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Prediction of incidence and stability of alcohol use disorders by latent internalizing psychopathology risk profiles in adolescence and young adulthood

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ABSTRACT

Background: Comorbid internalizing mental disorders in alcohol use disorders (AUD) can be understood as putative independent risk factors for AUD or as expressions of underlying shared psychopathology vulnerabilities. However, it remains unclear whether: 1) specific latent internalizing psychopathology risk-profiles predict AUD-incidence and 2) specific latent internalizing comorbidity-profiles in AUD predict AUD-stability.
Aims: To investigate baseline latent internalizing psychopathology risk profiles as predictors of subsequent AUD-incidence and -stability in adolescents and young adults.
Methods: Data from the prospective-longitudinal EDSP study (baseline age 14–24 years) were used. The study-design included up to three follow-up assessments in up to ten years. DSM-IV mental disorders were assessed with the DIA-X/M-CIDI. To investigate risk-profiles and their associations with AUD-outcomes, latent class analysis with auxiliary outcome variables was applied.
Results: AUD-incidence: a 4-class model (N = 1683) was identified (classes: normative-male [45.9%], normative-female [44.2%], internalizing [5.3%], nicotine dependence [4.5%]). Compared to the normative-female class, all other classes were associated with a higher risk of subsequent incident alcohol dependence ($p < 0.05$). AUD-stability: a 3-class model (N = 1940) was identified with only one class (11.6%) with high probabilities for baseline AUD. This class was further characterized by elevated substance use disorder (SUD) probabilities and predicted any subsequent AUD (OR 8.5, 95% CI 5.4–13.3).
Conclusions: An internalizing vulnerability may constitute a pathway to AUD incidence in adolescence and young adulthood. In contrast, no indication for a role of internalizing comorbidity profiles in AUD-stability was found, which may indicate a limited importance of such profiles – in contrast to SUD-related profiles – in AUD stability.

1. Introduction

Alcohol use disorders (DSM-IV alcohol abuse or dependence, AUD) are associated with substantial morbidity and mortality (Rehm et al., 2009; Rehm et al., 2013). Identifying risk factors for AUD onset and stability is crucial for tailoring preventive and intervention efforts (Perkonigg et al., 1998). Prospective-longitudinal epidemiological studies have identified a range of different mental disorders (MD) as risk factors for AUD onset, including several anxiety and substance use disorders (SUD), bipolar and conduct disorder (Behrendt et al., 2011; Brückl et al., 2007; Elkins et al., 2007; Lieb et al., 2016; Swendsen et al., 2010). However, existing evidence is somewhat more consistent for externalizing compared to internalizing MD in SUD prediction (Farmer et al., 2015). Thus, the importance of an 'internalizing pathway' to AUD onset warrants further research as it remains unclear, whether specific internalizing MD (Buckner et al., 2008), specific combinations thereof (Grant et al., 2015a) or a general underlying internalizing vulnerability (Elkins et al., 2006) might contribute to the inconsistent associations between internalizing MD and AUD.

Many studies on MD as risk factors for AUD have carefully controlled for other putatively important MD to ensure an association is not merely an artefact of comorbidity. Undoubtedly, this is important for understanding the role of specific internalizing MD in AUD aetiology. However, the identification of a specific MD as a single risk factor

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beyond the role of other MD may bear a conceptual disadvantage as it does not take into account the putative role of specific combinations of MD risk or underlying vulnerabilities. High MD comorbidity and heterotypic continuity frequently found in AUD (de Graaf et al., 2003; Hasin et al., 2007; Jacobi et al., 2015, 2014; Kessler et al., 2012; Lahey et al., 2014; Lai et al., 2015; Zimmermann et al., 2003) can be understood as expressions of underlying shared vulnerabilities (Krueger and Markon, 2006). Several epidemiological studies in adult and adolescent/young adult populations on the comorbidity structure of MD find separate externalizing and internalizing underlying factors (Beesdo-Baum et al., 2009; Kendler et al., 2003; Kessler et al., 2011a), however limited stability of the model in different age groups and upon inclusion of additional MD diagnoses has been noted (Wittchen et al., 2009). Moreover, underlying vulnerability factors can be modelled as mediators in the association between prior MD and other MD incidence (Kessler et al., 2011a).

Given evidence for high comorbidity, underlying vulnerabilities, heterotypic continuity and the range of different MD identified as AUD risk factors, it is important for the clarification of the role of internalizing risk factors of AUD to go beyond single internalizing risk factor identification and retrospective identification of factors within AUD subtypes (Babor and Caetano, 2006; Cloninger et al., 1996) and determine internalizing MD risk profiles (i.e., clusters of risk for several internalizing MD with or without other MD) that predict AUD onset. Identifying such profiles can further the understanding of internalizing AUD risk factors that relies on single risk factor identification by identifying specific combinations of internalizing MD risk and their roles in AUD onset and create information for targeted prevention and intervention.

To our best knowledge, so far, one cross-sectional study has investigated associations between MD profiles and a latent factor representing DSM-IV AUD-criteria (Harford et al., 2015). Therefore, we aim to investigate the prospective association between latent groups with different risk profiles of a range of baseline DSM-IV MD and the risk of subsequent AUD incidence. As, with few exceptions (Lopez-Quintero et al., 2011), much less evidence is available for the role of internalizing MD in AUD *stability* compared to *onset*, and as correlates of stable vs. unstable AUD have been shown to differ (Hicks et al., 2010), we also aim to investigate in an explorative fashion latent AUD comorbidity profiles in a community sample and their prospective association with AUD stability.

For the prediction of AUD *incidence,* we hypothesize to find one baseline latent risk profile with a high risk of SUD diagnoses other than AUD, one with a high risk of internalizing MD including somatoform MD (Kendler et al., 2011) and one with low MD probabilities. For the prediction of AUD *stability* we hypothesize to find the same overall profile structure with AUD-risk being elevated within one SUD-related and one internalizing risk profile. Given existing results on MD as AUD risk factors, we expect the SUD-related and the internalizing profiles to be associated with a higher risk of subsequent AUD incidence and stability, however with stronger associations for SUD-related profiles.

2. Methods

2.1. Sample and overall design

The EDSP study is a 10-year prospective-longitudinal community study that has been described elsewhere (Beesdo-Baum et al., 2015; Lieb et al., 2000; Wittchen et al., 1998b). In short, the aim of the EDSP study is to investigate the course and risk-factors for substance use and SUD in a stratified sample of N = 3021 subjects aged 14–24 years at baseline. Focusing on early developmental stages of psychopathology, individuals aged 14–15 years were sampled at twice the probability of those aged 16–21 years. Individuals aged 22–24 years were sampled at half the probability of subjects aged 16–21 years. The baseline sample was drawn from metropolitan Munich (German government registries). Subjects were followed-up over a 10-year period with up to three follow-up examinations. The baseline survey took place in 1995 (T0, N = 3021). Follow-up examinations were conducted approximately after 1.6 years (T1, median interval since baseline, only for the younger cohort of N = 1228 subjects aged 14–17 years at baseline), 3.5 years (T2) and 8.2 years (T3). The response rates (proportion of T0 sample) was 70.8% at T0 (N = 3021), 84.3% (N = 2548) at T2 and 73.2% (N = 2210) at T3. The T3 age range was 21–34 years.

2.2. Diagnostic assessment

At each study wave, assessments were conducted with computer-assisted baseline and follow-up versions of the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI) (Wittchen et al., 1998a; Wittchen and Pfister, 1997). The M-CIDI is a fully standardized diagnostic interview for epidemiological research (Wittchen et al., 1998a), designed to assess symptoms, syndromes and diagnoses of 48 MD. The diagnoses presented here are based on computerized M-CIDI/DSM-IV algorithms. Test–retest reliability and validity of the DIA-X/M-CIDI diagnoses have been established (Reed et al., 1998; Wittchen, 1994; Wittchen et al., 1998a).

DSM-IV AUD, alcohol use (AU), nicotine dependence (ND), and any illegal drug use disorder (DUD) were assessed with the respective DIA-X/M-CIDI-sections for nicotine, alcohol, and medication and illegal substance use that have been described elsewhere in detail (Behrendt et al., 2009).

2.3. Statistical analysis

For descriptive analysis conducted with the Stata Software package 14.1 (StataCorp., 2015), data were weighted to account for different sampling probabilities at baseline, and response rates at baseline varying over age, sex, and geographic location.

2.3.1. Latent class analysis (LCA) with auxiliary outcome variables

To empirically identify groups with different MD risk profiles at baseline and to investigate the associations between these groups and observed AUD outcomes we applied LCA (Skrondal and Rabe-Hesketh, 2004) with auxiliary outcome variables (here: AUD-outcomes) using the DCAT- and BCH-method in MPlus version 7.31.

In line with our research goals to investigate AUD *incidence* and *stability* separately, two types of analysis with different subsamples were conducted: when AUD *incidence* was the outcome of interest ('incidence model') we excluded cases with baseline AUD (n = 257; unweighted mean age of AUD onset: 16.8 years; SD: 2.2) to enable identification of baseline latent MD risk profiles that predict incident AUD at follow-up (n = 352, unweighted mean age of AUD onset: 17.6 years, SD: 3.0). The respective weighted mean ages of onset were 17.0 years (SD: 2.3) before and 18.2 years (SD: 3.4) after baseline. When AUD *stability* was the outcome of interest ('stability model') we included baseline AUD to enable identification of baseline latent AUD comorbidity profiles that predict any subsequent AUD. In addition, for both analyses, subjects were excluded if they missed T2 or T3 or declined answering drug questions truthfully, leading to N = 1683 for the incidence model and N = 1940 for the stability model.

LCA is a probabilistic classification method based on the assumption that the association structure among a set of variables can be reduced to at least two latent classes and that given class status, the variables in the set are independent from one another within the latent classes ("local independence") (Muthén and Muthén, 1998-2006; Nylund et al., 2007). We fitted models with two to six (stability model) respectively two to five classes (incidence model). 6000 random sets of starting values were