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Research paper

The bidirectional relationship between anxiety disorders and alcohol use disorders in adults: Findings from a longitudinal population-based study

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ABSTRACT

Background: Anxiety disorders (AD) and alcohol use disorder (AUD) frequently co-occur, but the temporal order of the association is unclear. We have determined the association between AD and the presence and first-onset of AUD, and vice versa.

Methods: Data were used from n = 6.646 participants and four measurement waves (baseline, 3-, 6- and 9-years) of the Netherlands Mental Health Survey and Incidence Study 2 (NEMESIS-2), a cohort study of the Dutch general population aged 18–64 years. AD and AUD were assessed with the Composite International Diagnostic Interview 3.0. Multilevel logistic autoregressive models were controlled for previous-wave AD or AUD, socio-demographics (Model 1), smoking and clinical factors (Model 2).

Results: People with AUD had a higher risk of present (OR = 1.65, 95 % CI 1.11–2.43; Model 2) and first-onset (OR = 2.03, 95 % CI 1.17–3.51; Model 2) AD in 3-years follow-up intervals than people without AUD. Vice versa, people with AD also had a higher sociodemographics-adjusted risk of present and first-onset AUD over 3-years follow-up intervals, but these associations attenuated into insignificance after adjustment for smoking and clinical variables.

Limitations

For statistical power reasons we were not able to analyze 9-year follow-up data or distinguish between AD and AUD types.

Conclusions: Our results indicate a bidirectional relationship between AD and AUD; especially those with severe AD (medication use, comorbid depression) are at risk of developing AUD. Health care professionals should focus on prevention of AD in AUD patients and prevention of AUD in patients with (more severe) AD. Further research should investigate the mechanisms underlying the observed associations.

1. Introduction

Each year about 20 % of the general population suffers from a mental disorder (de Graaf et al., 2012; Kessler et al., 2005). Of these, anxiety disorders (AD) and alcohol use disorders (AUD) frequently occur (Kessler et al., 2005; Wittchen et al., 2011). The impact of these categories of disorders on individual lives and on society can be substantial: they are related to functional disability, lost quality of life, and increased economic and health care costs (Alonso et al., 2004; Buist-Bouwman et al., 2006; Konnopka and König, 2020; Mendlowicz and Stein, 2000; Olesen et al., 2012; Smit et al., 2006; Wittchen et al., 2011). Epidemiological surveys have shown that AD and AUD tend to occur in the same person during one's life (Castillo-Carniglia et al., 2019; Jané-Llopis and Matytsina, 2006; Kushner et al., 2000; Lai et al., 2015; Smith and Randall, 2012). People with lifetime AUD (14–16 % of the general population) (de Graaf et al., 2012; Regier et al., 1990) indeed have increased

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estimated lifetime prevalences of AD ranging 20 % to 40 % (Lai et al., 2015). Vice versa, among people with lifetime AD (15–20 % of the general population) (de Graaf et al., 2012; Regier et al., 1990), the lifetime prevalence of AUD has been estimated 18 % (Regier et al., 1990). Sometimes, AD and AUD even co-occur at the same time, which leads to even more negative consequences than the pure conditions, such as higher levels of disability, more suicidality and poorer treatment outcomes (Boschloo et al., 2012; Bruce et al., 2005; Prior et al., 2017). The temporal order of the association between AD and AUD is unclear. Establishing this temporal order could help to unravel mechanisms underlying this association (de Graaf et al., 2003) and thereby improve treatment interventions.

Over the past two decades, the reciprocal relationship between AD and AUD has been widely investigated, but with mixed results. Part of this variation may be explained by differences in study design and study population, duration of follow-up and adjustment for covariation. Based on retrospective age of onset data from cross-sectional epidemiological studies, AD often precedes the development of AUD and vice versa (Castillo-Carniglia et al., 2019; Kushner et al., 2000; Kushner et al., 2008; Smith and Randall, 2012; Merikangas et al., 1998). However, cross-sectional surveys are not able to determine the temporal relationship between AD and AUD precisely because of decreased validity of retrospective data (Kushner et al., 2000). Only a few longitudinal surveys have examined the temporal association between AD and AUD, with mixed results. A Dutch population-based study (NEMESIS-1) found that, after adjustment for age and sex, respondents with a 1-month prevalence of AD at baseline were more likely to develop first-incident AUD during the 3-year follow-up, but those with a 1-month prevalence of AUD had no higher risk of first-incident AD (Marquenie et al., 2007). In contrast, age- and sex-corrected NEMESIS-2 data showed that AD in the past year did not predict first-incident substance use disorder (SUD; AUD and drug use disorder) during 3-year follow-up, whereas SUD did predict first-incident AD (de Graaf et al., 2013a, 2013b). A population-based study in the United States (NESARC) found evidence for predictive associations in both directions over 3 years of follow-up, although only generalized anxiety disorder predicted AUD, and all associations became insignificant after adjustment for other psychiatric disorders (Grant et al., 2009). In addition, autoregressive and cross-lagged analyses based on 6-year follow-up data have shown reciprocal associations between AD and AUD in college students, independent of family history of AUD and sex (Kushner et al., 1999). These specific analyses have not been applied in a population-representative sample of adults yet, although they are better able to capture the temporal association between both present and first-onset AD and AUD.

In short, several cross-sectional and longitudinal studies have investigated the population-based association between AD and AUD, and vice versa, with mixed results. In general, follow-up duration, number of follow-up waves and adjustment for potential confounders were rather limited. A larger follow-up duration with different waves would increase incidence rates and therefore power. Moreover, it would enable the investigation of reciprocal associations between AD and AUD over time, taking into account intra-individual fluctuations regarding these conditions. The present study therefore aimed to expand current knowledge about the bidirectional longitudinal association between AD and AUD by addressing limitations of previous research as described above. Our analyses were adjusted for multiple potential confounders (sociodemographic factors; smoking; comorbidity of mood disorders, drug use disorders or somatic conditions; psychotropic medication). Data were used from four waves of a nationally representative cohort of adults, the second Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2), to determine whether having an AD at a certain measurement wave predicts both the presence and first-onset of an AUD at the next measurement wave and vice versa. Finally, we examined whether observed associations differed when using more and longer time intervals of 3 and 6 years. If we know more about the ways in which AD and AUD interact, we could improve treatment by being aware of specific client characteristics to forestall the onset of the secondary condition, or at least prevent it from becoming a full-blown comorbid disorder (de Graaf et al., 2003).

2. Methods

2.1. Study design

The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) is a psychiatric epidemiological cohort study of the Dutch general population aged 18–64 years at baseline. It is based on a multistage, stratified random sampling procedure.

The face-to-face interviews were computer-assisted. In the first wave (T0), performed from November 2007 to July 2009, 6646 persons were interviewed (response rate 65.1 %). This sample was nationally representative, although younger subjects were somewhat underrepresented (de Graaf et al., 2010). All T0 respondents were approached for follow-up three years (T1), six years (T2) and 9 years (T3) after T0. Of these, 5303 persons could be re-interviewed at T1 (response rate 80.4 %) (de Graaf et al., 2013a, 2013b), 4618 persons were interviewed again at T2 (response rate 87.8 %) (de Graaf et al., 2013a, 2013b), and 4007 persons could be re-interviewed at T3 (response rate 87.7 %).

Attrition between T0 and T3 was not significantly associated with any AD or AUD in the past 12_months at T0, after controlling for sociodemographic variables.

This study was approved by a medical ethics committee (the Medical Ethics Review Committee for Institutions on Mental Health Care, METIGG). Respondents provided written informed consent at each wave. For a more comprehensive description of the study design, see de Graaf et al. (2010).

2.2. Measures

In this study, AD included panic disorder, agoraphobia without panic disorder, social phobia and generalized anxiety disorder. AUD in this study included alcohol abuse and alcohol dependence.

AD and AUD according to DSM-IV were diagnosed using the Composite International Interview (CIDI) version 3.0, a fully structured lay-administered diagnostic interview. At T0, lifetime and 12-month disorders were assessed; at the follow-up waves 3-year and 12-month disorders were assessed. The CIDI 3.0 version used in NEMESIS-2 was an improvement of the Dutch version used in the World Mental Health Survey Initiative (Kessler and Ustün, 2004). Clinical calibration studies in various countries (Haro et al., 2006) found that the CIDI 3.0 assesses common mental disorders, like AD and AUD, with generally good validity and reliability in comparison to blinded clinical reappraisal interviews.

Based on previous research, a selection was made of variables related to AD and AUD.

Sociodemographic covariates were: sex, age, educational level (4 categories), and partner status.

Clinical covariates were: somatic disorder (i.e. presence of $\geq$1 of 12 other chronic somatic disorders, which are treated or monitored by a medical doctor in the previous 12_months), psychotropic medication (especially use of antidepressants or benzodiazepines in the previous 12_months prescribed by a physician), 12-month mood disorder and 12-month drug use disorder, both assessed with the CIDI 3.0. In addition we adjusted for smoking (in the past month).

2.3. Statistical analyses

To examine the bidirectional prospective associations between AD and AUD, we used multilevel logistic autoregressive models, one for the prediction of AD and one for the prediction of AUD (either presence or first-onset). Multilevel models have several advantages, as they take into account the nested character of the data with observations at the four

waves nested in individuals; can adequately deal with missing observations by using all available data so that participants with partially incomplete data are not removed from the analyses; and can examine a possible influence of follow-up duration. We examine both presence and first-onset of AD or AUD as outcomes. Whereas presence analyses provide evidence on whether having AUD adversely influences the prognosis of pre-existing AD (or vice versa), first-onset analyses provide evidence on whether AUD play a role in the development of AD (or vice versa).

The first set of analyses examined whether having any AUD predicted the presence of any AD at 3-year follow-up, and vice versa. In the model for AD, the presence of one or more AD at T1, T2, and T3 (AD_t) was predicted from the presence of AUD at the previous wave (AUD_{t-1}), adjusting for the presence of AD at the previous wave (AD_{t-1}). In the same way, in the model for AUD, the presence of AUD at T1, T2, and T3 (AUD_t) was predicted from the presence of one or more AD at the previous wave (AD_{t-1}), adjusting for the presence of AUD at the previous wave (AUD_{t-1}). In these models, associations between AD_{t-1} and AD_t (or AUD_{t-1} and AUD_t, respectively) are called autoregressive effects, whereas associations between AD_{t-1} and AUD_t (or AUD_{t-1} and AD_t, respectively) are called cross-lagged effects. The cross-lagged effects are our main interest. We used 12-months prevalence of the disorders at T0 and 3-years prevalence rates at T1, T2 and T3, to cover the entire interwave interval.

We adjusted the models for potential confounders in two steps: in the first step we adjusted for sociodemographic variables (age_{t-1}, gender, education, partner $status_{t-1}$). In the second step, we additionally adjusted for smoking and clinical variables (12-month mood $disorder_{t-1}$, 12-month drug use $disorder_{t-1}$, psychotropic $medication_{t-1}$ somatic $comorbidity_{t-1}$, $smoking_{t-1}$). All covariates were dichotomous (0/1), except education (ordinal variable with 4 levels) and age (continuous). We used lagged ($_{t-1}$) versions of all time-varying confounders, to preclude reverse causality. Because psychotropic medication can be an indicator for AD severity, and as such may overcorrect models investigating the association between AD and AUD, we also conducted sensitivity analyses without psychotropic medication as a covariate. Furthermore, as depression and anxiety are part of a latent internalizing construct, mood disorder may overcorrect the models as well. We therefore additionally conducted sensitivity analyses without both psychotropic medication and mood disorder as covariates.

To test cross-lagged effects at longer-term intervals (6-years), we tested whether the addition of lag-2 cross-lagged effect significantly contributed to the models using the Likelihood ratio test, additionally controlling for lag-2 autoregressive effects. We did not examine cross-lagged effects at 9-years intervals (lag-3 effects), because the number of cases was too low for these analyses according to post-hoc power calculations.

The second set of analyses examined whether having any AUD predicted the first-onset of any AD at 3-year follow-up, and vice versa. In the model for AD, participants without a lifetime history of AD at T0 were selected. For those who developed an AD at T1 or T2, observations at later waves were removed from the dataset, to ensure that all cases at later waves were first-onset cases. In the same way, in the model for AUD, we selected the participants without a lifetime history of AUD at T0 and, for those who developed any AUD at T1 or T2, removed observations at later waves. The datasets for predicting first-onset cases by definition do not include predictors for autoregressive effects as the at risk group included those without a lifetime history of the index disorder. Apart from that, the same analysis steps were performed as in the first set of analyses.

Models were estimated in Stata 16.1 using the melogit command. Robust standard errors were used for the regression coefficients. Models with different random effects and covariance structures were tested, and the most optimal model was selected using the Bayesian Information Criterion (BIC). Model fit of the final models was evaluated by inspection of plots of predicted versus observed probabilities. Marginal predicted probabilities were calculated using Stata's margins command.

3. Results

3.1. Characteristics of the study population

Table 1 shows the sociodemographic, smoking and clinical characteristics of the baseline sample. Of the total sample of 6646 participants, the mean age was 44.3 years and about half of the sample was female.

Table 2 shows the prevalence of AD and AUD, for each of the four measurement waves. The upper panel shows the percentage of participants having one or more AD, the lower panel shows the percentage of participants having one or more AUD. Twelve-month prevalence figures for AD and AUD at baseline (T0) were somewhat higher than those at follow-up waves. Lifetime age of onset for AD and AUD was low: median 14 years and 20 years, respectively.

3.2. AUD as a predictor of the presence of AD at follow-up and vice versa

3.2.1. Short term effects (3-years intervals)

Table 3 shows the results of the multilevel logistic autoregressive models for the prediction of AD (upper panel) and AUD (lower panel) from previous-wave AUD and AD. When only demographic variables were adjusted for (model 1), previous-wave AUD significantly predicted AD at follow-up (AUD_{t-1}: OR = 1.96). When smoking and clinical variables were also adjusted for (Model 2), this cross-lagged association was somewhat reduced but still significant (OR = 1.65). In the lower panel of Table 3 it can be seen that the reverse effect was also significant, i.e. previous-wave AD was predictive of AUD at follow-up, adjusted for demographic variables (AD_{t-1}: OR = 1.84). This effect was substantially reduced and not significant anymore after smoking and clinical variables were adjusted for (OR = 1.35).

The size of the cross-lagged effect of AUD_{t-1} in the prediction of AD in the full model (OR = 1.65) implies that the odds of having an AD at follow-up was 65 % higher for participants having an AUD at the previous wave compared to participants with no AUD at the previous wave. In terms of marginal predicted probabilities this means that having an AUD increases the probability of having an AD at a later wave from 4.5 % to 6.7 % (marginal on observed values of all other covariates).

The size of the autoregressive effects for AD and AUD was very large in model 1, but the autoregressive effect of AD was substantially reduced in model 2. In the full model (Model 2) predicting the presence of AD, female gender, having no partner, lower age, presence of mood disorder, presence of drug use disorder, using psychotropic medication, somatic comorbidity and smoking significantly increased the risk of AD. In the full model predicting the presence of AUD, male gender, having no partner, lower age, using psychotropic medication and smoking significantly increased the risk of AUD.

Table 1
Baseline characteristics of the sample (N = 6646).

	Mean/%	SD/n
Age (mean, SD)	44.3	12.5
Gender (% female, n)	55.3 %	3672
Education (%, n)		
Primary, basic vocational	5.0 %	332
Lower secondary	27.5 %	1826
Higher secondary	32.3 %	2145
Higher professional, university	35.3 %	2343
Living without a partner (%, n)	32.2 %	2140
Mood disorder (12-month prevalence) (%, n)	6.2 %	410
Drug use disorder (12-month prevalence) (%, n)	1.4 %	90
Psychotropic medication (%, n)	6.4 %	415
Somatic conditions (%, n)	35.9 %	2338
Smoking (%, n)	30.6 %	1988

Note. Some observations are missing for some of the baseline variables.

Table 2
Prevalence of anxiety disorder (upper part of the table) and alcohol use disorder (lower part of the table) at the four measurement waves.

Anxiety disorder	T_0 N = 6646	T_1 N = 5303	T_2 N = 4618	T_3 N = 4007
Lifetime prevalence, n (%)	1014 (15.3 %)			
12-month prevalence, n (%)	407 (6.1 %)	201 (3.8 %)	174 (3.8 %)	144 (3.6 %)
3-year prevalence, n (%)	–	251 (4.7 %)	213 (4.6 %)	199 (5.0 %)
Age of onset, median (IQR)	14 (10–26)	43 (34–52)	47 (38–54)	50 (39–56)

Alcohol use disorder	T_0 N = 6646	T_1 N = 5303	T_2 N = 4618	T_3 N = 4007
Lifetime prevalence, n (%)	938 (14.1 %)			
12-month prevalence, n (%)	226 (3.4 %)	126 (2.4 %)	101 (2.2 %)	88 (2.2 %)
3-year prevalence, n (%)	–	182 (3.4 %)	150 (3.2 %)	110 (2.7 %)
Age of onset, median (IQR)	20 (17–26)	37 (26–51)	41 (29–52)	44 (33–54)

Note. IQR = interquartile range. Age of onset at T_0 reflects lifetime onset (i.e. first-onset). Age of onset at T_1, T_2, and T_3 reflects 3-years onset (i.e. onset of interval episode).

3.2.2. Longer-term effects (6-years intervals)

Six-years interval effects were studied by running the models of Table 3 again, but now including lag-2 cross-lagged effects and lag-2 autoregressive effects. The total number of observations in these models was reduced to 8625 (N = 4618) but was still sufficient according to power calculations. The addition of the lag-2 cross-lagged effects did not significantly improve model fit (AUD_{t-2} in the model for AD: LR-test $chi^2(1) = 1.62$, p = 0.20, AD_{t-2} in the model for AUD: $chi^2(1) = 0.00$, p = 0.96). Thus, including longer-term cross-lagged effects (i.e. 6-years interval) did not improve the models examining 3-year interval effects.

3.3. AUD as a predictor of the first-onset of AD at follow-up and vice versa

3.3.1. Short term effects (3-years intervals)

At baseline (T0), 5632 participants had no lifetime history of AD (84.7 %). At 3-year follow-up (T1), 131 participants had experienced a first-onset of AD (2.9 % of the 4479 remaining participants at T1), at 6-year follow-up (T2) there were 89 first-onset AD cases (2.3 % of the 3813 remaining participants at T2), and at 9-year follow-up (T3) there were 80 first-onset AD cases (2.5 % of the 3232 remaining participants at T3).

The upper panel of Table 4 shows the results for this model. Previous-wave AUD was significantly predictive of first-onset AD (OR = 2.56, p < 0.001; Model 1). When smoking and clinical variables were adjusted for, the OR was reduced to 2.03 but still significant (Model 2). Effects of covariates were rather similar to those in Model 1, although some were not significant anymore (e.g. having no partner and smoking in Model 2).

The ORs for previous-wave AUD in the prediction of first-onset AD were somewhat larger than in the original model of Table 3. The size of the cross-lagged effect of AUD_{t-1} in model 2 (OR = 2.03) implies that the odds of developing a first-onset AD at follow-up was twice as high for participants having an AUD at the previous wave compared to participants with no AUD at the previous wave. In terms of marginal predicted probabilities this means that having an AUD increases the probability of developing a first-onset AD at a later wave from 2.5 % to 4.8 % (marginal on observed values of the other covariates).

Table 3
Multilevel logistic autoregressive models for the prediction of anxiety disorder (upper part of the table) and alcohol use disorder (lower part of the table) from previous-wave alcohol use disorder and anxiety disorder (3-years intervals).

	Model 1			Model 2		
	OR	95 % CI	p	OR	95 % CI	p
Anxiety disorder$_t$						
Alcohol use disorder$_{t-1}$	1.96	1.37–2.79	<0.001	1.65	1.11–2.43	0.012
Anxiety disorder$_{t-1}$	5.01	3.46–7.25	<0.001	1.88	1.17–3.04	0.010
Female gender	1.53	1.28–1.83	<0.001	1.42	1.18–1.71	<0.001
Education	0.86	0.78–0.95	0.002	0.95	0.86–1.05	0.304
No partner$_{t-1}$	1.50	1.26–1.79	<0.001	1.21	1.01–1.46	0.044
Age$_{t-1}$	0.98	0.98–0.99	<0.001	0.98	0.97–0.99	<0.001
Mood disorder$_{t-1}$				3.19	2.41–4.22	<0.001
Drug use disorder$_{t-1}$				2.06	1.11–3.82	0.022
Psychotropic medication$_{t-1}$				2.90	2.22–3.80	<0.001
Somatic disorder$_{t-1}$				1.62	1.35–1.95	<0.001
Smoking$_{t-1}$				1.27	1.05–1.54	0.014
Alcohol use disorder$_t$						
Anxiety disorder$_{t-1}$	1.84	1.23–2.76	0.003	1.35	0.86–2.16	0.208
Alcohol use disorder$_{t-1}$	4.94	2.75–8.90	<0.001	4.52	2.57–7.95	<0.001
Female gender	0.35	0.26–0.47	<0.001	0.36	0.27–0.48	<0.001
Education	0.87	0.75–1.00	0.058	0.93	0.80–1.07	0.303
No partner$_{t-1}$	2.48	1.91–3.22	<0.001	2.25	1.73–2.91	<0.001
Age$_{t-1}$	0.96	0.95–0.97	<0.001	0.96	0.95–0.97	<0.001
Mood disorder$_{t-1}$				1.34	.86–2.09	0.203
Drug use disorder$_{t-1}$				1.62	0.80–3.27	0.177
Psychotropic medication$_{t-1}$				1.75	1.13–2.71	0.012
Somatic disorder$_{t-1}$				0.85	0.66–1.10	0.222
Smoking$_{t-1}$				1.87	1.45–2.42	<0.001

Note. N = 5303, total number of observations = 13,928. Significant random autoregressive effect in Anxiety model, significant random intercept in Alcohol model.

At baseline (T0) 5708 participants had no lifetime history of AUD (85,9 %). At 3-year follow-up (T1), 87 participants developed an AUD (1.9 % of the 4542 remaining participants at T1), at 6-year follow up (T2) there were 52 new AUD cases (1.3 % of the 3893 remaining participants at T2), and at 9-year follow-up (T3) there were 37 new AUD cases (1.1 % of the 3320 remaining participants at T3).

Previous-wave AD significantly predicted first-onset AUD in Model 1 (OR = 1.99, p = 0.01) but not in Model 2. The size of the cross-lagged effect was similar to the one in Model 1. Effects of covariates were also similar to those in Model 1.

Sensitivity analyses were done while excluding psychotropic medication and additionally mood disorder as covariates. Models without adjustment for psychotropic medication showed results which were comparable to those of the original Models 2, although the cross-lagged effects between AD and AUD or vice versa were a bit stronger (data not shown) and mood disorder became a significant predictor of the presence of AUD (OR = 1.58, p = 0.04). In contrast to the original Model 2, the associations between previous-wave AD and AUD were still significant when both psychotropic medication and mood disorder were not adjusted for (AUD presence: OR = 1.66, p = 0.02; first-onset: OR = 1.89, p = 0.02). In addition, repeating the analyses above while using the variable alcohol use instead of AUD gave similar patterns (see Supplement 1).

Table 4
Multilevel logistic autoregressive models for the prediction of the first-onset of anxiety disorder (upper part of the table) and the first-onset of alcohol use disorder (lower part of the table) from previous-wave alcohol use disorder and anxiety disorder (3-years intervals).

	Model 1			Model 2		
	OR	95 % CI	p	OR	95 % CI	p
First-onset of anxiety disorder$_t$						
Alcohol use disorder$_{t-1}$	2.56	1.61–4.08	<0.001	2.03	1.17–3.51	0.011
Female gender	1.59	1.25–2.02	<0.001	1.46	1.13–1.89	0.003
Education	0.87	0.76–1.00	0.053	0.97	0.84–1.12	0.646
No partner$_{t-1}$	1.30	1.02–1.67	0.037	1.06	0.81–1.38	0.662
Age$_{t-1}$	0.98	0.97–0.98	<0.001	0.97	0.96–0.98	<0.001
Mood disorder$_{t-1}$				3.78	2.44–5.84	<0.001
Drug use disorder$_{t-1}$				2.95	1.21–7.24	0.018
Psychotropic medication$_{t-1}$				3.72	2.51–5.52	<0.001
Somatic disorder$_{t-1}$				1.72	1.33–2.22	<0.001
Smoking$_{t-1}$				1.22	0.94–1.60	0.138
First-onset of alcohol use disorder$_t$						
Anxiety disorder$_{t-1}$	1.99	1.17–3.39	0.011	1.57	0.82–2.99	0.173
Female gender	0.35	0.26–0.48	<0.001	0.36	0.26–0.49	<0.001
Education	0.92	0.76–1.10	0.355	0.98	0.81–1.19	0.853
No partner$_{t-1}$	1.94	1.42–2.66	<0.001	1.83	1.34–2.50	<0.001
Age$_{t-1}$	0.95	0.94–0.96	<0.001	0.95	0.93–0.96	<0.001
Mood disorder$_{t-1}$				1.05	0.54–2.04	0.895
Drug use disorder$_{t-1}$				0.32	0.04–2.33	0.261
Psychotropic medication$_{t-1}$				1.82	1.02–3.23	0.041
Somatic disorder$_{t-1}$				1.01	0.71–1.42	0.964
Smoking$_{t-1}$				2.03	1.49–2.76	<0.001

Note. N = 4479, total number of observations = 11,524 (model Anxiety disorder); N = 4542 total number of observations = 11,755 (model Alcohol use disorder); random effects not significant.

4. Discussion

4.1. Summary

Using a representative sample of the Dutch adult population, the present study examined whether having an AUD at a certain measurement wave predicts both the presence and first-onset of an AD at the next measurement wave, and vice versa. This study expands previous research in different ways. First, we used three follow-up waves, which increased power substantially and enabled the examination of different follow-up durations (i.e. 3- and 6 years intervals). Second, we investigated reciprocal associations between AUD and AD over time, taking into account intra-individual fluctuations regarding these conditions. Lastly, our analyses were adjusted for multiple potential confounders or mediators (sociodemographic factors; smoking; comorbidity of mood disorders, drug use disorders; somatic conditions; use of psychotropic medication). After full adjustment, we found that people with AUD more often had (both present and first-incident) AD over a 3-year interval as compared with people without AUD. Conversely, the significant sociodemographics-adjusted associations between having an AD and the presence and first-onset of any AUD over a 3-year interval, however, became non-significant after additional adjustment for smoking and clinical variables.

4.2. Main findings

After adjustment for smoking, sociodemographic -and clinical variables, having AUD was associated with first-onset AD over 3 years of follow-up. No indications were found for stronger effects when examining the longer-term follow-up. These findings suggest that the psychopathology underlying AUD or its consequences contributes to the onset of AD and that this occurs after a relatively short time period. This is consistent with most previous longitudinal studies which also found a sociodemographics-adjusted association between AUD and first-onset AD (de Graaf et al., 2013a, 2013b; Grant et al., 2009; Kushner et al., 1999). Alcohol dependence was unrelated to first-incident AD based on NEMESIS-1 data, which may have been due to low power because of the small number of novo AD (Marquenie et al., 2007). In contrast to our fully adjusted models, a NESARC study found that the predictive association between AUD and one-year first-incident specific AD (i.e. social phobia, panic disorder or generalized AD, instead of AD as a category) turned insignificant after adjustment for other psychiatric disorders, including other AD (Grant et al., 2009). This inconsistency could be explained by the fact that in NESARC, participants at baseline were not free from any AD, but from a specific AD diagnosis. The sociodemographics-adjusted associations found between AUD and either social phobia, or panic disorder, or generalized AD appear to be partly explained by other AD at baseline, as we know that one AD increases the risk of developing another AD (Grant et al., 2009; Scholten et al., 2013). Our findings additionally show that AUD is associated with the presence (as opposed to first-onset) of AD at a later moment in time, which was not studied in earlier prospective surveys and suggests that AUD may contribute to a worse prognosis of any coinciding or pre-existing AD. Furthermore, using weekly alcohol use categories as the outcome variable, it was shown that particularly people who used no alcohol (including those with a history of problematic alcohol use) or were excessive drinkers at a previous measurement wave had the highest risk of later AD. This confirms the positive association we found between AD and AUD. The finding that AUD predicts the presence and first-onset of AD is in line with the theory that anxiety symptoms could be a consequence of AUD, for example, caused by neurochemical effects after alcohol withdrawal (Breese et al., 2005; Kushner et al., 2000; Wolitzky-Taylor et al., 2012).

The findings concerning the inverse relationship - AD as a predictor of AUD – shows that, after adjustment for sociodemographics, having AD also predicted both the presence and the first-onset of AUD over 3 years of follow-up, but that these associations attenuated into insignificance after additional adjustment for smoking and clinical variables. No indications were found for stronger effects when examining the longer term follow-up. These findings are mostly in accordance with previous longitudinal studies which have shown that AD predict first-onset alcohol dependence when controlling for demographic variables (Grant et al., 2009; Kushner et al., 1999; Marquenie et al., 2007). A previous NEMESIS-2 study, however, found no sociodemographics-adjusted association between AD and first-incidence of substance use disorder (SUD) (de Graaf et al., 2013a, 2013b). SUD is a broader outcome which includes both AUD and drug use disorders, which could explain the discrepancy with our findings, although the fact that AD predicted both first-onset AUD and drug use disorder in a NESARC study (Grant et al., 2009) undermines this explanation. Our finding that AD predicts both the presence and first-onset of AUD after adjusting for sociodemographic variables is in line with the self-medication hypothesis in which people decrease their anxiety symptoms by using alcohol, which can lead to the pathological use of alcohol (Kushner et al., 2000). The positive effects of alcohol are attributed to neurochemical mechanisms, for example acute alcohol intoxication affects GABA receptors in a way similar to the effect of benzodiazepines (Kushner et al., 2000; Wolitzky-Taylor et al., 2012). The attenuation of the association between AD and AUD in fully adjusted models has shown that especially psychotropic medication use and smoking contributed to this

association. Because particularly people with more severe AD or comorbidity (e.g. depression) use psychotropic medication, adjustment for medication may be an overcorrection, but the association between AD and AUD continued to be insignificant after exclusion of this factor. Furthermore, because depression and anxiety are both part of a latent internalizing construct, mood disorder may overcorrect the models as well (Carragher et al., 2015; Forbes et al., 2017). Indeed, Model 2 associations between AD and AUD became significant when mood disorder (and medication use) were not corrected for. Our findings therefore suggest that a substantial part of the association between AD and AUD is driven by individuals with more severe psychopathology.

4.3. Strengths and limitations

Our study has important strengths, including the large population-based sample of adults, the use of a standardized diagnostic instrument (CIDI 3.0) to assess the presence and first-ever onset of AD and AUD, the prospective design covering 3- and 6-year follow-up measurements, and the fact that we have adjusted for a range of potential confounding or mediating factors. Moreover, our data illustrate why cross-sectional surveys using retrospective age of onset data are not able to determine the temporal relationship between AD and AUD precisely. Like a previous NEMESIS-2 study (de Graaf et al., 2013a, 2013b), the ages of onset for AD (14 years) and AUD (20 years) could indicate that AD precedes AUD, but our more advanced multilevel logistic autoregressive models have shown associations in both directions, in which AUD was an even stronger predictor of AD than vice versa.

Yet, some limitations in this study merit discussion. First, although the results gave no indications for a stronger or different effect over a longer follow-up period than 3 year, effects for longer intervals could not be tested (e.g. 9 years) for statistical power reasons. Second, despite the fact that the number of cases per category of disorders in this study was reasonably high, numbers were too low to further distinguish between the different types of AD and AUD. However, this limitation may be mitigated by recent research supporting a more dimensional approach to the classification of AD (Hovenkamp-Hermelink et al., 2016; Scholten et al., 2013, 2016) and the current DSM-5 classification where AUD is based on the integration of the two formerly separate diagnoses of alcohol abuse and alcohol dependence.

Third, although this sample is nationally representative, findings cannot be generalized to groups of adolescents and elderly, institutionalized adults, adults with no permanent residential address, adults with an insufficient mastery of Dutch and people of non-western origin, because these groups were underrepresented or not part of the study sample frame (de Graaf et al., 2010). Fourth, the assessment of AD and AUD is based on self-report. Especially the validity of recalled lifetime symptoms at baseline has been questioned because of hampered accuracy, resulting in underreporting of lifetime symptoms at baseline (de Graaf et al., 2013a, 2013b; Moffitt et al., 2010). The presented incidence rates might therefore be somewhat overestimated. Finally, the modest number of first-onset AUD-cases resulted in a somewhat lower power in the fully adjusted AD to AUD models (0.8 instead of 0.9 in the AUD to AD models), which may have precluded a statistically significant association between AD and AUD.

4.4. Implications

Our findings are indicative of a bidirectional relationship between AD and AUD. It is important to prevent the onset of the secondary condition in order to prevent the negative consequences of this comorbidity (e.g. higher levels of disability, more suicidality and poorer treatment outcomes). Based on our results, AUD contributes to the onset and presence of AD. In mental health care, it is important to be alert of specific characteristics in patients with AUD that are associated with a greater risk of developing AD: excessive drinking (weekly intake of >14 for women and >21 for men) or attempts to stop drinking which could cause withdrawal symptoms, that in turn induces anxiety. Furthermore, people with AD are at greater risk of developing AUD, particularly those with severe psychopathology, as reflected in comorbid depression and psychotropic medication use. Thus, caregivers in mental health care could provide psychoeducation to patients with AUD to raise awareness about the risk of developing AD, and vice versa, to patients with more severe AD (e.g. comorbid depression) about the risk of developing AUD.

Further prospective research should focus on more detailed measurement of the different types of AD to learn more about the association with specific AD diagnoses and AUD. Furthermore, to better understand the mechanisms underlying the associations between AUD and AD it is advisable to pay attention to the role of more specific confounding, mediating and moderating variables.

5. Conclusion

Our results are indicative of a bidirectional relationship between AD and AUD; especially those with severe AD are at risk of developing AUD. Health care professionals should focus on the prevention of AD in patients with AUD and on the prevention of AUD in patients with (more severe) AD.

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CRediT authorship contribution statement

Sophie Ummels, Adrie Seldenrijk, Elisabeth Bos, Ron de Graaf, Marleen ten Have and Neeltje Batelaan designed the study. Elisabeth Bos conducted the statistical analysis. Sophie Ummels and Adrie Seldenrijk wrote the first draft of the manuscript. Which was reviewed and edited by Elisabeth Bos, Ron de Graaf, Marleen ten Have and Neeltje Batelaan. All authors contributed to and have approved the final manuscript. Sadly, Elisabeth Bos passed away during the preparation of this manuscript.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.06.091.

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