Drinking Distilled. Onset, course and treatment of alcohol use disorders in the general population
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Chapter 7

General discussion
KEY FINDINGS

This thesis confirms that most people in the general population with an alcohol use disorder have mild and transient problems, but also shows that an important minority suffers from severe and/or persistent problems. Importantly, most people with an alcohol use disorder in the general population do not drink excessively and this is even true for many of those with a large number of symptoms, i.e. those with DSM-IV alcohol dependence or with a moderate/severe DSM-5 alcohol use disorder. Nonetheless, excessive drinking is essential for the identification of people with a persistent alcohol use disorder, as are the number of alcohol use disorder criteria and the presence of comorbid psychiatric disorders (e.g. externalizing childhood disorders, adult anxiety disorder). Treatment seeking for alcohol use disorders is quite rare, but the mostly favorable course and the generally rational self-selection into treatment suggest that the public health relevance of this ‘treatment gap’ is limited.

METHODOLOGICAL CONSIDERATIONS

The findings in this thesis are based on data from the second Netherlands Mental Health Survey and Incidence Study (NEMESIS-2). This longitudinal study investigates the presence and course of mental disorders in a representative sample of the Dutch general adult population [1]. Such data is quite unique: worldwide only a handful of similar studies were performed in the past three decades [2-8]. This kind of research provides important information for prevention programs, the optimization of guidelines, and the planning of treatment services. Yet, some important restrictions should be noted.

First, despite the overall representativeness of general population studies, some important subgroups are generally excluded, such as institutionalized or homeless individuals. Others are underrepresented, for example due to non-contact or refusal. Conceivably, heavy and problematic alcohol use are related to this selection, as it can be assumed that marginalized alcohol users are more often institutionalized or homeless, non-responders, or lost to follow-up. Thus, even though both response (65%) and retention rate (80%) of NEMESIS-2 are quite high, selection bias could be present and accordingly, a disproportionate number of people with (severe) alcohol use disorder may have been missed. Therefore, the prevalence, severity, persistence and the risk of relapse may have been underestimated in this thesis.

Second, most general population studies, including NEMESIS-2, rely on self-report. Generally, alcohol consumption observed in community studies is lower than the per capita alcohol consumption [9;10], suggesting underreporting. First, due to social stigma, people might be reluctant to report high alcohol consumption levels [11]. Also, the usual quantity of alcohol per drinking day tends to be lower than the arithmetic mean of a person’s varying consumption pattern, since heavy drinking occasions are underrepresented in this measure [12] and no distinction is made between drinking
during weekdays and in the weekend in NEMESIS-2. Nonetheless, alcohol consumption in NEMESIS-2 was largely in agreement with the rates observed in other population-based studies in Western countries [13-15]. However, the prevalence of alcohol use disorder, and especially of alcohol dependence, was lower than what has previously been observed in general population studies, especially compared to the United States [16;17], but also in comparison to the first NEMESIS study [18]. As these previous high prevalence rates have been suggested to overestimate the problem, NEMESIS-2 findings may in fact represent a more realistic estimate [19]. Yet, methodological and cultural differences between the various studies cannot be precluded as sources of bias [20;21] and thus, NEMESIS-2 findings could underestimate the problem. Importantly, the low prevalence rate of alcohol dependence and thus of alcohol use disorders in NEMESIS-2 resulted in low statistical power for some of the analyses presented in this thesis.

Third, the choice for a dichotomous alcohol use disorder diagnosis imposes important restrictions. This dichotomy leads to an oversimplification of the gradual process associated with onset and course of alcohol use disorders: one symptom more or less can make the difference between fulfilling a diagnosis or not and hence, a negative outcome or not. This also implies that an unknown proportion of the observed transitions may be due to measurement error. Although DSM-5 still applies a single cut-off point for the presence or absence of the disorder, a severity indicator has been introduced: mild, moderate and severe alcohol use disorder based on the number of criteria. The present research was one of the first worldwide to examine the prevalence and course of DSM-5 alcohol use disorder in the general population while taking into account the role of this graded severity. Yet, it should be noted that the CIDI 3.0 used in the present research was designed and validated for the assessment of DSM-IV disorders [22], not for DSM-5 disorders. Although the criteria used in DSM-IV and DSM-5 are very similar, the reliability of the DSM-5 alcohol use disorder diagnosis based on the CIDI 3.0 is unknown and could be lower than for DSM-IV. More specific, the CIDI 3.0 assesses the DSM-IV clustering criterion (≥ 3 criteria in the same 12-month period for alcohol dependence), but not the DSM-5 clustering criterion (≥ 2 criteria in the same 12-month period). As this clustering criterion could not be part of the DSM-5 alcohol use disorder diagnosis, the prevalence, persistence and/or relapse of the disorder may have been overestimated.

Lastly, alcohol use disorders are complex maladaptive behaviors and there are many different ways to conceptualize the problem [23]. Recently, an overarching framework has been proposed (the COM-B model) suggesting that addictive behaviors (e.g. alcohol use disorder) are the result of three interacting conditions: Capability (e.g. deficient self-regulation), Opportunity (e.g. alcohol availability) and Motivation (e.g. relief from discomfort) [23]. This model describes a wide range of concepts that influence alcohol use disorders, including, but not limited to, the aspects examined in this thesis such as psychopathology (related to both motivation and capability) and socioeconomic status (related to opportunity). It should be noted that this integrated model (and other
models) contain many more predictors for the onset and course of alcohol use disorders than were examined in this thesis.

SUMMARY AND DISCUSSION OF FINDINGS

In chapter 1, the main objective of this thesis was explained: to enhance our understanding of the onset, course and treatment of alcohol use disorders in the general population. First, chapter 2 examined the role of childhood attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD) in the initiation of drinking and the onset of alcohol use disorders in order to improve our understanding of the groups in the general population that are more likely to develop alcohol problems. Second, the relationship between excessive drinking and alcohol use disorders was determined and characteristics associated with the presence of either one or both of these aspects of problematic alcohol use were examined (chapter 3). Third, it was investigated how many of those with an alcohol use disorder showed spontaneous remission (chapter 4) and relapse after initial remission (chapter 5). These chapters also examined predictors associated with a negative course. Fourth, chapter 6 explored the magnitude and the nature of the ‘treatment gap’ by examining the percentage of people with an alcohol use disorder in contact with the treatment system and the main indicators for this process of treatment seeking. The main findings are summarized and discussed here.

Onset of drinking and of alcohol use disorders

Chapter 2 demonstrated that nearly all respondents ever consumed alcohol (94%), that the vast majority (86%) drank regularly at some point in their life (≥ 12 drinks per year), and that about one in five (19%) ever met criteria for a DSM-IV alcohol use disorder (abuse or dependence). The respective average ages of onset for these conditions were 15, 17 and 19 years. These high rates confirm that (regular) alcohol use is rather normative, but that most people seem to be able to control their drinking. Only a minority of all drinkers develop an alcohol use disorder, so targets for selective prevention are needed to efficiently prevent the development of alcohol use disorders. This thesis investigated two potential candidates: childhood ADHD and childhood CD.

Previous research has shown a strong link between substance use disorders and externalizing childhood disorders (ADHD and CD) [24-30]. The presence of such a relationship was confirmed in chapter 2, showing that childhood ADHD was associated with a higher prevalence of all stages of alcohol use and alcohol use related problems (i.e. alcohol initiation, regular alcohol use, and alcohol use disorder). Moreover, it was demonstrated that childhood ADHD is strongly related with CD and although CD was not associated with the first two stages of alcohol use (alcohol initiation and regular alcohol use), it was a strong predictor of alcohol use disorder and an earlier onset of the disorder. It should be noted that, after adjustment for age and sex, neither ADHD nor CD was associated with an earlier age of onset of (regular) alcohol use. Possibly
respondents' difficulties in remembering ages of onset challenged the detection of such an effect.

To interpret the relationship between ADHD, CD and alcohol use (disorder), two conceivable pathways were examined. The first pathway hypothesized that ADHD influences the development of CD, which in turn would result in a higher risk of alcohol use (disorder). Findings of chapter 2 supported this pathway. When the relationship between childhood ADHD and the presence of an alcohol use disorder was adjusted for the presence of CD, this relationship was no longer statistically significant. In combination with the temporality in average ages of onset of ADHD (7 years), CD (12 years) and alcohol use disorder (19 years), these findings suggest the presence of an underlying developmental sequence. The second pathway hypothesized that children with both ADHD and CD represent a distinct subgroup with an especially high risk for alcohol use (disorder) compared to children with ADHD only or CD only. Chapter 2 found no evidence for this proposition in an adult sample: a history with the combination of childhood ADHD and CD did not result in a particularly high risk of alcohol use (disorder) compared to a history with only ADHD or only CD.

The presence of an alcohol use disorder cannot be fully explained by the proposed developmental pathway: alcohol use disorders are more prevalent than CD and ADHD, and thus other pathways are operating as well [31]. Moreover, the effect of ADHD may not be fully explained by the simultaneous presence of CD [32]. Therefore, the current findings indicate that recognition of both ADHD and CD is important. Treatment of ADHD should preferably include measures to prevent the development CD and should ensure detection and treatment of CD when this occurs. Moreover, treatment of ADHD and of CD may help to prevent escalation of alcohol use and the development of alcohol use disorders [33-36]. Furthermore, the differential role of CD in the three stages of alcohol use (i.e. no role in the first two stages, but an important role in the last stage) illustrates that the influence of CD becomes stronger over time and this stresses the importance of the study of such processes while including all alcohol use disorders, not only those with an early onset as is done when using adolescent samples. The differential role of CD may also indicate that CD is associated only with the pathological aspects of alcohol use (and not with normative behaviors), possibly due to a phased expression of an underlying dimension of externalizing behavior [37;38]. It has been suggested that this underlying mechanism might be related to common neurobehavioral deficiencies in behavioral inhibition and reward sensitivity in ADHD and alcohol use disorders, possibly due to common genetic factors [39;40]. However, the role of CD in such a process is not well understood and the current findings suggest that this is an important avenue for future research.

Relationship between excessive drinking and alcohol use disorder

In chapter 3, the relationship between excessive alcohol consumption and the presence of an alcohol use disorder was examined. Even though it seems obvious that excessive
drinking is needed for an alcohol use disorder diagnosis, limited overlap was observed: of those with a DSM-IV alcohol use disorder only 18% reported excessive drinking (defined quite strictly as the presence of both high average consumption and frequent heavy drinking days). It should, however, be noted that the overlap was substantially higher for alcohol dependence (55%) than for alcohol abuse (10%). Overall, the DSM-5 diagnosis alcohol use disorder showed a larger overlap with excessive drinking (25%) than the DSM-IV diagnosis (18%). Yet, the overlap between mild DSM-5 alcohol use disorder and excessive drinking was still very small (17%), indicating that only moderate (30%) and particularly severe DSM-5 alcohol use disorder (65%) should be interpreted as equivalents of DSM-IV alcohol dependence.

Nonetheless, even though clinical research suggests that a persistent pattern of heavy drinking is needed to develop an alcohol use disorder [41], chapter 3 confirmed that this might not be the case in the general population: non-heavy drinkers are identified as people having an alcohol use disorder diagnosis in the general population. This finding could have been a consequence of the strict definition of heavy drinking in the current study, but similar results were obtained with more lenient definitions of heavy drinking (i.e. high average alcohol consumption or frequent heavy drinking days). To better understand the reasons for this limited overlap, a series of post-hoc analyses were conducted looking at the historical relationship between excessive drinking and the presence of an alcohol use disorder diagnosis. These analyses showed that half of those with an alcohol use disorder but without excessive drinking did drink at a high level in the past. Conversely, more than one-third of those who drank excessively but did not have a 12-month alcohol use disorder had a lifetime history of an alcohol use disorder. The limited concurrent overlap could thus partly result from recovery from one aspect of problematic alcohol use (e.g. alcohol use disorder) whilst the other aspect continued to exist (e.g. excessive drinking).

In addition, we examined the differences between the subgroups of problematic alcohol users (excessive drinking only; alcohol use disorder only; both excessive drinking and alcohol use disorder) and non-problematic alcohol users. As compared to non-problematic drinkers, subjects of all three subgroups of problematic alcohol users on average also experienced more problems in domains of living other than drinking: more current mental disorders (mood, anxiety and drug use disorders), more childhood mental disorders (ADHD) and diminished mental functioning. All these subgroups thus seem clinically relevant and the magnitude of problematic alcohol use may therefore be bigger than assumed when only one aspect, either alcohol use disorder or excessive alcohol consumption, is considered. Nonetheless, the group with both aspects of problematic alcohol use was most affected and they had the highest rate of anxiety disorder, suicidal thoughts, and antisocial personality disorder. Notably, chapter 3 also observed that low educational level, low income, and living without a partner occurred most frequently in this group. Together with similar observations in previous prospective research on
excessive drinking [42], this suggests that these sociodemographics may help to identify people at risk of severe problematic alcohol use.

The data of chapter 3 are also relevant for the current discussion about the role of alcohol consumption in the definition of problematic alcohol use. DSM-5 has invoked discussions about the inclusion of a consumption criterion, including both mean daily alcohol consumption and the number of heavy drinking days [43;44]. Although this notion has been rejected, partly because of the lack of a cross-nationally accepted threshold for heavy alcohol use [45], it was recently proposed to identify problematic alcohol use solely based on the level of alcohol use [46]. A diagnosis based on a (complex) set of criteria was considered redundant mainly because heavy drinking would be a prerequisite for a diagnosis [46;47]. Although our data confirm that excessive drinking is important in the determination of severe problematic alcohol use, our data also show that the alcohol use disorder diagnosis is not redundant: there are people with an alcohol disorder without excessive drinking and these people would then be missed. It has been argued that these individuals are not much of public health concern as their drinking is within acceptable boundaries [46]. Yet, as described above, many of them have been drinking excessively in the past and current alcohol-related problems could indicate a continued struggle with maintaining a healthy drinking pattern. Also, the lack of excessive drinking in this group could reflect the individuals’ difficulty in estimating their alcohol consumption levels [12], whereas the problems related to alcohol use might be easier to recognize and report. Research on these individuals with an alcohol use disorder but without excessive drinking is needed to better understand the nature of their problems. Furthermore, it is important to note that although excessive drinking in itself was associated with various other problems, these problems were worse for those who additionally had an alcohol use disorder. A study among the elderly showed a similar pattern [48] suggesting that the presence of alcohol-related problems is an indication of the urgency of the problematic alcohol use. Moreover, people who only consume excessively may need different motivational techniques to decrease their drinking pattern than people who perceive problems with alcohol use [49]. Altogether, the results of this thesis indicate that both aspects should be considered in clinical work (screening and monitoring) and in research, in order to establish optimal treatment.

**Course of alcohol use disorders**

To unravel why some individuals go into stable remission from alcohol problems while others do not, the course of alcohol use disorders in the adult general population was examined. Both 3-year persistence of alcohol use disorder (chapter 4) and relapse into another episode of alcohol use disorder among those in diagnostic remission (chapter 5) were studied. It was explicitly assessed whether individuals in diagnostic remission achieved abstinence or a (very) low level of drinking, and whether higher levels of drinking during remission were associated with an increased risk of relapse.
Persistence

In *chapter 4*, it was confirmed that DSM-5 alcohol use disorders in the general population generally show a favorable course: 70% showed diagnostic remission during a 3-year period. This is quite similar to findings of the first NEMESIS study regarding 3-year remission rates of DSM-IV alcohol dependence (74%), but lower than DSM-IV alcohol abuse (85%). It should be noted that the DSM-IV dependence diagnosis cannot be directly ‘translated’ to DSM-5 alcohol use disorders, thus similar remission rates do not equate to similar disorder severity. In fact, DSM-IV alcohol dependence likely implies greater severity, given its higher symptom threshold (3 out of 7 criteria) compared with DSM-5 alcohol use disorder (2 out of 11 criteria). For example, people meeting (several criteria of) DSM-IV alcohol abuse, possibly combined with one or two DSM-IV dependence criteria, would be in diagnostic remission of DSM-IV alcohol dependence, but persistent according to the DSM-5 diagnosis alcohol use disorder. Moreover, although the high remission rates of DSM-5 alcohol use disorder seem encouraging, they should be interpreted with some caution. While diagnostic remission of DSM-5 alcohol use disorder was associated with a decrease in drinking levels, abstinence was rarely achieved and more than one-third of the individuals in diagnostic remission still drank considerably (more than 7/14 drinks weekly for women/men). This puts them at risk of physical and mental harm related to excessive alcohol consumption [50-53] as well as relapse (*chapter 5*).

Nonetheless, within three years, spontaneous remission was frequently achieved and this suggests that it may not be necessary to offer expensive treatment to everyone with an alcohol use disorder in the general population: watchful waiting and/or brief interventions may be sufficient for most, whereas for some, more intensive treatment is needed. To identify those people at risk for a persistent course and more intensive treatment, a large number of predictors of persistence was studied in *chapter 4*, including many clinical and sociodemographic characteristics. Altogether, these predictors explained 25% of the variance in the persistence of alcohol use disorder. Other factors, not included in this study, thus also play a role in persistence of alcohol use disorders. This should be kept in mind when interpreting the results. Clinical characteristics related to the severity of problematic alcohol use predicted persistence: more alcohol use disorder criteria, disability due to alcohol use disorder and a larger number of weekly drinks. This is consistent with findings from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), the only other longitudinal population-based study on predictors of persistence of alcohol use disorder (i.e. DSM-IV alcohol dependence) [54] and from a Dutch study on the 2-year persistence of alcohol dependence in a sample of mainly anxious or depressed individuals [55]. Robustness of findings is thus suggested. Importantly, *chapter 4* also showed that the number of weekly drinks predicted persistence independent of the number of alcohol use disorder criteria. This underscores that alcohol consumption may really help to identify patients with a persistent or even chronic alcohol use disorder.
Further determination of who is at risk of a persistent course of alcohol use disorder was difficult. Socioeconomic status (low educational level, unemployment, low income), smoking and vulnerability factors (e.g. childhood abuse) were not associated with a chronic course of an alcohol use disorder when other indicators were taken into account. However, changes in some of these factors (e.g. employment status, income and partner status) might be important in the prediction of persistence. For example, a recent study – also using data from NEMESIS-2 – observed that the economic crisis in the Netherlands was associated with an increase in the incidence of mental disorders [56]. It may very well be that such changes (at the population or the individual level) also play an important role in the persistence of an alcohol use disorder. Of the comorbid psychiatric disorders (mood, anxiety, drug use disorders) considered in chapter 4, only anxiety disorder emerged as an independent indicator of a persistent course. Clinical studies suggest that anxious people continue to use alcohol to alleviate their anxiety [57;58]; current findings provide first evidence that this might also be true in the general population. The role of the specific anxiety disorders in the course of alcohol use disorder in the general population is however still unknown and this should be addressed in future research.

**Relapse**

**Chapter 5** showed that relapse after remission from an alcohol use disorder was rare in the general population. Only one in ten individuals in remission from a DSM-5 alcohol use disorder relapsed into a new episode within the course of three years. This corroborates previously observed DSM-IV relapse rates [51;55;59] and findings that alcohol use disorders are usually not chronic in the general population [60]. It was subsequently examined whether predictors of persistence (i.e. number of criteria of alcohol use disorder and level of alcohol consumption) were also predictors of relapse. **Chapter 5** indeed showed that more alcohol use disorder criteria (≥ 6 criteria) and a higher level of alcohol intake (more than 14/21 drinks weekly for women/men) were independently associated with a higher risk of relapse. Another new finding of **chapter 5** was that risky drinking (more than 7/14 drinks weekly for women/men) during remission strongly increased the risk of relapse, especially among people with a lifetime history of a severe alcohol use disorder and among people with higher past levels of alcohol consumption. Thus, even if people no longer experience problems with their alcohol use, continued risky drinking could indicate that they did not completely recover and accordingly, that they had an increased risk of relapse. On the other hand, abstinence at follow-up was rare but sustained remission was not. Therefore, psychologically or pharmacologically supported reduced drinking might be an option for recovery [61].

**Chapter 5** also determined the predictive value of individual diagnostic criteria on relapse of alcohol use disorder. This is an under-researched issue even though previous community studies showed that specific symptoms differentially contribute to the incidence and persistence of substance use disorders [62-64]. Only lack of control
emerged as an important independent predictor of relapse. The importance of this symptom is not surprising as already in the early definitions of alcohol use disorder, lack of control was portrayed as a key element of maladaptive alcohol use [65;66]. Lack of control could be due to a deficiency in cognitive control (e.g. impulsivity) and/or the presence of increased drive/reward sensitivity [67]. Notably, both impulsivity and reward sensitivity also play a role in ADHD [39;67] and chapter 2 showed that ADHD was significantly associated with alcohol use disorder via conduct disorder. The exact role of these neurobiological deficiencies in both onset and course of the disorders may thus be an important avenue for future research.

**Treatment seeking for alcohol use disorders**

Treatment seeking for an alcohol use disorder is quite rare in the general population. Only one in ten individuals with an alcohol use disorder established contact with a professional for alcohol-related problems within a 4-year period (chapter 6). Another third made contact with the health care system for other mental health problems. More than half of the people with an alcohol use disorder did not receive any professional treatment during a period of four years. These and similar findings (e.g. [68;69]) may be interpreted as an indication for the existence of a large treatment gap; an undesirable situation that needs to be resolved. However, given the mostly mild nature and benign course of alcohol use disorders in the general population (low persistence rate; chapter 4 and low relapse rate; chapter 5), the clinical and societal relevance of such a ‘treatment gap’ can be questioned.

Findings in chapter 6 indicate that treatment seeking for an alcohol use disorder is largely adequate, with those seeking such treatment meeting more alcohol use disorder criteria, having higher levels of impairment and having more comorbid mood or anxiety disorders than those not seeking alcohol treatment. This corresponds with previous research in the US [70;71] and this seems reassuring: the limited capacity of services is mostly used by individuals with the most severe clinical characteristics and the highest risk of persistence and not by less severe cases with a generally favorable natural course. A new finding was that those receiving treatment for other mental health problems more often had a comorbid emotional disorder than non-treatment users, suggestive of adequate treatment seeking. Importantly, low educational level or unemployment, were not associated with lower rates of treatment utilization. Strikingly, while this thesis consistently showed that the level of alcohol consumption plays a key role in predicting severity and course of alcohol use disorders, it only played a limited role in the decision to seek treatment.

Previous population-based research failed to examine the course of alcohol use disorders in people who decided not to seek treatment. However, such information is crucial to establish the clinical relevance of the treatment gap. Specifically, chapter 6 showed high spontaneous remission rates for both non-treatment users (78%) and people using treatment for other mental health problems (64%). This is much higher
than the remission rate in the group using treatment services for their alcohol problems (29%), suggesting that many persistent cases adequately seek treatment from addiction treatment services. Moreover, especially in the group receiving treatment for other mental health problems, very few persistent cases had a moderate or severe alcohol use disorder at follow-up (10% as compared to 60% of the persistent cases without any treatment and 80% of the persistent cases with specialized alcohol treatment), indicating that the need for (additional) alcohol treatment is indeed very small in this group. Chapter 6 further observed that long-term functioning of non-treatment users with an alcohol use disorder at baseline was similar to that of the healthy reference group (people from the general population who never had an alcohol use disorder or another mental disorder). This suggests that non-treatment users largely function at a normal level and their unmet need for treatment is likely limited to the individuals with a persistent disorder. It is uncertain whether this latter subgroup did actually perceive a need for treatment but did not access it due to perceived barriers or lack of motivation, or that there was no perceived need for treatment. This was not the subject of this thesis but such knowledge is important to develop better guidance to treatment for these individuals.

**CLINICAL IMPLICATIONS**

The findings in this thesis are not only of scientific interest, they are also of practical importance. Particularly, this thesis illustrates how common drinking alcohol is: the vast majority of the Dutch adults drinks and most people seem able to control their drinking. However, a minority of one in five adults develops an alcohol use disorder. It therefore seems efficient to tailor selective prevention to those individuals at risk of developing such a disorder. Most individuals with an alcohol use disorder experience mild and transient problems, but some suffer from severe and persistent problems. This indicates the importance of tailoring treatment intensity. In short, the findings of this thesis underscore that selective prevention is desirable, as well as treatment tailored to those individuals at risk of severe alcohol problems. Some suggestions are made here.

**Selective prevention and treatment in youngsters**

This thesis confirms that alcohol consumption as well as alcohol use disorder generally start at an early age. In combination with the observation that ‘only’ one in five alcohol users subsequently develop an alcohol use disorder, prevention methods tailored to youngsters at high risk for escalated alcohol use are highly recommended. Specifically, the observed developmental sequence from ADHD to alcohol use disorder via CD suggests that effective treatment of youngsters with these externalizing childhood disorders [33;34;72] may help to prevent the development of an alcohol use disorder. This treatment of ADHD and CD should also pay attention to the initiation of drinking
and development of alcohol-related problems [35;36;73]. Regarding CD, effective treatment can indeed prevent development of early onset substance use [35]. The effects of early ADHD treatment are, however, less clear. Although a recent meta-analysis suggested that stimulant treatment of children with ADHD has no influence on the risk of developing an adolescent or adult alcohol use disorder [73], a recent Dutch study showed that early stimulant treatment of children with ADHD prevented the development of a substance use disorder until at least age 17, even in those with severe ADHD or with comorbid CD [36]. In addition to medication, awareness of substance use in treatment of ADHD and CD may help to prevent subsequent alcohol use disorders and this thesis underscores the need for such a focus.

These findings also suggest that universal prevention programs directed at all school children need to be complemented with selective intervention programs directed at the relatively small group of children with an increased risk, including amongst others [31] children with ADHD/CD. As universal prevention programs with a parental component can reduce (heavy) weekly drinking in youngsters [74], such programs could serve as a first step to address underage drinking and accordingly reduce associated individual and societal costs. However, there is no proof that these universal prevention programs also prevent the development of alcohol use disorder and selective prevention therefore seems essential [75]. In fact, a selective alcohol intervention program that identifies adolescent risk groups (aged 13-15) who subsequently receive two 90 minute group sessions adapted to their personality profile (including profiles on sensation seeking and impulsivity) is currently being tested [76]. If this intervention proves to be effective, it may help to detect children with externalizing problems and address their drinking habits. Further, it could be used to identify those with serious externalizing problems and refer them for medication or behavioral therapy.

Prevention and treatment priorities among adults

This thesis consistently highlights the importance of both alcohol-related problems and excessive drinking to detect severe and/or chronic alcohol use disorder indicating that both aspects could serve as easily quantifiable risk markers for escalating problems. This is important, because the development of an alcohol use disorder is a gradual process with several intermediate stages. Findings of this thesis thereby extend previous suggestions to use staging and profiling for treatment allocation. Not only alcohol-related problems [77-79], but also excessive drinking, should be targeted by different treatment strategies ranging in intensity. It was beyond the scope of this thesis to specifically address best practices for different stages. Yet, moderate drinking levels and/or mild alcohol-related problems can effectively be targeted with low-intensity interventions in primary care such as effective e-health interventions [80] or brief motivational interventions [81], whereas for severe excessive drinking and/or moderate or severe alcohol use disorders additional pharmacotherapy or referral to specialized care may be indicated. Further research is needed to verify which cut-off points of
each dimension, alcohol-related problems and excessive drinking, offer the best match between patients and interventions (see Future studies).

Although chapter 6 showed that the treatment seeking and selection process was generally adequate, some individuals with persistent alcohol problems did not establish contact with any professional about their alcohol problems or other mental health problems in a four-year period. These chronically ill individuals can be identified by the general practitioner (GP) or the primary care mental health nurse practitioner (so called MHNP or POH-GGZ) when the person is making a primary care visit for alcohol-related physical problems, e.g. hypertension [44]. Screening in the form of a short check-up of their alcohol use (e.g. AUDIT-C or Five shot) is an efficient way to signal alcohol problems [82]. Yet, these are currently not supported in guidelines for GPs, which only recommend assessment of drinking levels with no particular validated questions [83]. This thesis strongly advocates that screening directed at the level of alcohol consumption is complemented with a few questions about alcohol-related problems. GPs are often aware of the benefits of screening, but it is not always applied in a consistent manner [84]. Additional training of GPs during medical school on benefits of screening of alcohol problems has proven to increase the use of screening in the long-term [84], implementation of such extra training may be worthwhile for experienced GPs as well.

Importantly, this thesis points to various actions by the primary care MHNP once alcohol problems have been signaled. First, mostly mild alcohol use disorders were observed in the general population and these can be treated with low-intensity interventions. The MHNP could deliver brief motivational interventions addressing the level of alcohol use and mapping the pros and cons of drinking in a non-judgmental manner [85]. Second, the MHNP could promote e-health interventions addressing alcohol problems when individuals fear labeling or stigma. Alcoholism is a severely stigmatized mental disorder [86] and this could be a reason to reject face-to-face treatment. Many e-health interventions are both effective [80;87] and cost-effective [88], and are therefore valuable alternatives in such circumstances. Third, the findings of this thesis strongly suggest that interventions should be directed at abstinence or very low drinking levels, especially for those individuals with more severe clinical characteristics. Such a level may be achieved by brief interventions or cognitive behavior therapy, but some individuals prefer or need pharmacotherapy to reach this goal [89-92]. It would thus appear beneficial when the GP (assisted by the MHNP) can timely initiate pharmacological treatment. Fourth, as said, this thesis observed that persistent and relapsing alcohol problems are especially likely in individuals with many criteria of an alcohol use disorder and/or a high level of alcohol intake. Such individuals may be in need of intensive treatment that cannot be provided in primary care. The GP and the MHNP should be able to timely identify such individuals and refer them to specialized treatment [85]. Notably, these recommended actions are largely in accordance with recent transitions in the Dutch mental health care system, in which primary care is appointed a key role in the detection and treatment of mild mental health problems.
Monitoring of this transition seems advisable to ensure that it results in optimal care for people suffering from problematic alcohol use.

**FUTURE RESEARCH**

Findings of this thesis are among the first to examine prevalence and course of DSM-5 alcohol use disorder. This thesis showed that the presence of more DSM-5 criteria of alcohol use disorder was associated with a chronic course of the disorder. Still, DSM-5 has only recently been released and there remains much to be learned about the newly defined alcohol use disorder. First, more research is needed for a better understanding of the course of the disorder for each of the distinguished severity levels of the DSM-5 (mild, moderate, severe) as well as the transition from one severity level to the next. Inclusion of detailed data on when specific criteria are present or not may help future studies to understand such fluctuations in the course of the disorder. Second, this thesis showed that, while examining a broad range of static baseline characteristics, prediction of persistence and relapse is very challenging with only a small proportion of variance explained by the combination of baseline predictors. A similarly small predictive value was observed for the persistence of DSM-IV alcohol dependence [54]. As a consequence, it is difficult to develop and implement tailored treatments. However, qualitative research suggests that dynamic predictors (e.g. life events or changes in social relationships) are associated with a persistent course of cannabis dependence [93]. Examination of the direct relation between such dynamic, time-dependent factors and changes in severity of alcohol use disorder over time may thus be worthwhile. Third, DSM-5 alcohol use disorder is diagnosed when at least 2 of 11 criteria are present and the disorder can thus be heterogeneous. Our findings indicate that the presence of certain criteria can be important in the prediction of relapse. Similarly, a recent study suggested that a mixture of the number and type of criteria could be valuable to define the severity of the disorder [94]. Such combinations may also be used in the definition of adequate cut-off points for a stepped care approach.

This thesis showed that the level of excessive drinking plays a major role in the course of an alcohol use disorder. Thus, assessment of problematic alcohol use can be improved by inclusion of both alcohol use disorders and excessive drinking instead of only taking one aspect into account. Moreover, public health studies show that the level of drinking is exponentially associated with morbidity [95] and mortality [96]. Yet, the natural course of drinking patterns in the general population is largely unknown and needs to be studied more comprehensively. Although repeated measures of alcohol consumption in longitudinal population-based research are extremely valuable, inclusion of more advanced assessment techniques is needed to obtain detailed and ecological valid information. Specifically, momentary assessment could help to establish accurate information on drinking patterns and this can easily be applied via smart phones [12;97]. It may be efficient to apply such in-depth measures to a random subsample of a general
population study, with oversampling of individuals with alcohol use disorder symptoms. Alcohol consumption could then be monitored asking a few questions daily for a specific time period (e.g. one month) and could subsequently be linked to observed (alcohol-related) problems to further improve our understanding of this relationship.

Lastly, findings of this thesis suggest that developing and promoting a stepped care approach based on the underlying graded severity of problematic alcohol use should be guided by both the level of alcohol consumption and the number of alcohol use disorder criteria. Further research is however recommended to examine which interventions should be connected to each of these aspects of problematic alcohol use. Such studies should also focus on the identification of cut-off points as this is needed for a structured allocation of treatment. Of course, more factors play a role in the development and course of alcohol use disorders than excessive drinking and alcohol-related problems. This thesis also showed that symptom type, levels of impairment, and comorbid pathology (e.g. anxiety) play an important role in the course of the disorder. It should be noted that there are many other influences known to play a role in the development and course of alcohol use disorders, as is portrayed in a recent overarching framework presented by West [23]. This framework integrates the different theories that try to explain addictive behaviors, including theories covering automatic processes, neurobiological mechanisms, social network aspects and economic approaches. It is important to note that some of these other influences are also important for prevention, treatment seeking and treatment provision, e.g. social network aspects [98] and perceived stigma [99]. These aspects should thus also be taken into account when developing a stepped care approach for the treatment of alcohol use disorders (similar to the way this was done for depression [100]).

IN CONCLUSION
Alcohol use disorders among adults in the general population occur frequently (19%), but the disorder is often mild:

- 75-80% do not drink excessively
- 70% remits spontaneously within three years
- 12% of those in remission relapse in the course of three years

Only 10% of the people with an alcohol use disorder establish contact with a professional for these problems, but the treatment seeking seems to be quite adequate with those most in need of help having the highest contact rate. As only one in five adults develop an alcohol use disorder, it seems efficient to tailor selective prevention to those individuals at risk of developing such a disorder, and not to those who are able to control their drinking. As childhood externalizing disorders proved to be strong predictors of later alcohol problems, the need for early recognition and treatment of individuals with childhood ADHD or CD is highlighted. Moreover, the mild nature and
benign course of most alcohol use disorders suggests that it is efficient to allocate treatment resources to those at risk of a severe and/or chronic alcohol use disorder: those with a high drinking level, a high number of alcohol use disorder criteria, and comorbid psychopathology, specifically anxiety disorders. As the treatment gap (i.e. people with an alcohol use disorder not receiving treatment) appeared less problematic than often assumed, efforts to increase treatment access should primarily focus on the individuals at highest risk of a severe chronic course.

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