficit/hyperactivity disorder (ADHD) in childhood. This focus was chosen because previous research suggests that childhood ADHD may be especially useful for timely detection of alcohol-related problems: ADHD generally presents itself at an early age and meta-analyses have shown that ADHD is related to a higher prevalence of alcohol use disorder [27;28]. However, the nature of the link between ADHD and alcohol use disorders is not completely clear and other factors may play an important (confounding) role in this relation [27]. One such factor is conduct disorder (CD): children with ADHD often have a comorbid CD [29], which is also associated with a high risk of alcohol use disorders [30;31]. Previous research showed that children with both ADHD and CD have a higher rate of alcohol use disorders than children with only ADHD [32;33]. The few studies explicitly addressing the role of CD in the association between ADHD and alcohol use (disorder) were inconclusive and pointed to different underlying processes [34-39]. Moreover, most of these studies focused on adolescents or young adults [35-39] and were thus limited to early onset alcohol use disorders. To extend our knowledge into later alcohol use disorders, this thesis examines the role of CD in the relationship of childhood ADHD with alcohol use and alcohol use disorder using retrospective data of a large adult general population sample.

Table 1.2. Alcohol use disorder: DSM-IV vs. DSM-5

The fifth edition of the DSM was released in 2013 [12]. Instead of the two disorders defined in DSM-IV (alcohol abuse [≥ 1 of 4 criteria] and alcohol dependence [≥ 3 of 7 criteria]) [11], DSM-5 has only one alcohol use disorder with three severity levels: mild (2-3 of 11 criteria), moderate (4-5 of 11 criteria), and severe (≥ 6 of 11 criteria) alcohol use disorder. The main reasons for these changes were [59;60]:

- Limited reliability, validity and clinical relevance of alcohol abuse. Alcohol abuse only required presence of one criterion, a diagnosis could thus easily be obtained and was associated with limited stability [61]. DSM-5 removed the diagnosis alcohol abuse and the threshold for an alcohol use disorder diagnosis was set at presence of two criteria.

- Although people with two dependence criteria but no alcohol abuse generally showed more severe pathology than those with a single abuse criterion, they were not diagnosed with an alcohol use disorder in DSM-IV [62;63]. With the new DSM-5 threshold of two or more criteria, these individuals are diagnosed with a mild alcohol use disorder.

- The DSM-IV assumed that abuse preceded the development of alcohol dependence, but research showed otherwise: abuse and dependence criteria are arrayed along a continuum of severity with abuse criteria not always representing the lower level of severity [64]. Therefore, abuse and dependence criteria are combined in DSM-5. Notably, one criterion (legal problems) was removed and another criterion (craving) was added.
Relationship between excessive drinking and alcohol use disorder

The diagnosis of an alcohol use disorder according to psychiatric classification systems such as the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) does not require a minimum level of alcohol consumption [11;12]. It could be argued that excessive drinking is necessary for the development of alcohol-related problems and therefore is an implicit characteristic of the disorder. Although this widespread assumption is supported by the frequently quoted strong link between alcohol use disorders and heavy drinking [8;40;41], findings from the first Netherlands Mental Health Survey and Incidence Study (NEMESIS-1) revealed that this notion is not true for the majority of individuals in the general population with an alcohol use disorder [42]. Only one-third of the individuals with DSM-III-R alcohol abuse and only half of those with alcohol dependence were risky drinkers, defined as drinking more than 14/21 (women/men) drinks per week. In addition, other community studies showed that alcohol-related problems may already occur at relatively low levels of consumption [43;44]. However, the limited overlap between alcohol consumption levels and the presence of alcohol use disorders is not properly understood, partly because these aspects of problematic alcohol use are generally examined separately. Psychiatric surveys mainly report on alcohol use disorder diagnoses without addressing related alcohol consumption levels, whereas public health studies tend to focus on excessive drinking and largely disregard the presence of alcohol use disorders [45].

Simultaneous investigation of excessive drinking and alcohol use disorder is needed to gain more insight in the degree of overlap, and to increase our knowledge about different groups of problematic alcohol users: excessive drinkers without alcohol-related problems, people with alcohol-related problems who do not drink excessively, and people with both characteristics. Moreover, these subgroups may be associated with different patterns of comorbid psychopathology (e.g. mood or anxiety disorders) or functioning. Information regarding such clinical characteristics could thus provide an indication of the clinical relevance of the subgroups. This thesis will therefore address the overlap and differences between excessive drinking and alcohol use disorders by comparing characteristics of excessive drinking only, alcohol use disorder only or both.

Course of alcohol use disorders

Research among patients in addiction treatment suggests that the course of alcohol use disorder is usually chronic and associated with repeated relapses [19]. Information regarding the course of alcohol use disorder in the general population is scarce, mainly because this requires longitudinal population-based research. Yet, the course of alcohol use disorder in the general population has been mapped out by two such studies: NEMESIS-1 and the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), conducted in the United States. In contrast with observations in clinical samples, these community studies observed that alcohol use disorders in the general population generally have a favorable course: approximately 60-85% showed
spontaneous (i.e. without formal treatment) diagnostic remission within three years [20;46], with only a small minority of those in remission experiencing relapse [20;21].

Given these high sustained spontaneous remission rates it seems essential to identify risk indicators for the minority with an alcohol use disorder in the general population at risk of a persistent or relapsing course. Specifically, such indicators may improve allocation of care as low intensity interventions could be sufficient for most people while those at risk of a persistent course may need more intensive treatment. Predictors of a chronic course in the general population are available only from the NESARC study, showing that neither sociodemographics nor the presence of psychiatric comorbidity were strongly associated with the persistence of an alcohol use disorder. However, a higher number of alcohol use disorder criteria (i.e. severity) did predict both a persistent course [22] and relapse [21]. Persistence was also associated with a higher level of alcohol consumption [22], but the role of consumption was not examined with respect to relapse. This thesis extends the previous observations in two important ways. First, it aims to replicate the findings of NESARC regarding the persistence of alcohol use disorders in order to verify the validity of these findings for the Netherlands. Second, it aims to study the role of the level of alcohol consumption on relapse after diagnostic remission. This is important, because diagnostic remission from an alcohol use disorder is not the same as abstinence from alcohol use since continued high levels of drinking may occur during remission. This would not only suggest that high remission rates should be interpreted with caution, it may in fact mark an increased risk of relapse of an alcohol use disorder.

**Treatment seeking for alcohol use disorders**

A robust worldwide finding of previous research has been that the number of individuals with an alcohol use disorder greatly exceeds the number of people in treatment [47]. This is also true for the Netherlands. According to NEMESIS-2, approximately 478,000 adults aged 18-64 were affected by an alcohol use disorder in The Netherlands in the period 2007 to 2009 [14]. However, according to the Dutch national alcohol and drugs information system (LADIS), only a little over 30,000 people (i.e. 6.5% of those with an alcohol use disorder) entered addiction treatment because of alcohol problems in 2008 [48]. This very low rate of addiction treatment for people with an alcohol use disorder has been stable for the past five years [48].

Concerns about this treatment gap have been raised for decades [49-51], and several solutions have been proposed [52]. However, the magnitude of the treatment gap can be questioned given the high spontaneous remission rate of alcohol use disorders in the general population [20;22]. It is undesirable when severe cases do not receive treatment, but when non-treatment users turn out to be mild cases with a favorable course, their decision not to seek treatment may be justified and cost-effective. It is therefore important to understand to what extend severe clinical characteristics of alcohol use disorder are associated with treatment seeking. This has not been examined in the Netherlands so far, but a study in the United States found that illness severity in terms
of number of criteria and impairment played a role in the decision to seek treatment [18]. However, the level of consumption was not taken into account in that study. Particular attention should be paid to the potential unmet need for treatment of two distinct groups. First, people who do not seek treatment specifically for their alcohol problems but who do seek treatment for their comorbid mental health problems. When needed, these individuals can for example be guided to additional alcohol treatment via attention to dual diagnosis [53]. Second, people who neither seek treatment for mental health nor for alcohol problems. This group is more difficult to reach but possibly their unmet need for treatment could be signaled when they make a primary care visit for physical problems related to their excessive drinking [54].

**METHOD**

In this thesis, the onset, course and treatment of people with an alcohol use disorder in the general population are examined using data from the second Netherlands Mental Health Survey and Incidence Study (NEMESIS-2). NEMESIS-2 is an ongoing prospective cohort study examining the prevalence, incidence, course and consequences of mental disorders - including alcohol use disorders - in the general Dutch adult population. For the present thesis, data from the first two waves were available.

NEMESIS-2 is based on a multistage, stratified, random sampling of households, with one respondent randomly selected in each household. In the first wave (T₀), performed from November 2007 to July 2009, a total of 6,646 persons aged 18-64 were interviewed (response: 65.1%). The average interview duration was 95 minutes. This sample was nationally representative, although younger subjects were somewhat underrepresented [55]. All T₀ respondents were approached for follow-up (T₁), three years after T₀ from November 2010 to June 2012. Of this group, a total of 5,303 persons were interviewed again (response: 80.4%, with those deceased excluded). The average interview duration at the second wave was 84 minutes and the mean period between the two interviews was 3 years and 7 days. Attrition was not significantly linked to any of 12-month mental disorders at baseline, after controlling for sociodemographic variables such as age and sex [56]. Note that this was also true for the mental disorders under study here, alcohol use disorders.

Both waves consisted of a face-to-face interview, mostly held at the respondents’ home. The assessment included detailed information on sociodemographics, mental and physical functioning, service utilization, and mental disorders (i.e. externalizing childhood disorders, mood disorders, anxiety disorders, and substance use disorders). More specific, mental disorders according to the criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV [11]) were assessed using the third version of the Composite International Diagnostic Interview (CIDI 3.0) [57]. Clinical calibration studies conducted in various countries have found that the CIDI 3.0 assesses anxiety, mood and substance use disorders with generally good validity.
compared to blinded clinical reappraisal interviews [58]. Besides the diagnosis of alcohol use disorders, the alcohol section of the CIDI 3.0 also assesses: onset and recency of the disorder; age of first alcohol use and age of first regular use; quantity and frequency of alcohol use in the past 12 months and in a person’s most severe drinking period; the degree of alcohol-related functional impairment; and treatment contact for alcohol problems. In NEMESIS-2, a lifetime CIDI version was used at $T_0$; a CIDI version with the period between $T_0$ and $T_1$ as timeframe was used at $T_1$. Both at $T_0$ and $T_1$, also the presence of 12-month mental disorders was assessed.

**AIMS AND OUTLINE OF THIS THESIS**

The main objective of this thesis is to enhance our understanding of the onset, course and treatment of alcohol use disorder in the general population, with special emphasis on the role of ADHD and CD in the onset of alcohol use disorders and the level of alcohol consumption in remission and relapse. The core aspects of the thesis are described below. Notably, the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM), introducing a single alcohol use disorder, appeared in the period that NEMESIS-2 was conducted and the chapters of this thesis were written [12]. To provide up-to-date findings, the chapters that were written after the DSM-5 release (chapter 3 to chapter 6) focused on the DSM-5 alcohol use disorder.

- **Chapter 2** retrospectively examines the relationship of childhood ADHD and CD with (age of) onset of three stages of alcohol use measured at $T_0$: alcohol initiation, regular drinking (defined as $\geq 12$ drinks per year), and DSM-IV alcohol use disorder.
- **Chapter 3** examines the cross-sectional overlap between excessive alcohol consumption and both DSM-IV and DSM-5 alcohol use disorder at $T_0$. Three subgroups of problematic drinkers (excessive drinking only, alcohol use disorder only, excessive drinking and alcohol use disorder) are compared with non-problematic drinkers on demographics, psychiatric comorbidity, functioning and treatment utilization.
- **Chapter 4** investigates 3-year persistence rates and predictors of a persistent course of DSM-5 alcohol use disorders. Special attention is paid to the level of alcohol consumption in those achieving diagnostic remission.
- **Chapter 5** examines relapse at $T_1$ among those people with a lifetime but not a past-year DSM-5 alcohol use disorder at $T_0$. Also, predictors of relapse were examined with special emphasis on the number of lifetime alcohol use disorder criteria and the level of alcohol consumption.
- **Chapter 6** examines the 4-year treatment gap for DSM-5 alcohol use disorders. The process of treatment seeking is addressed by an examination of determinants of treatment seeking as well as by an investigation of how those without specialized alcohol treatment are functioning at follow-up.
- **Chapter 7** summarizes and discusses the main findings of the studies included in this thesis.
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