Running title: AUD comorbidity subtypes

Subtypes of alcohol use disorder comorbidity in the general population: A latent class analysis

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Highlights

- Three subtypes of AUD were empirically derived in a Swiss community sample
- Subtypes: 1.) low, 2.) depressive-anxious, 3.) drug-dependent antisocial comorbidity
- 1.) Males, less severe AUD, less risk factors and consequences, late onset
- 2.) Mainly females, late onset, less severe AUD, more impairment, early adversity
- 3.) Young age and onset, severe AUD, impaired, life adversity, alcohol consequences
- Lower helpseeking and use of psychotropic medication was reported in LOW
- More informal sources of helpseeking for alcohol problems were used by DD-AS

Abstract

Alcohol use disorders (AUD) are often comorbid with other disorders with high levels of impairment, which is of relevance for the development and the progression of the disease. Evidence shows that AUD varies greatly with regard to its aetiology, which might lead to distinct clinical representations with important implications for treatment. The current study aimed to apply latent class analysis (LCA) techniques to investigate how comorbidity patterns in AUD vary with regard to specific explanatory factors. A Swiss community sample of N=439 individuals with AUD was subjected to LCA in order to find empirical AUD subtypes of comorbid psychiatric conditions. The subtypes were further validated based on a range of external criteria, including clinical and psycho-social factors as well as treatment variables. A three-class solution of empirical subtypes of AUD comorbidity (low, depressive-anxious, and drug-dependent antisocial) provided the best fit to the data. The three AUD subtypes showed homogeneous comorbidity patterns but varied along dimensions of psycho-social risk factors, consumption patterns and consequences as well as treatment history. Our findings provide strong evidence that AUD in non-treated samples can be described as a multidimensional disorder in terms of its comorbidity structure with distinct etiological factors and important consequences for treatment.

Keywords

Alcohol use disorders; subtyping; comorbidity; latent class analysis; general population; internalizing disorders; externalizing disorders.

Introduction

Excessive alcohol consumption is a risk factor for a number of health problems and a higher mortality; it ranges at the eighth position of leading causes for death and represents the third-leading risk factor for disease and disability worldwide (WHO, 2011). According to the Global Status Report on Alcohol and Health of the World Health Organization (WHO) of the year 2014, Europe was the most affected continent with a global mean prevalence of 7.5% (versus 4.1% worldwide) of alcohol use disorders (AUD) (WHO, 2014). The variability of prevalence between European countries was high, whereof Switzerland belonged to those countries that rank above the European average with almost twice as high prevalence as the global mean (WHO, 2014). Indeed, almost one fifth (18%) of the Swiss population were estimated to suffer from AUD at least once during their lives (Angst et al., 2006). However, as suggested by large community studies, there are only a small proportion of those with AUD that actually sought treatment for their problems (Alonso et al., 2004; Wu et al., 2007). This might be problematic since AUD is associated with significantly impaired functioning, which has important consequences for society and represents an enormously high socio-economic burden (Grant et al., 2015; Rehm et al., 2009).

In general, males are diagnosed with AUD approximately twice as often as females (Sher et al., 2005) but there also other factors that are frequently linked to a higher risk of AUD, such as genetic (Mayfield et al., 2008) and environmental factors (Barnow et al., 2002; Rose et al., 2003). Often related to these factors but also independent, an early initiation of regular or heavy drinking may lead to more and heavier symptoms due to longer periods of consumption (Hingson et al., 2006).

AUD is also associated with a broad range of comorbid mental health problems – either as causal factors or as a consequence (Falk et al., 2008; Flensborg-Madsen et al., 2009; Kessler et al., 1997). Evidence from large epidemiological studies has shown that AUD is frequently associated with other psychiatric conditions, including depression, anxiety disorders as well as personality disorders, polysubstance misuse and suicidality (Briere et al., 2014; Cullen et al., 2013; Fuehrlein et al., 2016; Glass et al., 2014; Pacek et al., 2013). However, large heterogeneity among individuals with AUD has been recognized with respect to clinical and also etiological factors, which largely affects the treatment process and its outcome (Wu et al., 1999). Initial attempts to classify individuals with AUD suggested binary typologies that primarily posit the distinction between mild and severe forms of AUD (Leggio et al., 2009). However, in order to account for the broader clinical and etiological variation among individuals with AUD alternative models suggested typologies ranging to up to five AUD subtypes that added evidence for the distinction of internalizing (e.g. mood and anxiety) and externalizing (e.g. antisociality and substance use) phenotypes in AUD (Leggio et al., 2009), although a mix of both is possible as well (Chan et al., 2008; Dawson et al., 2010). In fact, all typologies more or less agreed that AUD with comorbid internalizing psychopathology is associated with greater AUD severity and impairment, suicidal behaviour, and predominantly female gender (Bolton et al., 2006; Briere et al., 2014; Dawson et al., 2010; Schneier et al., 2010). Those individuals typically used alcohol to relieve boredom and symptoms of depression and anxiety, subsequently developed persistent alcohol dependence and were more likely to seek help for their problems than others (Mojtabai et al., 2002). Alcoholics with comorbid externalizing psychopathology, in contrast, comprised rather young and male, clinically more severe, alcoholics with early-life

drinking onsets that, however, received treatment for their problems less often and if so, with poorer treatment success than others (Goldstein et al., 2010; Kranzler et al., 1996). Therefore, a subtype-based representation of AUD might provide insight into underlying mechanisms of differential treatment responses, which allow targeting these differences in the treatment process, but also highlight the need for early identification and referral for these problems. However, most research on AUD subtyping stems from clinical studies while data from non-treatment seeking samples is rather limited (Windle and Scheidt, 2004). There is, however, epidemiological support from several large community studies that Switzerland has a largely distinct prevalence of common mental disorders (Ajdacic-Gross et al., 2016; Angst et al., 2005; Rodgers et al., 2015; Vandeleur et al., 2017) than that reported elsewhere (Kessler et al., 2005; Martin, 2003). To our knowledge, this is the first study that examined AUD subtypes with respect to their comorbidity profiles in the Swiss population.

Thus, this study aimed to develop a population-based typology of AUD comorbidity based on a representative non-helpseeking general population sample of Swiss individuals with AUD. These subtypes were further validated with a range of external criteria, including sociodemographic, clinical, and psychosocial factors. Therefrom, we hope to gain insight into the discrepancy between common treatment needs and mental health care patterns that might be shared by individuals of a specific subtype, which is essential for successful clinical practice as well as future research on etiology, prevention and treatment.

Methods

Sample and procedure

All data were collected within the PsyCoLaus study (Preisig et al., 2009), a subsample from the larger CoLaus study (Firmann et al., 2008), a randomly selected population-based cohort study conducted in Lausanne, in the French-speaking part of Switzerland. From 2003 to 2006, a community sample of N=6,734 subjects aged between 35 and 75 years was recruited for the first wave of CoLaus, which was designed to assess the prevalence and determinants of cardiovascular risk factors and diseases. Sixty-seven percent of the subjects of the CoLaus study in the age range between 35 and 66 years (N=3,720) accepted to participate in the psychiatric exam (PsyCoLaus; see Preisig et al. 2009) for a detailed description). From this sample, about half (53.0%) were female and the mean age of the subjects was 50.9 years (SD=8.80).

For the purpose of the current study, the sample was restricted to those participants meeting lifetime criteria for AUD (N=439; 11.8%). From those, 22.6% were females and the mean age was 50.5 years (SD=8.6). The majority of participants were married (54.4%) and had basic education (59.2%) (i. e. completion of basic schooling until the age of 16 years, after which either an apprenticeship was undertaken or a professional school was attended). Socio-economic status (SES) was assessed according to the Hollingshead's index (Hollingshead, 1975). The mean SES was 3.3 (SD=1.3), indicating a middle class status on average. For more detailed information on sociodemographic characteristics please refer to Table 4.

Interviewers were required to be at least bachelor-level psychologists, and were trained over a one- to two-month period. During data collection, each interview was reviewed by an experienced senior clinical psychologist. The study was approved by the Ethics Committee

of the University of Lausanne, Switzerland. All participants provided written consent after being informed of the goal and funding of the study.

Measures and variables

The data of the PsyCoLaus study were derived from the French version (Leboyer et al., 1995) of the semi-structured Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994). In addition to demographic features, the French version of the DIGS comprises information on a broad spectrum of DSM-IV Axis I and Axis II criteria (including AUD, which comprised both abuse and dependence) as well as on suicide behavior and antisocial personality disorders (ASP) (Preisig et al., 2009). PTSD and generalized anxiety disorders were assessed using the relevant sections from the French version (Leboyer et al., 1991) of the Schedule for Affective Disorders and Schizophrenia – Lifetime and Anxiety disorder version (Endicott and Spitzer, 1978). In addition, the brief phobia chapter of the DIGS was replaced by the corresponding more extensive chapters of the SADS-LA which elicit information on agoraphobia with or without panic attacks, social and specific phobias. Psychiatric diagnoses were all considered with lifetime prevalence. Our DIGS version revealed excellent inter-rater reliability in terms of kappa or Yule's Y coefficients for depressive disorders (0.93;Preisig et al., 1999), SUD (range: 0.88-0.97) or ASP (0.97) (Berney et al., 2002), whereas the 6-week test-retest reliability was lower but still acceptable: (Depressive disorders 0.67; SUD range 0.48-0.91; ASP 0.64; Berney et al., 2002; Preisig et al., 1999). The French version of the anxiety sections of the SADS-LA revealed fair to good test-retest reliability (range 0.43-0.66; Leboyer et al., 1991), whereas in our own

reliability study we documented perfect inter-rater agreement for all specific anxiety disorders except for agoraphobia (Yule's Y = 0.96) and fair to good 6-week test-retest reliability (range 0.44-0.77) for all anxiety disorders (Rougemont-Buecking et al., 2008).

The following categories, based on the DSM-IV criteria, were considered as comorbid conditions of AUD: substance use disorder (abuse or dependence) of cannabis, cocaine, and other substance-related disorders (narcotics, sedatives, stimulants, hallucinogens combined due to low prevalence), major depressive disorder, simple phobia, social phobia, PTSD, separation anxiety disorder, and other anxiety disorders (agoraphobia, generalized anxiety disorder, and panic disorder combined due to low prevalence), ADHD, antisocial personality disorder, and suicide attempts.

Participants were further asked about chronically adverse or dysfunctional environments during childhood, such as whether they had had an unhappy childhood, had feared to be punished by their parents, had been placed in a foster home, whether they ever ran away from home, had not been raised by their biological parents, or had had divorced or separated parents during their childhood. A further question on income during adulthood documented the amount per annum which was dichotomized into lower or higher than CHF 50,000. Furthermore, participants were asked whether they had first degree relatives with relevant mental health problems (AUD, SUD, depression, anxiety disorders). Then, alcohol-related variables documented consumption patterns (age of AUD onset, the average amount of alcohol intake in grams per day and whether alcohol was consumed to relieve symptoms of psychological distress), problems and consequences of alcohol consumption (indicators of harmful use such as the experience of alcohol-related blackouts and binge-drinking sessions as well as physical and social consequences). Health-related functioning over the

lifespan was assessed in two ways – first by a single item question on functional impairment in areas of work, school or daily life responsibilities and, second, by the Global Assessment of Functioning (GAF) score. The GAF score was assigned according to the definition in the DSM-IV manual, and provides an interviewer assessment of the severity and the duration of all psychiatric symptoms that affected the subject's psychological, social and occupational functioning over the lifespan.

Then, information on treatment was obtained for general mental health problems, such as the utilization and age of first professional treatment, hospitalization and age of first admission and use of psychotropic medication as well as alcohol-specific treatment – overall as well as separately for professional and non-professional (Alcoholics Anonymous or others) help-seeking.

All alcohol- and treatment-related variables except self-medication were based on single items from the DIGS. Self-medication of psychological distress was indexed by endorsing the question of whether alcohol was used to relieve the symptoms surveyed in any diagnostic section of the DIGS at least once.

Statistical considerations

Prevalences of comorbid conditions were provided for the study sample and compared to those from the overall PsyCoLaus sample including subjects who were not included in the current study. Chi-square test statistics were calculated and p-values were Bonferroni-corrected.

Latent class analysis (LCA) was used to identify distinct comorbidity patterns in the sample of individuals diagnosed with AUD. This methodological procedure allows identifying homogeneous groups of individuals based on similar patterns of comorbid conditions. Model building was conducted in two steps: first, an unconditional model was run followed by a conditional model, which was accounted for by sex, age and amount of daily alcohol intake as covariates to the latent class variable. Fit statistics that allow testing for multiple class solutions were computed. Accordingly, starting with a single (full sample) class solution, we tested solutions with increasing numbers of classes (up to five classes) in each of the three steps described above. We evaluated the relative fit of different models using the Bootstrapped Likelihood Ratio Test (BLRT; (McLachlan and Peel, 2000), the Lo-Mendell-Rubin adjusted likelihood ratio test (LMR-A; (Lo et al., 2001), the Bayesian information criterion (BIC) and the sample-size-adjusted BIC (BIC-A), and the Akaike information criterion (AIC; (McLachlan and Peel, 2000). Significant LMR-A and BLRT values suggest that a model is preferable over another model with the next lower number of classes. A non-significant LMR-A or BLRT value indicates that the solution includes too many classes (Nylund et al., 2007). Lower values of BIC, AIC and BIC-A for a given model indicate an improved model fit relative to another model with more or less classes. Conditional probabilities for each latent class indicator were calculated via thresholds using the following formula:

$$Prob(class) = 1/(1 + exp(class\ threshold))$$

Descriptive statistics for socio-demographics, risk and otherwise related factors were calculated for the study sample as well as for stratified AUD comorbidity subtypes. Chi-square tests for categorical variables and One-way-analyses of variance (ANOVA) for

continuous variables were used to test for differences across classes. P-values of class comparisons were table-wise (by domain of predictor), adjusted using the Bonferroni correction.

LCAs were conducted using MPlus v6 (Muthen and Muthen, 1998-2011). Information on class membership for each case was saved to a separate file, which was then imported to STATA/SE 12 (StataCorp, 2011) and merged with basic data for further processing. All subsequent analyses were conducted using Stata/SE 12.

Results

Table 1 displays the prevalence of those psychiatric conditions considered as comorbid disorders in AUD for the entire PsyCoLaus sample – stratified for having AUD (our current study sample) versus not having AUD. In the full sample the most prevalent condition was major depression, followed by simple and social phobia, other anxiety disorders and suicidality. Except for depression, which was comparable, all other psychiatric conditions were more frequent in individuals with AUD (lowest prevalence 5%) than in those without AUD (lowest prevalence < 1%), for which substance use disorders, PTSD, ADHD, antisocial personality disorder and suicide attempts significantly differed (for more details please refer to Table 1).

LCA modelling of AUD comorbidity revealed the following results. The unconditional model clearly revealed two classes according to BIC and LMR (not tabulated). After adding covariates (sex, age and amount of daily alcohol intake) to the latent class variable, the model fit improved substantially. Fit indices for the 1-5 competing latent class models are

provided in Table 2. Accordingly, the BIC was at its minimum with three classes while the AIC and the sample-size-adjusted BIC indicated the best fit with the four-class model. The LMR indicated an improvement up to the three-class and the BLRT up to the four-class solutions. In the case of a disagreement between BLRT and LMR, it was recommended to rely on BIC for deciding on the number of latent classes (Nylund et al., 2007). Therefore, we finally decided to keep the three-class solution of AUD subtypes for further analyses (see Figure 1).

-Figure 1–

-Table 1 & 2–

Table 3 displays the conditional probabilities of the three latent classes of AUD comorbidity. Class 1 (n=46) was specifically featured by medium to high probabilities of comorbid polydrug misuse and antisocial personality disorder; class 2 (n=120) was specifically associated with major depression and most anxiety disorders (despite higher probabilities, social phobia and PTSD were not statistically different from class 1); ADHD and suicidality were linked to both classes 1 and 2 at lower levels. Class 3 (n=273) contains those cases with low probabilities for almost all comorbid conditions. According to this, we labeled class 1 as the *drug-dependent antisocial* (DD-AS), class 2 as the *depressed-anxious* (DEP-ANX), and class 3 as the *low comorbidity* AUD subtype (LOW). For the sake of comprehensibility we have rearranged the order of subtypes (classes) for subsequent analyses as follows: 1. LOW, 2. DEP-ANX, and 3. DD-AS.

AUD subtypes differed in a number of socio-demographic characteristics (Table 4). While more than two-thirds from the DEP-ANX and one-third from the DD-AS subtype were females, almost all members from LOW were male (except for one subject). Members from DD-AS were younger than the others, followed by DEP-ANX and finally LOW with the highest mean age. Subjects from LOW were more often married than single compared to the other subtypes. Subtypes did not differ significantly regarding education and SES.

-Table 3 & 4 –

Table 5 displays the prevalence of early developmental and psychosocial risk factors, as well as familial liability for mental health problems across classes of AUD comorbidity. Overall, to mention the most prevalent factors, more than one third of the sample had grown up with no biological parent, more than 40% had a first degree relative with AUD, about one fourth had a relative with depression; and more than one quarter had a rather low income. Except for familial liability, all other risk factors were more often reported by members from the DEP-ANX or DD-AS subtypes. However, after Bonferroni's correction only two factors remained significant: having had an unhappy childhood as well as the persistent fear of being punished by their parents were almost equally linked to DEP-ANX and DD-AS. For more detailed information on psychosocial risk factors please refer to Table 5.

-Table 5–

Table 6 summarizes the distribution of alcohol-related variables across AUD subtypes. Accordingly, compared to others DD-AS had an earlier onset of AUD, consumed more pure alcohol daily, reported alcohol-related blackouts and symptoms of withdrawal as well as adverse social consequences resulting from alcohol consumption more often. Both DEP-ANX and DD-AS reported to self-medicate symptoms of psychological distress through the use of alcohol and higher functional impairment in important life domains more often than LOW and had lower overall lifetime GAF scores.

-Table 6–

As shown in Table 7, the majority of individuals with AUD had received professional treatment for mental health problems, those from the DEP-ANX and DD-AS subtypes even more often than LOW. DEP-ANX and DD-AS ever used psychotropic medication for mental health problems approximately twice as often as LOW. Classes did not differ either in age of first professional help received nor of first hospitalization. DD-AS sought non-professional help for alcohol-related problems in particular more often than the others. For more detailed information on treatment utilization please refer to Table 7.

-Table 7–

Discussion

We analyzed a subsample of individuals with AUD from a large cross-sectional community survey in the Swiss population to explore empirical subtypes of AUD based on groups with homogeneous comorbidity patterns. Subtypes were derived using LCA and were further validated based on a range of external criteria including risk factors, clinical and treatment-related variables.

Results showed that the best-fitting model was a three-class solution that best describes the variation of comorbidity among individuals with AUD along latent dimensions termed low (LOW), depressed-anxious (DEP-ANX), and drug-dependent antisocial (DD-AS) comorbidity. While LOW contains almost pure AUD cases, i.e. those with no or less comorbid conditions, DD-AS was primarily characterized by higher probabilities for other substance use disorders and antisocial personality disorder, and DEP-ANX was most likely to have comorbid major depression and anxiety disorders. On the one hand our results strongly support the validity of the two primary AUD comorbidity dimensions of internalizing and externalizing psychopathology, on the other hand we found evidence that the majority of individuals with AUD had no or less additional psychopathology.

A pure AUD subtype has been well-described in earlier typologies (Babor et al., 1992; Cloninger et al., 1981; Del Boca and Hesselbrock, 1996; Windle and Scheidt, 2004) and shares a number of characteristics with our findings. Thus, our LOW type contains individuals with less severe and later-onset AUD, lower impairment, less risk factors and social and physical consequences. In contrast to those earlier subtypes, which more or less found both sexes to be equally affected (e.g. Cloninger et al., 1981; Hill, 1992), was our

subtype completely male-limited. However, it has been shown that males are more likely to develop AUD without comorbid conditions while females are more likely to drink to self-medicate psychological distress associated with co-occurring psychopathology, especially depressive and/or anxious symptoms (Dawson et al., 2010). For males, drinking is more normative and socially acceptable than for females. Males often drink hazardously just due to peer pressure and are therefore at high risk to develop independent alcohol problems (Studer et al., 2014). A clinical study using Babors typology (1992) found a similar proportion of patients classified as LOW (i.e. termed "Type A" 68% vs. 62% classified as LOW in the current study) (Bottlender et al., 2006), which supports the validity of this subtype.

The second-largest subtype, DEP-ANX, in contrast, was more frequent among females, and was characterized by a high association with depressive and anxiety disorders, a later drinking onset, high functional impairment and early life adversity. Earlier attempts similarly found support for a subtype that led to alcohol abuse or dependence through the path of negative affect and depressive symptoms - often in response to developmental stressors (Earnshaw et al., 2017; Luk et al., 2010). Indeed, the self-medication hypothesis (Khantzian, 1985) suggests that individuals with internalizing problems, such as depression and anxiety, begin drinking to "treat" or self-medicate difficult symptoms and psychological distress associated with the disorder (Bolton et al., 2009; Robinson et al., 2009). Initially, alcohol may be used to relax, to help find sleep and to relieve stress and anxiety (Kushner et al., 1994), which over time, might lead to an independent AUD.

One out of ten individuals with AUD were classified as most affected (DD-AS), i.e. with highest and most harmful consumption levels as well as social consequences and functional

impairment. This type comprises predominantly male and rather young individuals with AUD (Regier et al., 1990). Similar-feature subtypes were suggested in previous typologies, for example the "Chronic/antisocial subtype" (Windle and Scheidt, 2004), the "Young antisocial type" (Moss et al., 2007), or "Externalizing subtype" (Del Boca and Hesselbrock, 1996). Consistent with those other typologies, DD-AS individuals reported an AUD onset of lower than 24 years compared to the others with onsets of 30 years and over. In fact, externalizing problems were found to be specifically linked to an early initiation of drinking (Zernicke et al., 2010). It has been suggested that early drinking onset is frequently linked to disinhibitory personality traits, which also activate processes that are common in other substance use problems and antisocial behavior. It might also be possible that higher drug use in this group is an artifact of younger age, which is up to 8 years lower than the others. In those with younger age the drug use was socially more acceptable and even more readily available while, in contrast, older people had rather limited exposure to drug use during developmental periods when drug exploration was highest (Golub and Johnson, 2001; Han et al., 2009). Moreover, this severe AUD subtype was associated with more psychosocial risk factors and a tendency for an overall higher and more harmful substance misuse, i.e. more daily alcohol intake and consumption of other drugs. Those individuals are also more likely to experience serious alcohol-related social consequences and functional impairment than others. Although our findings are still cross-sectional, this is compatible with earlier findings that both psychopathological and psychosocial distress indicators are often precursors of increased alcohol consumption, and moreover lead to more severe clinical presentations of AUD (Abler et al., 2014).

Although self-medication is usually associated with accounts of internalizing problems it was not more often reported by DEP-ANX than by DD-AS. Indeed, antisocial tendencies or behaviors often co-occur with AUD as a consequence of the social inhibition- and anxiety-lowering effect of alcohol, which makes a person feel more relaxed (Kushner et al., 2000). Those individuals typically suffer from elevated levels of behavioral undercontrol; therefore are more likely to benefit from the stress response dampening effect of alcohol and to effectively use it as a way to cope with stress (Chassin et al., 2013). Our findings of high self-medication tendencies in that male-limited subtype were previously reported by Bolton et al. (2009) who suggested that males with anti-social personality disorders were likely to self-medicate psychological distress with alcohol while females were not.

Interestingly, our findings suggest a somewhat different AUD-type composition in the Swiss community compared to reports from abroad (Glass et al., 2014; Moss et al., 2007). In contrast to other reports, we found AUD more likely to be linked to internalizing than to externalizing comorbid psychopathology. In fact, there is shared epidemiological support from three population-based studies that internalizing disorders, especially mood disorders, were found to be more prevalent in Switzerland (Angst et al., 2005) than elsewhere (Kessler et al., 2005). We added evidence that this proportion did not alter through the co-occurrence of AUD. The somewhat smaller association of AUD with externalizing problems might be due to opposite trends. Although we found almost similar rates of overall lifetime antisocial personality disorders as reported elsewhere (Compton et al., 2005), associations with AUD found in the current study were comparably smaller (Grant et al., 2015; Guy et al., 2018; Morgenstern et al., 1997). Moreover, other key indicators of the externalizing spectrum, such as cannabis and cocaine use disorder, were

overall less prevalent in the current sample (Compton et al., 2005; Grant et al., 2016) as well as showed weaker associations as reported in other community studies (Stinson et al., 2006).

Our findings further suggest that AUD comorbidity was associated with a higher likelihood for suicidality while pure AUD was not. This supports earlier findings suggesting that the risk for suicidality increases with higher symptom load and greater impairment (Briere et al., 2014). Although suicidality is primarily associated with internalizing problems, such as depression and anxiety (Fuehrlein et al., 2016; Ganz and Sher, 2009), there is increasing scientific evidence showing that externalizing disorders, such as antisocial personality disorders, enhance this association as well (Hoertel et al., 2018). Those individuals typically struggle with poor impulse control, which may make them vulnerable to participate in risky problematic alcohol and drug use as well as other self-destructive behaviors (Sher, 2006).

Although there is evidence that genetic factors generally play a crucial role in the development of AUD (Kendler et al., 2015), we found no additional support for specific associations of AUD subtypes and specific family liability, at least to say for AUD, SUD, depression, and anxiety. Despite overall high prevalence of familial depression and substantial proportions of anxiety disorders among first degree family members there were no AUD subtype-specific associations. However, this is not surprising since there is no clear agreement so far on whether internalizing (Prescott et al., 2000) or externalizing features (Cloninger et al., 1981) have a stronger genetic component in the development of AUD. Instead, our findings rather suggest that developmental factors have distinct associations with more severe AUD subtypes. It has been suggested that early adversity, such as an unstable childhood and familial environment may lead to early initiation and more severe

drinking (Kauhanen et al., 2011). However, it might also be possible that early developmental factors covary or interact with genetic factors (Enoch, 2011), which, however was not tested in the current study.

The majority of individuals with AUD received treatment for mental health problems at any point of their lives, however, our findings support the notion that especially individuals with additional comorbid conditions are even more likely to seek help for their problems than those with pure AUD (Cohen et al., 2007). Thus, it is quite alarming that individuals from the DD-AS type, i.e. with early-onset and more severe AUD, did not seek professional help more often than DEP-ANX and not earlier than others. An early drinking onset is possibly associated with a longer duration of alcohol-related and other mental health problems and consequently with longer periods of untreated problems. Higher clinical severity and overall impairment places this subtype into an even more important position for higher alcohol treatment needs. It is important to note that only a small proportion of individuals with AUD ever received alcohol-specific treatment, which may suggest that high numbers of affected individuals were simply not detected. Individuals from the DD-AS subtype, however, did not report more alcohol-specific treatments but, however, higher informal helpseeking for alcohol problems than the others. Thus, despite greater impairment there is evidence that individuals with comorbid antisocial personality and/or substance use disorders often have poor insight into their problems (Black, 2018) and overall negative attitudes towards mental health services (Jagdeo et al., 2009), and therefore were less likely to voluntarily seek alcohol treatment than others (Goldstein et al., 2010). This, in turn, might explain why those individuals reported to utilize informal sources of help remarkably more often. Brown et al. (Brown et al., 2014) found informal

help-seekers more often than formal helpseekers to rate themselves as healthier and less functionally impaired. Moreover, our broad definition of informal help might lead to possible misconceptions with behaviors such as an association with antisocial peers, which was personally understood as support but might not be considered as positive from a health-promoting perspective (Rickwood and Thomas, 2012).

Strengths of the study doubtlessly include a representative, community-based sample and the use of reliable and valid measures of AUD and comorbid psychopathology. To our knowledge this is the first study that systematically examined the complexity of AUD comorbidity in the Swiss community. As we have found specific etiological as well as other risk factors, it is important to estimate the prevalence of these factors in the general population. Future research is needed to understand the relationship between these factors and alcohol problems to devise effective interventions. Another strength is the model-based approach (LCA) used to identify latent subtypes of AUD that qualitatively differ with respect to their patterns of comorbidity. The fact that the internalizing and externalizing subtypes differed with respect to etiological factors lends further support for their discriminant validity.

Despite its strengths, this study has a number of limitations that have to be acknowledged when interpreting the results. First and most importantly, the cross-sectional design of our study does not allow us to draw conclusions regarding causality since results are based on retrospectively reported ages of onset. Thus, the use of lifetime diagnoses did not allow us to determine whether AUD was of primary or secondary concern within a co-occurrence with other disorders, i.e. whether AUD was determined by another disorder or was the preceding condition. Although onsets of comorbid conditions varied across classes, their

prevalences were too low, except for depression, to find significant differences to determine temporal associations between disorders. Our results should be replicated in a larger longitudinal sample. Second, our results are based on data collected more than 10 years ago, which may not reflect current comorbidity trends but, however, may illustrate the interrelations of psychiatric conditions co-occurring with AUD. Third, we did not assess all psychiatric diagnoses but only the most common ones. Fourth, the use of a non-clinical sample might limit the generalizability of our findings to clinical samples of individuals with AUD. Fifth, as psychosocial and developmental adversity were reported retrospectively, data might be subject to recall bias, especially in subjects of older age. These reports may have been further influenced by current affective states or other unknown factors that were not assessed in this study. Therefore, we cannot exclude the possibility that the recollection of adverse experiences, rather than the actual experience itself, was associated with higher alcohol consumption (patterns) or comorbid conditions. Sixth, the fact that younger individuals reported earlier AUD onsets might also be the consequence of an inaccurate recall – a bias that was often observed in cross-sectional data. This effect, known as "foreward telescoping", describes the phenomenon of foreward shifting of recalled individual onset ages by increasing ages of the surveyed subject (Golub et al., 2000). Thus, younger persons sometimes were placed at risk for early problem use while the same person might not be identified as at-risk when surveyed at a later age. Therefore, appropriate caution should be exercised in interpreting these findings. Future studies should further address these aspects, which extend beyond the scope of the present research. Seventh and finally, the semi-structured interview that was used to determine AUD and comorbid disorders was based on the diagnostic criteria of DSM-IV while DSM-5 is

now currently in use. Therefore, the presence of DSM-5 AUD and its associated comorbid conditions needs to be determined in further research.

In sum, this study provides evidence for three AUD subtypes in the Swiss community that vary along dimensions of comorbidity as well as clinical and etiological factors with important implications for treatment. The presence of substantial "high impact" comorbidity in individuals with AUD that do not seek specialized treatment suggests the need for comprehensive diagnostic assessments at all health service facilities, regardless of whether one presents for alcohol problems in specialized mental health or in general medical settings. Low engagement in treatment stresses the need to identify high-risk individuals in order to develop appropriate strategies to engage this group in treatment for all identified disorders. Identifying specific developmental and risk factors that are AUD-promoting but potentially modifiable may present important targets for prevention and early intervention.

References

Abler, L.A., Sikkema, K.J., Watt, M.H., Eaton, L.A., Choi, K.W., Kalichman, S.C., Skinner, D., Pieterse, D., 2014. Longitudinal cohort study of depression, post-traumatic stress, and alcohol use in South African women who attend alcohol serving venues. BMC Psychiatry 14, 224.

Ajdacic-Gross, V., Rodgers, S., Muller, M., Hengartner, M.P., Aleksandrowicz, A., Kawohl, W., Heekeren, K., Rossler, W., Angst, J., Castelao, E., Vandeleur, C., Preisig, M., 2016. Pure animal phobia is more specific than other specific phobias: epidemiological evidence from the Zurich Study, the ZInEP and the PsyCoLaus. Eur Arch Psychiatry Clin Neurosci 266 (6), 567-577.

Alonso, J., Angermeyer, M.C., Bernert, S., Bruffaerts, R., Brugha, T.S., Bryson, H., de Girolamo, G., Graaf, R., Demyttenaere, K., Gasquet, I., Haro, J.M., Katz, S.J., Kessler, R.C., Kovess, V., Lepine, J.P., Ormel, J., Polidori, G., Russo, L.J., Vilagut, G., Almansa, J., Arbabzadeh-Bouchez, S., Autonell, J., Bernal, M., Buist-Bouwman, M.A., Codony, M., Domingo-Salvany, A., Ferrer, M., Joo, S.S., Martinez-Alonso, M., Matschinger, H., Mazzi, F., Morgan, Z., Morosini, P., Palacin, C., Romera, B., Taub, N., Vollebergh, W.A., EsemeD/Mhedea Investigators, E.S.o.t.E.o.M.D.P., 2004. Use of mental health services in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl(420), 47-54.

Angst, J., Gamma, A., Endrass, J., Rossler, W., Ajdacic-Gross, V., Eich, D., Herrell, R., Merikangas, K.R., 2006. Is the association of alcohol use disorders with major depressive disorder a consequence of undiagnosed bipolar-II disorder? Eur Arch Psychiatry Clin Neurosci 256 (7), 452-457.

Angst, J., Gamma, A., Neuenschwander, M., Ajdacic-Gross, V., Eich, D., Rossler, W., Merikangas, K.R., 2005. Prevalence of mental disorders in the Zurich Cohort Study: a twenty year prospective study. Epidemiol Psichiatr Soc 14 (2), 68-76.

Babor, T.F., Hofmann, M., DelBoca, F.K., Hesselbrock, V., Meyer, R.E., Dolinsky, Z.S., Rounsaville, B., 1992. Types of alcoholics, I. Evidence for an empirically derived typology based on indicators of vulnerability and severity. Arch Gen Psychiatry 49 (8), 599-608.

Barnow, S., Schuckit, M.A., Lucht, M., John, U., Freyberger, H.J., 2002. The importance of a positive family history of alcoholism, parental rejection and emotional warmth, behavioral problems and peer substance use for alcohol problems in teenagers: a path analysis. J Stud Alcohol 63 (3), 305-315.

Berney, A., Preisig, M., Matthey, M.L., Ferrero, F., Fenton, B.T., 2002. Diagnostic interview for genetic studies (DIGS): inter-rater and test-retest reliability of alcohol and drug diagnoses. Drug Alcohol Depend 65 (2), 149-158.

Black, D., 2018. Treatment for Antisocial Personality Disorder, in: Central.com, P. (Ed.). APA.

Bolton, J., Cox, B., Clara, I., Sareen, J., 2006. Use of alcohol and drugs to self-medicate anxiety disorders in a nationally representative sample. J Nerv Ment Dis 194 (11), 818-825.

Bolton, J.M., Robinson, J., Sareen, J., 2009. Self-medication of mood disorders with alcohol and drugs in the National Epidemiologic Survey on Alcohol and Related Conditions. J Affect Disord 115 (3), 367-375.

Bottlender, M., Preuss, U.W., Soyka, M., 2006. Association of personality disorders with Type A and Type B alcoholics. Eur Arch Psychiatry Clin Neurosci 256 (1), 55-61.

Briere, F.N., Rohde, P., Seeley, J.R., Klein, D., Lewinsohn, P.M., 2014. Comorbidity between major depression and alcohol use disorder from adolescence to adulthood. Compr Psychiatry 55 (3), 526-533.

Brown, J., Evans-Lacko, S., Aschan, L., Henderson, M.J., Hatch, S.L., Hotopf, M., 2014. Seeking informal and formal help for mental health problems in the community: a secondary analysis from a psychiatric morbidity survey in South London. BMC Psychiatry 14 (1), 275.

Chan, Y.F., Dennis, M.L., Funk, R.R., 2008. Prevalence and comorbidity of major internalizing and externalizing problems among adolescents and adults presenting to substance abuse treatment. J Subst Abuse Treat 34 (1), 14-24.

Chassin, L., Sher, K.J., Hussong, A., Curran, P., 2013. The developmental psychopathology of alcohol use and alcohol disorders: research achievements and future directions. Dev Psychopathol 25 (4 Pt 2), 1567-1584.

Cloninger, C.R., Bohman, M., Sigvardsson, S., 1981. Inheritance of alcohol abuse. Cross-fostering analysis of adopted men. Arch Gen Psychiatry 38 (8), 861-868.

Cohen, E., Feinn, R., Arias, A., Kranzler, H.R., 2007. Alcohol treatment utilization: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug Alcohol Depend 86 (2-3), 214-221.

Compton, W.M., Conway, K.P., Stinson, F.S., Colliver, J.D., Grant, B.F., 2005. Prevalence, correlates, and comorbidity of DSM-IV antisocial personality syndromes and alcohol and specific drug use disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. J Clin Psychiatry 66 (6), 677-685.

Cullen, B.A., La Flair, L.N., Storr, C.L., Green, K.M., Alvanzo, A.A., Mojtabai, R., Pacek, L.R., Crum, R.M., 2013. Association of comorbid generalized anxiety disorder and alcohol use disorder symptoms with health-related quality of life: results from the National Epidemiological Survey on Alcohol and Related Conditions. J Addict Med 7 (6), 394-400.

Dawson, D.A., Goldstein, R.B., Moss, H.B., Li, T.K., Grant, B.F., 2010. Gender differences in the relationship of internalizing and externalizing psychopathology to alcohol dependence: likelihood, expression and course. Drug Alcohol Depend 112 (1-2), 9-17.

Del Boca, F.K., Hesselbrock, M.N., 1996. Gender and alcoholic subtypes. Alcohol Health & Research World 20 (1), 56-62.

Earnshaw, V.A., Elliott, M.N., Reisner, S.L., Mrug, S., Windle, M., Emery, S.T., Peskin, M.F., Schuster, M.A., 2017. Peer Victimization, Depressive Symptoms, and Substance Use: A Longitudinal Analysis. Pediatrics 139 (6).

Endicott, J., Spitzer, R.L., 1978. A diagnostic interview: the schedule for affective disorders and schizophrenia. Arch Gen Psychiatry 35 (7), 837-844.

Enoch, M.A., 2011. The role of early life stress as a predictor for alcohol and drug dependence. Psychopharmacology (Berl) 214 (1), 17-31.

Falk, D.E., Yi, H.Y., Hilton, M.E., 2008. Age of onset and temporal sequencing of lifetime DSM-IV alcohol use disorders relative to comorbid mood and anxiety disorders. Drug Alcohol Depend 94 (1-3), 234-245.

Firmann, M., Mayor, V., Vidal, P.M., Bochud, M., Pecoud, A., Hayoz, D., Paccaud, F., Preisig, M., Song, K.S., Yuan, X., Danoff, T.M., Stirnadel, H.A., Waterworth, D., Mooser, V., Waeber, G., Vollenweider, P., 2008. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. BMC Cardiovasc Disord 8, 6.

Flensborg-Madsen, T., Mortensen, E.L., Knop, J., Becker, U., Sher, L., Gronbaek, M., 2009. Comorbidity and temporal ordering of alcohol use disorders and other psychiatric disorders: results from a Danish register-based study. Compr Psychiatry 50 (4), 307-314.

Fuehrlein, B.S., Mota, N., Arias, A.J., Trevisan, L.A., Kachadourian, L.K., Krystal, J.H., Southwick, S.M., Pietrzak, R.H., 2016. The burden of alcohol use disorders in US military veterans: results from the National Health and Resilience in Veterans Study. Addiction 111 (10), 1786-1794.

Ganz, D., Sher, L., 2009. Suicidal behavior in adolescents with comorbid depression and alcohol abuse. Minerva Pediatr 61 (3), 333-347.

Glass, J.E., Williams, E.C., Bucholz, K.K., 2014. Psychiatric comorbidity and perceived alcohol stigma in a nationally representative sample of individuals with DSM-5 alcohol use disorder. Alcohol Clin Exp Res 38 (6), 1697-1705.

Goldstein, R.B., Dawson, D.A., Grant, B.F., 2010. Antisocial Behavioral Syndromes in Adulthood and Alcohol Use Disorder Treatment over Three-Year Follow-Up: Results from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. J Am Psychiatr Nurses Assoc 16 (4), 212-226.

Golub, A., Johnson, B.D., 2001. Variation in youthful risks of progression from alcohol and tobacco to marijuana and to hard drugs across generations. Am J Public Health 91 (2), 225-232.

Golub, A., Johnson, B.D., Labouvie, E., 2000. On Correcting Biases in Self-Reports of Age at First Substance Use with Repeated Cross-Section Analysis. J Quant Criminol 16 (1), 45-68.

Grant, B.F., Goldstein, R.B., Saha, T.D., Chou, S.P., Jung, J., Zhang, H., Pickering, R.P., Ruan, W.J., Smith, S.M., Huang, B., Hasin, D.S., 2015. Epidemiology of DSM-5 Alcohol Use Disorder: Results From the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA Psychiatry 72 (8), 757-766.

Grant, B.F., Saha, T.D., Ruan, W.J., Goldstein, R.B., Chou, S.P., Jung, J., Zhang, H., Smith, S.M., Pickering, R.P., Huang, B., Hasin, D.S., 2016. Epidemiology of DSM-5 Drug Use Disorder: Results From the National Epidemiologic Survey on Alcohol and Related Conditions-III. JAMA Psychiatry 73 (1), 39-47.

Guy, N., Newton-Howes, G., Ford, H., Williman, J., Foulds, J., 2018. The prevalence of comorbid alcohol use disorder in the presence of personality disorder: Systematic review and explanatory modelling. Personal Ment Health 12 (3), 216-228.

Han, B., Gfroerer, J., Colliver, J., 2009. An Examination of Trends in Illicit Drug Use among Adults Aged 50 to 59 in the United States, in: Studies, O.o.A. (Ed.). Substance Abuse and Mental Health Services Administration (SAMHSA).

Hill, S.Y., 1992. Absence of paternal sociopathy in the etiology of severe alcoholism: is there a type III alcoholism? J Stud Alcohol 53 (2), 161-169.

Hingson, R.W., Heeren, T., Winter, M.R., 2006. Age of alcohol-dependence onset: associations with severity of dependence and seeking treatment. Pediatrics 118 (3), e755-763.

Hoertel, N., Faiz, H., Airagnes, G., Blanco, C., Pascal De Raykeer, R., Franco, S., Ducoutumany, G., Lemogne, C., Limosin, F., 2018. A comprehensive model of predictors of suicide attempt in heavy drinkers: Results from a national 3-year longitudinal study. Drug Alcohol Depend 186, 44-52.

Hollingshead, A.B., 1975. Four-factor Index of Social Status, Unpublished manuscript.

Jagdeo, A., Cox, B.J., Stein, M.B., Sareen, J., 2009. Negative attitudes toward help seeking for mental illness in 2 population-based surveys from the United States and Canada. Can J Psychiatry 54 (11), 757-766.

Kauhanen, L., Leino, J., Lakka, H.M., Lynch, J.W., Kauhanen, J., 2011. Adverse childhood experiences and risk of binge drinking and drunkenness in middle-aged finnish men. Adv Prev Med 2011, 478741.

Kendler, K.S., Ji, J., Edwards, A.C., Ohlsson, H., Sundquist, J., Sundquist, K., 2015. An extended Swedish national adoption study of alcohol use disorder. JAMA Psychiatry 72 (3), 211-218.

Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62 (6), 593-602.

Kessler, R.C., Crum, R.M., Warner, L.A., Nelson, C.B., Schulenberg, J., Anthony, J.C., 1997. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Arch Gen Psychiatry 54 (4), 313-321.

Khantzian, E.J., 1985. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. Am J Psychiatry 142 (11), 1259-1264.

Kranzler, H.R., Del Boca, F.K., Rounsaville, B.J., 1996. Comorbid psychiatric diagnosis predicts three-year outcomes in alcoholics: a posttreatment natural history study. J Stud Alcohol 57 (6), 619-626.

Kushner, M.G., Abrams, K., Borchardt, C., 2000. The relationship between anxiety disorders and alcohol use disorders: a review of major perspectives and findings. Clin Psychol Rev 20 (2), 149-171.

Kushner, M.G., Sher, K.J., Wood, M.D., Wood, P.K., 1994. Anxiety and drinking behavior: moderating effects of tension-reduction alcohol outcome expectancies. Alcohol Clin Exp Res 18 (4), 852-860.

Leboyer, M., Barbe, T., Gorwood, P., Teherani, M., Allilaire, J.F., Preisig, M., Matthey, M.L., Poyetton, V., Ferrero, F., 1995. Interview diagnostique pour les études génétiques. Institut National de la Santé et de la Recherche Médicale, Paris.

Leboyer, M., Maier, W., Teherani, M., Lichtermann, D., D'Amato, T., Franke, P., Lepine, J.P., Minges, J., McGuffin, P., 1991. The reliability of the SADS-LA in a family study setting. Eur Arch Psychiatry Clin Neurosci 241 (3), 165-169.

Leggio, L., Kenna, G.A., Fenton, M., Bonenfant, E., Swift, R.M., 2009. Typologies of alcohol dependence. From Jellinek to genetics and beyond. Neuropsychol Rev 19 (1), 115-129.

Lo, Y., Mendell, N., Rubin, D., 2001. Testing the number of components in a normal mixture. Biometrika 88, 767-778.

Luk, J.W., Wang, J., Simons-Morton, B.G., 2010. Bullying victimization and substance use among U.S. adolescents: mediation by depression. Prev Sci 11 (4), 355-359.

Martin, P., 2003. The epidemiology of anxiety disorders: a review. Dialogues Clin Neurosci 5 (3), 281-298.

Mayfield, R.D., Harris, R.A., Schuckit, M.A., 2008. Genetic factors influencing alcohol dependence. Br J Pharmacol 154 (2), 275-287.

McLachlan, P., Peel, D., 2000. Finite mixture models. Wiley, New York.

Mojtabai, R., Olfson, M., Mechanic, D., 2002. Perceived need and help-seeking in adults with mood, anxiety, or substance use disorders. Arch Gen Psychiatry 59 (1), 77-84.

Morgenstern, J., Langenbucher, J., Labouvie, E., Miller, K.J., 1997. The comorbidity of alcoholism and personality disorders in a clinical population: prevalence rates and relation to alcohol typology variables. J Abnorm Psychol 106 (1), 74-84.

Moss, H.B., Chen, C.M., Yi, H.Y., 2007. Subtypes of alcohol dependence in a nationally representative sample. Drug Alcohol Depend 91 (2-3), 149-158.

Muthen, L.K., Muthen, B.O., 1998-2011. Mplus User's Guide, Sixth Edition ed. Muthén & Muthén, Los Angeles, CA.

Nurnberger, J.I., Jr., Blehar, M.C., Kaufmann, C.A., York-Cooler, C., Simpson, S.G., Harkavy-Friedman, J., Severe, J.B., Malaspina, D., Reich, T., 1994. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. Arch Gen Psychiatry 51 (11), 849-859; discussion 863-844.

Nylund, K.L., Asparoutiov, T., Muthen, B.O., 2007. Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. Structural Equation Modeling-a Multidisciplinary Journal 14 (4), 535-569.

Pacek, L.R., Storr, C.L., Mojtabai, R., Green, K.M., La Flair, L.N., Alvanzo, A.A., Cullen, B.A., Crum, R.M., 2013. Comorbid Alcohol Dependence and Anxiety Disorders: A National Survey. J Dual Diagn 9 (4).

Preisig, M., Fenton, B.T., Matthey, M.L., Berney, A., Ferrero, F., 1999. Diagnostic interview for genetic studies (DIGS): inter-rater and test-retest reliability of the French version. Eur Arch Psychiatry Clin Neurosci 249 (4), 174-179.

Preisig, M., Waeber, G., Vollenweider, P., Bovet, P., Rothen, S., Vandeleur, C., Guex, P., Middleton, L., Waterworth, D., Mooser, V., Tozzi, F., Muglia, P., 2009. The PsyCoLaus study: methodology and characteristics of the sample of a population-based survey on psychiatric disorders and their association with genetic and cardiovascular risk factors. BMC Psychiatry 9, 9.

Prescott, C.A., Aggen, S.H., Kendler, K.S., 2000. Sex-specific genetic influences on the comorbidity of alcoholism and major depression in a population-based sample of US twins. Arch Gen Psychiatry 57 (8), 803-811.

Regier, D.A., Farmer, M.E., Rae, D.S., Locke, B.Z., Keith, S.J., Judd, L.L., Goodwin, F.K., 1990. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA 264 (19), 2511-2518.

Rehm, J., Mathers, C., Popova, S., Thavorncharoensap, M., Teerawattananon, Y., Patra, J., 2009. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet 373 (9682), 2223-2233.

Rickwood, D., Thomas, K., 2012. Conceptual measurement framework for help-seeking for mental health problems. Psychol Res Behav Manag 5, 173-183.

Robinson, J., Sareen, J., Cox, B.J., Bolton, J., 2009. Self-medication of anxiety disorders with alcohol and drugs: Results from a nationally representative sample. J Anxiety Disord 23 (1), 38-45.

Rodgers, S., Ajdacic-Gross, V., Kawohl, W., Muller, M., Rossler, W., Hengartner, M.P., Castelao, E., Vandeleur, C., Angst, J., Preisig, M., 2015. Comparing two basic subtypes in OCD across three large community samples: a pure compulsive versus a mixed obsessive-compulsive subtype. Eur Arch Psychiatry Clin Neurosci 265 (8), 719-734.

Rose, R.J., Viken, R.J., Dick, D.M., Bates, J.E., Pulkkinen, L., Kaprio, J., 2003. It does take a village: nonfamilial environments and children's behavior. Psychol Sci 14 (3), 273-277.

Rougemont-Buecking, A., Rothen, S., Jeanpretre, N., Lustenberger, Y., Vandeleur, C.L., Ferrero, F., Preisig, M., 2008. Inter-informant agreement on diagnoses and prevalence estimates of anxiety disorders: direct interview versus family history method. Psychiatry Res 157 (1-3), 211-223.

Schneier, F.R., Foose, T.E., Hasin, D.S., Heimberg, R.G., Liu, S.M., Grant, B.F., Blanco, C., 2010. Social anxiety disorder and alcohol use disorder co-morbidity in the National Epidemiologic Survey on Alcohol and Related Conditions. Psychol Med 40 (6), 977-988.

Sher, K.J., Grekin, E.R., Williams, N.A., 2005. The development of alcohol use disorders. Annu Rev Clin Psychol 1, 493-523.

Sher, L., 2006. Alcohol consumption and suicide. QJM 99 (1), 57-61.

StataCorp, 2011. Stata Statistical Software, Release 13 ed. StataCorp LP, College Station, TX.

Stinson, F.S., Grant, B.F., Dawson, D.A., Ruan, W.J., Huang, B., Saha, T., 2006. Comorbidity Between DSM–IV Alcohol and Specific Drug Use Disorders in the United States. Alcohol Research & Health 29 (2), 94-106.

Studer, J., Baggio, S., Deline, S., N'Goran, A.A., Henchoz, Y., Mohler-Kuo, M., Daeppen, J.B., Gmel, G., 2014. Peer pressure and alcohol use in young men: a mediation analysis of drinking motives. Int J Drug Policy 25 (4), 700-708.

Vandeleur, C.L., Fassassi, S., Castelao, E., Glaus, J., Strippoli, M.F., Lasserre, A.M., Rudaz, D., Gebreab, S., Pistis, G., Aubry, J.M., Angst, J., Preisig, M., 2017. Prevalence and correlates of DSM-5 major depressive and related disorders in the community. Psychiatry Res 250, 50-58.

WHO, 2011. Global status report on alcohol and health, in: Organization, W.H. (Ed.). Department of Mental Health and Substance Abuse, Geneva.

WHO, 2014. Global status report on alcohol and health, in: Organization, W.H. (Ed.). Department of Mental Health and Substance Abuse, Geneva.

Windle, M., Scheidt, D.M., 2004. Alcoholic subtypes: are two sufficient? Addiction 99 (12), 1508-1519.

Wu, L.T., Kouzis, A.C., Leaf, P.J., 1999. Influence of comorbid alcohol and psychiatric disorders on utilization of mental health services in the National Comorbidity Survey. Am J Psychiatry 156 (8), 1230-1236.

Wu, L.T., Pilowsky, D.J., Schlenger, W.E., Hasin, D., 2007. Alcohol use disorders and the use of treatment services among college-age young adults. Psychiatr Serv 58 (2), 192-200.

Zernicke, K.A., Cantrell, H., Finn, P.R., Lucas, J., 2010. The association between earlier age of first drink, disinhibited personality, and externalizing psychopathology in young adults. Addict Behav 35 (5), 414-418.

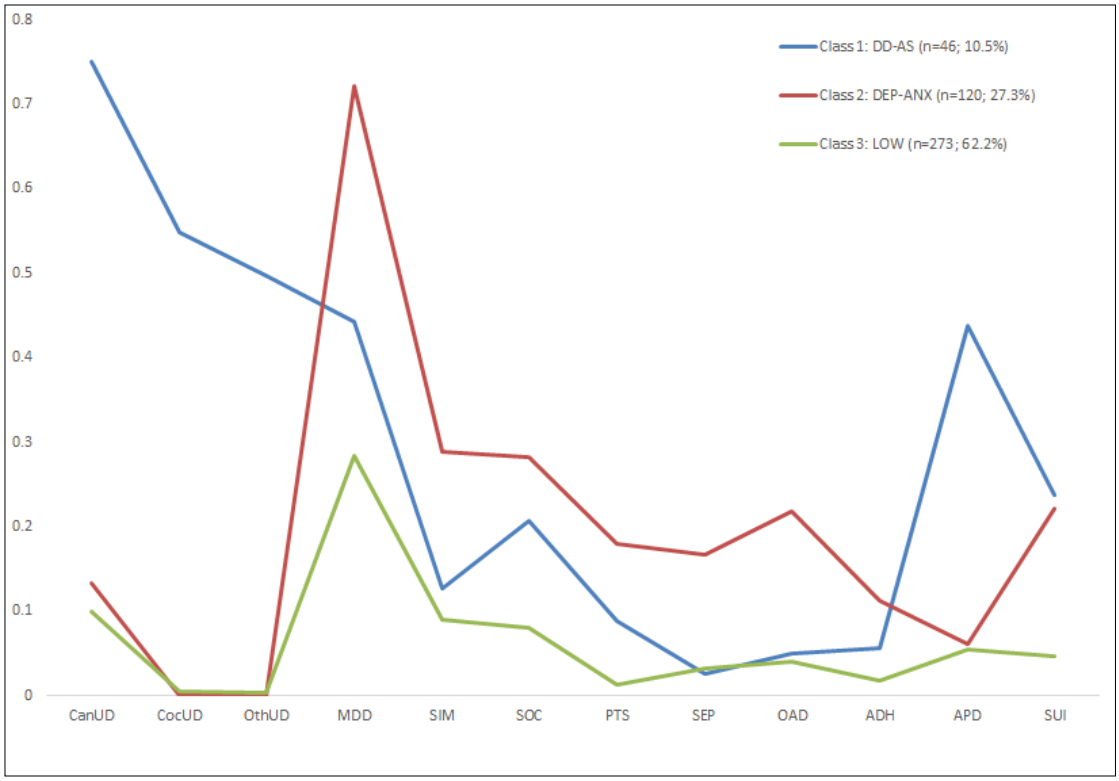

Figure 1. Three class solution of AUD comorbidity

Note: CanUD=Cannabis use disorder; CocUD=Cocaine use disorder; OthUD=Other use disorders; MDD=Major depression; SIM=Simple phobia, SOC=Social phobia; PTS= Posttraumatic stress disorder; SEP=Separation anxiety disorder; OAD=Other anxiety disorders; ADH= Attention deficit hyperactivity disorder; APD=Antisocial personality disorder; SUI=Suicide attempt.

Table 1. Lifetime prevalence of comorbid conditions in the PsyCoLaus baseline sample and in the subsample of 439 individuals with AUD versus those without AUD

	Total sample N=3,720	No AUD n=3,281	AUD n=439	p-value
	n(%)	n(%)	n(%)	
Cannabis use disorder	201 (5.4)	119 (3.6)	82 (18.7)	**<0.001**
Cocaine use disorder	67 (1.8)	37 (1.1)	30 (6.8)	**<0.001**
Other drug use disorders	56 (1.5)	29 (0.9)	27 (6.2)	**<0.001**
Major depression	1,626 (43.7)	1,437 (43.8)	189 (43.1)	0.768
Simple phobia	587 (15.8)	520 (15.9)	67 (15.3)	0.751
Social phobia	444 (11.9)	376 (11.5)	68 (15.5)	0.014
Posttraumatic stress disorder	147 (4.0)	116 (3.5)	31 (7.1)	**<0.001**
Separation anxiety disorder	203 (5.5)	172 (5.2)	31 (7.1)	0.115
Other anxiety disorders	329 (8.9)	288 (8.8)	41 (9.3)	0.699
Attention deficit hyperactivity disorder	96 (2.6)	74 (2.3)	22 (5.0)	**0.001**
Antisocial personality disorder	96 (2.6)	51 (1.6)	45 (10.3)	**<0.001**
Suicide attempt	221 (5.9)	168 (5.1)	53 (12.1)	**<0.001**

Note: Bold values are statistically significant after Bonferroni's correction.

Table 2. LCA fit statistics for the tested class solutions

	1 Class	*2 Classes*	*3 Classes*	*4 Classes*	*5 Classes*
AIC	12108.524	3533.090	3436.984	3417.688	3439.342
BIC	12182.045	3647.456	3616.702	3662.758	3749.764
Sample-size Adjusted BIC	12124.922	3558.598	3477.067	3472.347	3508.577
LMR-LRT	*na*	230.077	128.107	51.293	18.044
		p = 0.001	p = 0.002	p = 0.072	p = 0.553
Parametric BLRT	*na*	230.077	128.107	51.293	18.044
		p < 0.001	p < 0.001	p < 0.001	p = 0.600
n for each class	C1 = 439	C1 = 393	C1 = 46	C1 = 16	C1 = 39
		C2 = 46	C2 = 120	C2 = 44	C2 = 61
			C3 = 273	C3 = 200	C3 = 64
				C4 = 197	C4 = 32
					C5 = 243

Note: AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, BLRT = Bootstrapped Likelihood Ratio Test; LMR-LRT = Lo-Mendell-Rubin adjusted Likelihood Ratio Test; C1 = class 1; C2 = class 2; C3 = class 3; C4 = class 4; C5 = class 5.

Table 3. Parameter estimates for the three-class solution in 439 individuals with AUD

	Prevalence of indicators among the N=439 individuals with AUD n (%)	Class1 (DD-AS) n=46	Class2 (DEP-ANX) n=120	Class3 (LOW) n=273	
Probability of membership in each class		0.119	0.292	0.589	
Conditional probabilities of[1]:					
Cannabis use disorder	82 (18.7)	0.751	0.133	0.099	C1 > C2,C3***
Cocaine use disorder	30 (6.8)	0.548	0.000	0.005	C1 > C3***
Other drug use disorders	27 (6.2)	0.497	0.000	0.004	C1 > C3***
Major depression	189 (43.1)	0.443	0.721	0.284	C2 > C1,C3***
Simple phobia	67 (15.3)	0.127	0.289	0.090	C2 > C1*,C3***
Social phobia	68 (15.5)	0.207	0.282	0.081	C1*,C2*** > C3
Posttraumatic stress disorder	31 (7.1)	0.088	0.179	0.013	C1**,C2*** > C3
Separation anxiety disorder	31 (7.1)	0.025	0.167	0.032	C2 > C1*,C3***
Other anxiety disorders	41 (9.3)	0.050	0.218	0.041	C2 > C1*,C3***
Attention deficit hyperactivity disorder	22 (5.0)	0.056	0.113	0.018	C1*,C2*** > C3
Antisocial personality disorder	45 (10.3)	0.438	0.061	0.055	C1 > C2,C3***
Suicide attempt	53 (12.1)	0.238	0.222	0.047	C1,C2 > C3***

[1]Probability of each indicator among subjects of this class; *** $p \leq 0.001$; ** $p \leq 0.01$; * $p \leq 0.05$; C1=Class1; C2=Class2; C3=Class3.

Table 4. Distributions of sociodemographic characteristics among the three derived classes of AUD comorbidity

		Total sample	LOW %	DEP-ANX %	DD-AS %	P-value
	Female gender	22.6	0.4	68.3	34.8	**<0.001** DEP-ANX,DD-AS > LOW*** DEP-ANX > DD-AS***
	Age (M±SD)	50.5±8.6	51.9±8.4	49.8±8.7	43.6±4.8	**<0.001** LOW > DEP-ANX*,DD-AS*** DEP-ANX > DD-AS***
Marital status	Single	18.7	13.9	26.7	26.1	**<0.001** Married vs. single (Ref.): LOW > DEP-ANX***,DD-AS**
	Married	54.4	64.5	36.7	41.3	
	Divorced/separated	25.5	20.5	34.2	32.6	
	Widowed	1.4	1.1	2.5	0.0	
Education	Compulsory school not completed	1.1	1.1	1.7	0.0	0.817
	Obligatory schooling or apprenticeship	59.2	57.9	60.0	65.2	
	Professional school or technical higher education	20.3	21.3	17.5	21.7	
	University-level education	19.4	19.8	20.8	13.0	
SES	Hollingshead Index (M±SD)	3.3±1.3	3.4±1.3	3.2±1.3	3.2±1.1	0.586

Note: Bold values are statistically significant after Bonferroni's correction; SES = socio-economic status.

Table 5. Psychosocial and genetic risk factors

		Total sample %	LOW %	DEP-ANX %	DD-AS %	P-value
Psychosocial risk factors	Unhappy childhood	14.6	8.4	24.2	26.1	**<0.001** DEP-ANX***,DD-AS** > LOW
	Fear to be punished by parents	17.6	11.0	30.0	23.9	**<0.001** DEP-ANX***,DD-AS* > LOW
	Ran away from home	7.5	6.2	6.7	17.4	0.027
	Foster home	12.3	9.2	18.3	15.2	0.032
	Grown up without biological parents	37.1	31.5	48.3	41.30	0.005
	Parents divorced/separated	18.2	14.3	25.8	21.7	0.019
	Low income (< 50,000 CHF per year)	25.8	20.2	34.2	37.0	0.003
Psychopathology in first degree relatives	AUD	42.9	39.6	48.1	48.8	0.243
	SUD	8.3	6.3	12.3	9.8	0.166
	Depression	23.2	22.6	25.8	20.0	0.677
	Anxiety disorders	8.3	6.7	12.6	6.7	0.141

Note: Bold values are statistically significant after Bonferroni's correction; AUD = alcohol use disorders; SUD = substance use disorders.

Table 6. Alcohol use, chronicity, consequences and health-related functioning

		Total sample %	LOW %	DEP-ANX %	DD-AS %	P-value
	Onset age of AUD in years (M±SD)	29.8±10.6	30.1±10.4	31.5±11.3	23.7±6.6	**<0.001** LOW,DEP-ANX > DD-AS***
Consumption pattern	Daily alcohol intake in grams (M±SD)	51.5±54.5	45.8±42.9	48.2±47.7	91.3±99.7	**<0.001** DD-AS*** > LOW, DEP-ANX
Indicators of harmful use	Experience of alcohol-related blackouts	36.1	30.9	35.8	67.4	**<0.001** DD-AS*** > LOW, DEP-ANX
	Several episodes of binge-drinking	37.3	33.3	38.7	56.5	0.010
Drinking to self-medicate psychological distress		36.9	27.1	51.7	56.5	**<0.001** DEP-ANX,DD-AS > LOW***
Symptoms of withdrawal when not drinking (M±SD)		1.0±2.1	0.7±1.7	1.2±2.4	2.0±3.1	**<0.001** DD-AS > LOW**
Physical conditions resulting from alcohol consumption (M±SD)		0.4±0.8	0.3±0.8	0.4±0.9	0.6±1.1	0.103
Social consequences from drinking (M±SD)		0.9±0.9	0.9±0.9	0.8±0.9	1.4±1.0	**<0.001** DD-AS > LOW**,DEP-ANX***
Functionally impaired at school, work or other responsibilities due to mental health problems at least once in lifetime		28.6	18.0	47.9	41.3	**<0.001** DEP-ANX***,DD-AS** > LOW
GAF	Lifetime (M±SD)	68.7±11.1	71.6±10.7	65.0±9.9	61.0±10.0	**<0.001** LOW*** > DEP-ANX,DD-AS

Note: Bold values are statistically significant after Bonferroni's correction; AUD = alcohol use disorders; GAF = General Assessment of Functioning.

Table 7. Treatment-related variables

	Total sample	LOW %	DEP-ANX %	DD-AS %	P-value
Overall treatment					
Lifetime professional treatment for mental health problems	57.4	46.9	76.7	69.6	**<0.001** DEP-ANX***,DD-AS** > LOW
Age of first professional help for mental health problems in years (M±SD)	33.2±12.7	35.2 ±14.0	30.7 ±11.4	32.4±9.0	0.033
Lifetime use of psychotropic medication for mental health problems	45.3	33.0	69.2	56.5	**<0.001** DEP-ANX***,DD-AS** > LOW
Hospitalization for mental health problems	14.8	13.6	12.6	28.3	0.025
Age of first hospitalization for mental health problems in years (M±SD)	37.5±11.7	38.7±12.0	38.2 ±12.3	32.2 ±8.4	0.255
Alcohol-specific treatment					
Alcohol-specific treatments	16.2	15.8	15.0	21.7	0.546
Professional treatment	15.0	15.4	13.3	17.4	0.780
Non-professional help-seeking	5.9	5.1	3.3	17.4	**0.002** DD-AS** > DEP-ANX, LOW

Note: Bold values are statistically significant after Bonferroni's correction

Author Statement

The authors declare that there are no conflicts of interests.

MM: Conceptualization**,** Methodology, Formal analysis, Writing – Original Draft, Writing – Review & Editing

CV: Supervision, Investigation, Writing – Original Draft; Writing – Review & Editing

VAG: Supervision, Methodology, Writing – Review & Editing

ABV: Writing – Original Draft; Writing – Review & Editing

MP: Funding acquisition, Project administration, Writing – Review & Editing

EC: Data curation, Software, Resources

AL, SR, WR, SV, ES: Writing – Review & Editing