



Research report

Comorbidity and risk indicators for alcohol use disorders among persons with anxiety and/or depressive disorders Findings from the Netherlands Study of Depression and Anxiety (NESDA)

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ABSTRACT

Introduction: This study examines comorbidity of alcohol abuse and alcohol dependence as well as its risk indicators among anxious and/or depressed persons, also considering temporal sequencing of disorders.

Methods: Baseline data from the Netherlands Study of Depression and Anxiety (NESDA) were used, including 2329 persons with lifetime DSM-IV anxiety (social phobia, generalized anxiety disorder, panic disorder, and agoraphobia) and/or depressive (major depressive disorder and dysthymia) disorders and 652 controls. Lifetime diagnoses of DSM-IV alcohol abuse and dependence were established, as well as information about socio-demographic, vulnerability, addiction-related and anxiety/depression-related characteristics. Temporal sequencing of disorders was established retrospectively, using age of onset.

Results: Of persons with combined anxiety/depression 20.3% showed alcohol dependence versus 5.5% of controls. Prevalence of alcohol abuse was similar across groups ($\pm 12\%$). Independent risk indicators for alcohol dependence among anxious and/or depressed persons were male gender, vulnerability factors (family history of alcohol dependence, family history of anxiety/depression, openness to experience, low conscientiousness, being single, and childhood trauma), addiction-related factors (smoking and illicit drug use) and early anxiety/depression onset. Persons with secondary alcohol dependence were more neurotic, more often single and lonelier, while persons with primary alcohol dependence were more often male and more extravert.

Discussion: Alcohol dependence, but not abuse, is more prevalent in anxious and/or depressed persons. Persons with comorbid alcohol dependence constitute a distinct subgroup of anxious and/or depressed persons, characterized by addiction-related habits and vulnerability. However, considerable variation in characteristics exists depending on temporal sequencing of disorders. This knowledge may improve identification and treatment of those anxious and/or depressed patients who are additionally suffering from alcohol dependence.

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1. Introduction

Anxiety and depressive disorders as well as alcohol use disorders (alcohol abuse and alcohol dependence) are

widespread in the general population (Bijl et al., 1998; Bijl and Ravelli, 2000; Burns and Teesson, 2002; Hasin et al., 2007; Kessler et al., 1994, 2005; Rehm et al., 2005) and constitute a huge public health burden worldwide (World Health Organization, 2001; World Health Organization, 2003). In addition, comorbidity of alcohol use disorders and anxiety or depressive disorders is high. Studies in the general population show that persons with anxiety or depressive disorders have a 2- to 3-fold increased risk of alcohol use disorders (Burns and Teesson, 2002; de Graaf et al., 2003; Hasin et al., 2007; Merikangas et al., 1998; Pirkola et al., 2005). However, reliable estimates of comorbidity rates of alcohol abuse and alcohol dependence within a psychiatric population of anxious and/or depressed persons are not yet available.

Despite the large health burden of alcohol use disorders, studies show that most persons with these disorders do not receive appropriate treatment (Bijl and Ravelli, 2000; Hasin et al., 2007). Better treatment of alcohol use disorders starts with better recognition of alcohol use disorders. This is especially important in a group of persons at high risk for alcohol use disorders such as persons with anxiety and/or depressive disorders since alcohol use disorders have a negative effect on the course of anxiety and depressive disorders (Bruce et al., 2005; Hasin et al., 1996). Therefore, it is essential to identify which depressed or anxious persons are at increased risk of having alcohol use disorders. Previous studies in the general population have identified important clusters of risk indicators for pure alcohol use disorders, such as socio-demographics (e.g. male gender; Hasin et al., 2007), vulnerability (e.g. family history of psychiatric disorders, personality, childhood trauma; Bijl et al., 1998; Krueger and Markon, 2006) and addiction-related factors (e.g. smoking; Hasin et al., 2007). However, studies that simultaneously examine a broad range of risk indicators for alcohol use disorders in a population of anxious and/or depressed persons and, additionally, distinguish between alcohol abuse and alcohol dependence have been absent. These studies would be essential as risk indicators for comorbid disorders might differ from those for pure disorders (de Graaf et al., 2003). To date, existing knowledge on risk indicators in anxious and/or depressed persons is limited to studies examining alcohol abuse and alcohol dependence together or even the mixed group of all substance use disorders. Considering socio-demographic factors, persons with comorbid alcohol or substance use disorders are more often male compared with other anxious or depressed persons (Burns and Teesson, 2002; de Graaf et al., 2002a,b; Marquenie et al., 2007; Schade et al., 2004), but findings regarding age (Burns and Teesson, 2002; de Graaf et al., 2002a,b; Marquenie et al., 2007; Rae et al., 2002) and socioeconomic status (Burns and Teesson, 2002; de Graaf et al., 2002a,b; Schade et al., 2004) are inconsistent. Concerning vulnerability factors, parental psychiatric history and childhood trauma have been implicated as risk indicators for alcohol use disorders in depressed persons (de Graaf et al., 2002a,b; Schade et al., 2004), whereas information about personality is lacking. In addition, persons with comorbid substance use disorder and alcohol dependence are more likely to be single (de Graaf et al., 2002a,b; Schade et al., 2004). Finally, studies examining clinical characteristics show that persons with comorbid

alcohol dependence have more anxiety or depressive symptoms (Rae et al., 2002; Schade et al., 2004).

Thus, although some knowledge of risk indicators for comorbid alcohol use disorders in anxious and/or depressed persons exists, a considerable degree of uncertainty remains. It may be important to distinguish alcohol abuse and alcohol dependence, since both conditions differ in their association with anxiety and depressive disorders (Hasin et al., 2007). Additionally, risk indicators for alcohol use disorders preceding anxiety/depressive disorders (primary alcohol use disorders) may differ from risk indicators for alcohol use disorders following anxiety/depressive disorders (secondary alcohol use disorders). According to a causal model of comorbidity, secondary alcohol use disorders may result from self-medication of anxiety and/or depressive symptoms with alcohol (Bolton et al., 2006, 2008), while anxiety and depressive disorders may be consequences of (chronic) alcohol intoxication and/or withdrawal in primary alcohol use disorders (Falk et al., 2008). Consequently, risk indicators might typically correspond to risk indicators for the first emerging disorder. Whether risk indicators for primary or secondary alcohol use disorders indeed differ is still insufficiently understood, but may provide important insight into mechanisms of comorbidity of alcohol use disorders with anxiety and depressive disorders.

The present study examines comorbidity rates of both alcohol abuse and alcohol dependence in a large sample of anxious and/or depressed persons. In addition, risk indicators for comorbid alcohol use disorders will be studied, taking into account a broad range of socio-demographic and vulnerability factors as well as addiction-related and anxiety/depression-related characteristics. Concerning the temporal sequencing of disorders, we aimed to compare risk indicators for primary and secondary alcohol use disorders.

2. Methods

2.1. Study sample

Data were derived from the Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2008), an ongoing cohort study aimed at examining the long-term course and consequences of depressive and anxiety disorders in the adult (18–65 years) population. For the baseline assessment in 2004–2007, the study sample consisted of 2329 persons with anxiety and/or depressive disorders and 652 healthy controls. To represent various settings and stages of psychopathology, depressed or anxious participants were recruited from community (19%), primary care (54%) and specialized mental health care (27%). Community-based subjects had previously been identified in a population-based study; primary care subjects were identified through a three-stage screening procedure (involving the K10 (Kessler et al., 2002) and the short-form Composite International Diagnostic Interview (CIDI) psychiatric interview by phone) conducted among patients of 65 General Practitioners; and mental healthcare patients were recruited when newly enrolled at one of the 17 participating mental health organization locations. Persons with insufficient command of the Dutch language or a primary clinical diagnosis (serving as the main reason for mental health care consultation) of

bipolar disorder, obsessive compulsive disorder, severe substance use disorder, psychotic disorder or organic psychiatric disorder as reported by themselves or their mental health practitioner, were excluded. A detailed description of the NESDA study design and sampling procedures can be found elsewhere (Penninx et al., 2008). The research protocol was approved by the Ethical Committee of participating universities and all participants provided written informed consent.

2.2. Assessment of psychopathology

Diagnoses of psychiatric disorders were established with the Composite International Diagnostic Interview (CIDI) (Wittchen et al., 1991), version 2.1, which classifies diagnoses according to DSM-IV criteria (American Psychiatric Association, 2001). The CIDI is reliable and valid in assessing psychopathology and was administered by specially trained research staff. The following lifetime diagnoses were assessed: anxiety disorders (generalized anxiety disorder, social phobia, panic disorder, and agoraphobia), depressive disorders (major depressive disorder and dysthymia) and alcohol use disorders (alcohol abuse and alcohol dependence). The CIDI hierarchy criteria for diagnosing alcohol use disorders are based on the DSM-IV and exclude the possibility of a diagnosis of alcohol abuse when a lifetime diagnosis of alcohol dependence is present. This allowed us to examine the unique contribution of alcohol abuse, after eliminating confounding of the more severe alcohol dependence.

2.3. Temporal sequencing

Among anxious and/or depressed persons with comorbid alcohol use disorders, temporal sequencing was retrospectively determined using data on lowest age of disorder onset of either anxiety or depressive disorder or alcohol use disorder, as assessed by the CIDI interview. Respondents were categorized into three groups based on relative age of disorder onset (in years): (1) primary alcohol use disorder: alcohol use disorder preceded anxiety/depressive disorder; (2) secondary alcohol use disorder: alcohol use disorder became manifest after anxiety/depressive disorder; and (3) concurrent onset: alcohol use disorder and anxiety/depressive disorder initially occurred at the same age.

2.4. Risk indicators

Known risk indicators for anxiety and/or depressive disorders or alcohol use disorders in the general population were selected as potential risk indicators for comorbid alcohol use disorders in anxious and/or depressed persons. Four clusters of variables were assessed.

2.4.1. Socio-demographic factors

Gender, age and years of education were assessed during the baseline interview.

2.4.2. Vulnerability factors

Vulnerability factors consisted of family history, personality and social factors. Information about the presence of psychiatric disorders among first degree relatives (not

including offspring) was obtained using the family tree method (Fyer and Weissman, 1999). Both family history of anxiety or depressive disorders and family history of alcohol addiction were assessed. Personality was assessed using the NEO personality questionnaire (Costa and McCrae, 1995), a 60-item questionnaire measuring five personality domains: neuroticism, extraversion, openness to experience, agreeableness and conscientiousness. With regard to social factors, information about current partner status was obtained during the interview, whereas subjective loneliness was measured with the 11-item De Jong-Gierveld self-report questionnaire (DeJong Gierveld and Kamphuis, 1985). Based on the childhood trauma inventory, a cumulative childhood trauma index (range 0–8) was constructed considering emotional neglect, psychological abuse, physical abuse and sexual abuse before the age of 16 years (Wiersma et al., 2009). Presence of a childhood life event referred to the occurrence of at least one of the following events before the age of 16 years: parental divorce, being placed in a juvenile prison, raised in a foster family or placed in a child home. In addition, a total count of 12 negative life events in the past year was made using Brugha's List of Threatening Experiences (Brugha et al., 1985).

2.4.3. Addiction-related characteristics

As an indication for addiction to substances other than alcohol, we obtained information about smoking status (never smoked, former smoker, or current smoker) during the interview. Illicit drug use (cannabis, ecstasy, speed, cocaine, heroine or LSD) in the past month was assessed with a self-report questionnaire. In addition, as benzodiazepines have a high potential of being addictive (e.g. O'Brien, 2005), use of benzodiazepines was assessed by drug container inspection of medication used in the past month, classified according to the World Health Organization Anatomical Therapeutic Chemical classification (ATC-codes N03AE, N05BA, N05CD and N05CF) (World Health Organization Collaborating Centre for Drug Statistics Methodology, 2007), and was considered present when taken at least 50% of the days.

2.4.4. Anxiety/depression-related characteristics

A distinction was made between early (<25 years) and late (≥ 25 years) onset of anxiety and/or depressive disorders, a cutoff that has been used frequently by others (e.g. Parker et al., 2003). Duration was assessed by the Life Chart method (Lyketsos et al., 1994), which uses a calendar method to assess the presence of anxiety, depressive and avoidance symptoms during the past four to five years. As a measure of duration, the percentage of time during which symptoms were present was computed. Severity of symptoms in the past week was assessed by the 30-item Inventory of Depressive Symptomatology (Rush et al., 1996), which includes an anxiety symptom subset and is highly correlated with the Beck Anxiety Inventory (Beck et al., 1988) ($r = .78$).

2.5. Statistical analyses

Lifetime comorbidity rates of alcohol abuse and alcohol dependence with anxiety and/or depressive disorders were determined using Chi-square tests and logistic regression analyses. Characteristics of anxious and/or depressed persons

without versus with alcohol use disorders were summarized using descriptive statistics. Then, logistic regression analyses were used to identify independent risk indicators for comorbid alcohol use disorders within the subsample of anxious and/or depressed persons. Characteristics with a $p < .10$ in univariable logistic regression analyses were entered into multivariable analyses per cluster of characteristics and again those with a $p < .10$ in these analyses were entered into the final model. To provide insights into the nature of the association of the various risk indicators and alcohol use disorders, results of the univariable analyses as well as the multivariable models per cluster and a final model are shown. A liberal cutoff of $p < .10$ was chosen for model building to ensure all important risk indicators were included in the final model. In the final model, a $p < .05$ was considered significant.

Next, among anxious and/or depressed persons with comorbid alcohol use disorders, the distribution of primary and secondary alcohol use disorders and concurrent onset was compared across anxiety and depressive disorder subgroups, using Chi-square statistics. Descriptive statistics were used to summarize characteristics of persons with primary and secondary alcohol use disorders, respectively. Within anxious and/or depressed persons, univariable multinomial logistic regression analyses were performed to identify risk indicators of primary alcohol use disorders and secondary alcohol use disorders, respectively, compared to persons without alcohol use disorders. All characteristics with a $p < .10$ for either primary or secondary alcohol use disorders in these univariable analyses were entered into a multivariable model to identify independent risk-indicators. The same selection of characteristics was entered into a multivariable logistic regression analysis directly comparing persons with secondary alcohol use disorders versus primary alcohol use disorders (reference).

3. Results

3.1. Comorbidity of alcohol abuse and alcohol dependence

Mean age of the sample was 41.9 (SD = 13.1) years and 66.4% were women. Lifetime prevalence rates of alcohol abuse and alcohol dependence were 11.8% and 15.4%, respectively. Table 1 shows the prevalence of alcohol abuse and alcohol dependence for persons with and without lifetime anxiety and/or depressive disorders as well as the results of the logistic regression analyses comparing the odds of alcohol abuse and alcohol dependence in anxious and/or depressed persons with a reference group of persons without an anxiety or depressive disorder. Alcohol abuse was not more common among anxious and/or depressed persons

than among controls (overall prevalence: 11.8%, $p = .43$). However, the prevalence of alcohol dependence varied from 5.5% in persons without anxiety or depressive disorder to 20.3% in persons with both anxiety and depressive disorder ($p < .001$). Compared with healthy controls, the odds of alcohol dependence were significantly increased in persons with pure anxiety disorder (OR = 2.41, 95% CI = 1.52–3.83) or pure depressive disorder (OR = 3.39, 95% CI = 2.26–5.07), and was highest in persons with both anxiety and depressive disorder (OR = 4.35, 95% CI = 3.03–6.24). Considering the different subtypes of anxiety and depressive disorders (results not tabulated), all disorders were significantly associated with the presence of comorbid alcohol dependence (all $p < .001$). However, the association with alcohol dependence appeared to be somewhat stronger for dysthymia than for major depressive disorder (dysthymia versus major depressive disorder: OR = 1.50, 95% CI = 1.19–1.88) and for social phobia and panic disorder than other anxiety disorders (social phobia versus other: OR = 1.68, 95% CI = 1.32–2.15; panic disorder versus other: OR = 1.47, 95% CI = 1.16–1.87). Since alcohol abuse showed no association with anxiety and/or depressive disorders, further analyses were restricted to alcohol dependence.

3.2. Risk indicators for alcohol dependence

Table 2 summarizes the characteristics of anxious and/or depressed persons ($n = 2329$) without versus with comorbid alcohol dependence and additionally, shows the results of univariable and multivariable logistic regression analyses examining possible risk indicators for comorbid alcohol dependence in this sample of anxious and/or depressed persons. Within the cluster of socio-demographic factors, only male gender, but not age or years of education, was associated with an increased risk of comorbid alcohol dependence in univariable and multivariable analyses. In univariable analyses, persons with comorbid alcohol dependence differed significantly from persons without comorbid alcohol dependence in all examined vulnerability characteristics, except childhood life-events. After adjustment for other variables in the final model, family history of both alcohol dependence and anxiety or depressive disorders, high openness to experience, low conscientiousness, having no partner and childhood trauma were still significantly associated with higher odds of comorbid alcohol dependence. Addiction-related characteristics such as being a current or former smoker and illicit drug use in the last month were more prevalent in persons with comorbid alcohol dependence in the unadjusted as well as adjusted analyses. Although early onset, more chronic and more severe anxiety

Table 1

Comorbidity rates of lifetime alcohol abuse and alcohol dependence with anxiety and/or depressive disorders ($n = 2981$).

	Alcohol abuse					Alcohol dependence				
	n	%	OR ^a	95% CI	p	n	%	OR ^a	95% CI	p
No anxiety/depressive disorder	83	12.7%	REF			36	5.5%	REF		
Anxiety disorder only	46	12.9%	1.02	.69–1.50	.93	44	12.4%	2.41	1.52–3.83	<.001
Depressive disorder only	71	12.7%	1.00	.71–1.41	.99	92	16.5%	3.39	2.26–5.07	<.001
Both anxiety/depressive disorder	153	10.8%	.83	.62–1.10	.20	287	20.3%	4.35	3.03–6.24	<.001

^a Based on logistic regression analyses.

Table 2

Risk indicators of comorbid alcohol dependence in persons with a lifetime anxiety and/or depressive disorder (n = 2329).

	No AD (n = 1906)	AD (n = 423)	AD univariable ^a			AD multivariable (cluster) ^b			AD multivariable (full) ^c		
	μ (SD)/n (%)	μ (SD)/n (%)	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
<i>Sociodemographics</i>											
Gender (male)	553 (29.0%)	197 (46.6%)	2.13	1.72–2.64	<.001	2.13	1.72–2.64	<.001	2.19	1.72–2.79	<.001
Age (years)	42.1 (12.7)	42.2 (12.0)	1.00	.99–1.01	.84	–	–	–	–	–	–
Education (years)	12.0 (3.3)	12.0 (3.3)	1.00	.97–1.03	.89	–	–	–	–	–	–
<i>Vulnerability</i>											
<i>Family history</i>											
Anx/dep disorder (yes)	1551 (81.4%)	378 (89.4%)	1.92	1.38–2.67	<.001	1.60	1.14–2.25	.007	1.66	1.17–2.37	.005
Alcohol dependence (yes)	452 (23.7%)	167 (39.5%)	2.10	1.68–2.62	<.001	1.84	1.46–2.33	<.001	1.68	1.31–2.15	<.001
<i>Personality</i>											
Neuroticism ^d	38.5 (8.1)	40.7 (7.7)	1.33	1.19–1.48	<.001	1.09	.94–1.26	.26	–	–	–
Extraversion ^d	35.6 (6.9)	34.5 (7.4)	.85	.76–.94	.003	1.09	.95–1.25	.23	–	–	–
Openness to experience ^d	31.1 (5.3)	32.1 (5.4)	1.20	1.08–1.33	.001	1.17	1.05–1.31	.006	1.16	1.03–1.30	.01
Agreeableness ^d	43.6 (5.2)	42.0 (5.4)	.74	.67–.82	<.001	.80	.71–.90	<.001	.90	.80–1.02	.09
Conscientiousness ^d	36.9 (5.9)	35.2 (6.3)	.75	.67–.83	<.001	.83	.73–.95	.006	.86	.76–.98	.02
<i>Social factors</i>											
No partner	586 (30.7%)	166 (39.2%)	1.45	1.17–1.81	.001	1.28	1.01–1.62	.04	1.37	1.08–1.73	.01
Loneliness ^d	5.0 (3.5)	6.0 (3.4)	1.35	1.20–1.51	<.001	1.12	.97–1.28	.13	–	–	–
Childhood trauma (total score)	1.8 (2.1)	2.4 (2.3)	1.14	1.09–1.19	<.001	1.05	1.00–1.10	.07	1.06	1.01–1.12	.02
Childhood life-events (yes)	337 (17.7%)	84 (19.9%)	1.15	.88–1.51	.29	–	–	–	–	–	–
N neg life-events (last year)	.7 (1.0)	.8 (1.1)	1.11	1.01–1.23	.04	1.05	.94–1.16	.38	–	–	–
<i>Addiction-related</i>											
Smoking	Never	36 (8.5%)	REF			REF			REF		
	Former	637 (33.4%)	2.99	2.03–4.41	<.001	3.02	2.04–4.45	<.001	3.13	2.10–4.66	<.001
	Current	711 (37.3%)	5.76	3.99–8.29	<.001	5.21	3.61–7.54	<.001	4.97	3.41–7.24	<.001
Illicit drug use (yes)	123 (6.5%)	67 (15.8%)	2.73	1.98–3.75	<.001	2.07	1.48–2.89	<.001	1.43	1.00–2.04	.05
Benzodiazepine use (yes)	163 (8.6%)	53 (12.5%)	1.53	1.10–2.13	.01	1.53	1.09–2.15	.01	1.36	.94–1.97	.10
<i>Anxiety/depression-related</i>											
Early (<25 years) onset	1206 (63.3%)	303 (71.6%)	1.47	1.17–1.85	.001	1.37	1.08–1.73	.008	1.32	1.02–1.70	.03
Duration	.4 (.4)	.5 (.4)	1.83	1.38–2.42	<.001	1.41	1.03–1.92	.03	1.24	.88–1.73	.22
Severity ^d	24.5 (13.1)	28.1 (13.5)	1.31	1.18–1.46	<.001	1.23	1.10–1.38	<.001	1.05	.92–1.21	.47
Age of onset anxiety/depression	23.1 (12.8)	20.2 (11.9)	–	–	–	–	–	–	–	–	–

AD = Alcohol dependence.

^a Based on univariable logistic regression analyses.^b Based on multivariable logistic regression analyses, including all variables within the same cluster that had a p < .10 in univariable analyses.^c Based on multivariable logistic regression analyses, including all variables that had a p < .10 in the cluster models.^d OR per SD increase: neuroticism: SD = 8.1; extraversion: SD = 7.0; openness to experience: SD = 5.4; agreeableness: SD = 5.3; conscientiousness: SD = 6.1; loneliness: SD = 3.7; severity of symptoms: SD = 13.4.

and/or depressive disorders were associated with comorbid alcohol dependence in univariable analyses and multivariable analyses per cluster, in the final model only early onset remained significantly associated. When analyses of Table 2 were performed separately for persons with anxiety disorders and those with depressive disorders, no substantial differences in risk indicator profiles were found (results not shown).

3.3. Temporal sequencing

Fig. 1 shows the temporal sequencing of comorbid alcohol dependence in anxiety and depressive disorder subgroups for whom complete data on age of onset were available ($n=416$). Comorbid alcohol dependence was secondary in 50.6% of persons with pure depressive disorder, 71.4% of persons with pure anxiety disorder and 83.9% in persons with both depressive and anxiety disorder ($p<.001$). As would be expected from the above, mean age of onset of anxiety and/or depressive disorder was lower (mean = 16.3, SD = 9.2 versus mean = 34.4, SD = 10.8; $p<.001$; not in table) and mean age of onset of alcohol dependence was higher (mean = 29.9, SD = 11.1 versus mean = 24.1, SD = 7.7; $p<.001$) among persons with secondary versus primary alcohol dependence. Additional analyses (not tabulated), showed that alcohol dependence was more likely to be secondary to dysthymia than to major depressive disorder (dysthymia versus major depressive disorder: OR = 3.00, 95% CI = 1.51–5.93). Similarly, alcohol dependence was more likely to be secondary to social phobia than to other anxiety disorders (social phobia versus other: OR = 4.13, 95% CI = 1.91–8.96). Although this was also reflected in the lower age of onset for social phobia than for other anxiety disorders (mean = 17.7, SD = 11.1 versus mean = 26.0, SD = 12.7), no differences in age of onset were found for dysthymia and major depressive disorder (mean = 28.7, SD = 12.7 versus mean = 27.6, SD = 12.3). Persons with a concurrent onset of alcohol dependence and anxiety and/or depressive disorder were relatively rare ($n=39$) and could therefore not be analyzed as a separate group in further analyses.

3.4. Risk indicators for primary and secondary alcohol dependence

Table 3 summarizes characteristics of persons with primary ($n=63$) and secondary ($n=314$) alcohol depen-

dence, respectively. Since temporal sequencing of disorders is closely related to age of onset of anxiety and/or depressive disorders, this latter variable was not included in these analyses. To identify characteristics that were independent risk indicators for primary alcohol dependence or secondary alcohol dependence compared with anxious and/or depressed persons without alcohol dependence (=reference), a multivariable multinomial logistic regression analysis was conducted including characteristics with a $p<.10$ in univariable analyses (Table 3). Male gender, high extraversion, low conscientiousness and being a current smoker were associated with higher odds of primary alcohol dependence. Male gender and being a current or former smoker were also associated with secondary alcohol dependence. However, in contrast with primary alcohol dependence, vulnerability factors such as family history of anxiety or depressive disorders as well as alcohol dependence, high neuroticism, high openness to experience, having no partner and the presence of childhood trauma were associated with higher odds of secondary alcohol dependence.

Finally, a multivariable logistic regression analysis was conducted to directly compare persons with secondary alcohol dependence ($n=314$) versus primary alcohol dependence ($n=63$; reference group). Although male gender was more prevalent among both persons with primary and secondary alcohol dependence, male gender was relatively less prevalent among persons with secondary alcohol dependence. Vulnerability factors such as high neuroticism, having no partner and high loneliness were more prevalent among persons with secondary compared with primary alcohol dependence.

4. Discussion

The present study shows that alcohol dependence is highly prevalent among anxious and/or depressed persons. In persons with both lifetime anxiety and depressive disorders the prevalence of lifetime alcohol dependence was even as high as 20.3% compared with 5.5% in controls. In contrast, alcohol abuse was not more prevalent among anxious and depressed persons than in controls. The results further show that male gender, vulnerability (family history, personality and social factors) and addiction-related characteristics, more than anxiety/depression-related characteristics, are important risk indicators for comorbid alcohol dependence. In

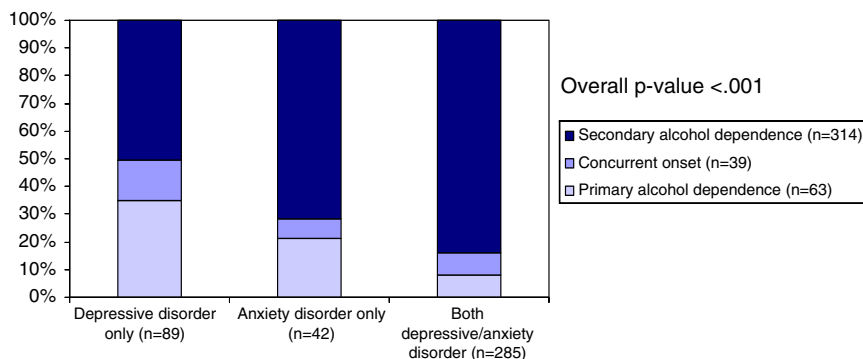


Fig. 1. Temporal sequencing of alcohol dependence in respect to depressive and/or anxiety disorders ($n=416$).

Table 3

Risk indicators of primary alcohol dependence versus secondary alcohol dependence among persons with anxiety and/or depressive disorders.

	Primary AD (n = 63)	Secondary AD (n = 314)	Primary AD versus no AD multivariable ^a			Secondary AD versus no AD multivariable ^a			Secondary versus primary AD multivariable ^b		
	μ (SD)/n (%)	μ (SD)/n (%)	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
<i>Socio-demographic factors</i>											
Gender (male)	38 (60.3%)	129 (41.1%)	3.98	2.25–7.05	<.001	1.80	1.36–2.38	<.001	.43	.22–.82	.01
Age (years)	44.1 (11.8)	41.9 (12.1)	–	–	–	–	–	–	–	–	–
Education (years)	12.2 (2.9)	12.1 (3.4)	–	–	–	–	–	–	–	–	–
<i>Vulnerability factors</i>											
Family history											
Anxiety/depressive disorder (yes)	53 (84.1%)	288 (91.7%)	1.21	.60–2.45	.60	2.11	1.35–3.28	.001	1.54	.64–3.70	.33
Alcohol dependence (yes)	20 (31.7%)	130 (41.4%)	1.45	.81–2.58	.21	1.75	1.33–2.31	<.001	1.14	.58–2.25	.70
Personality											
Neuroticism ^c	36.4 (9.1)	41.7 (7.1)	.86	.58–1.27	.45	1.33	1.08–1.62	.006	1.77	1.09–2.88	.02
Extraversion ^c	37.3 (7.0)	33.8 (7.4)	1.52	1.09–2.13	.01	1.04	.89–1.23	.60	.76	.53–1.09	.14
Openness to experience ^c	31.3 (5.4)	32.3 (5.4)	.98	.75–1.29	.89	1.22	1.07–1.39	.003	1.24	.88–1.75	.21
Agreeableness ^c	42.2 (5.1)	42.2 (5.4)	.82	.61–1.09	.17	.96	.83–1.10	.55	1.22	.89–1.69	.22
Conscientiousness ^c	36.1 (5.5)	34.8 (6.5)	.66	.49–.91	.01	.88	0.76–1.02	.08	1.28	.90–1.83	.17
Social factors											
No partner	14 (22.2%)	133 (42.4%)	.76	.40–1.44	.39	1.44	1.09–1.89	.01	2.03	1.00–4.10	.05
Loneliness ^c	4.3 (3.6)	6.3 (3.2)	.76	.53–1.09	.13	1.14	.96–1.35	.13	1.72	1.12–2.66	.01
Childhood trauma (total score)	1.8 (2.3)	2.6 (2.3)	1.04	.92–1.19	.50	1.07	1.01–1.14	.03	1.04	.89–1.21	.64
Childhood life-events (yes)	13 (20.6%)	61 (19.4%)	–	–	–	–	–	–	–	–	–
N negative life-events (last year)	.7 (1.1)	.8 (1.1)	1.00	.77–1.30	.97	1.02	.90–1.16	.73	1.00	.74–1.33	.98
<i>Addiction-related characteristics</i>											
Smoking	Never	25 (8.0%)	REF			REF			REF		
	Former	18 (28.6%)	1.95	.80–4.75	.14	3.66	2.29–5.84	<.001	1.41	.46–4.30	.54
	Current	38 (60.3%)	3.46	1.51–7.94	.003	5.41	3.47–8.44	<.001	1.13	.41–3.17	.81
Illicit drug use (yes)	7 (11.1%)	51 (16.2%)	.97	.40–2.31	.94	1.46	.98–2.17	.06	1.59	.60–4.21	.35
Benzodiazepine use (yes)	8 (12.7%)	40 (12.7%)	1.92	.84–4.36	.12	1.26	.84–1.90	.27	.64	.25–1.68	.37
<i>Anxiety/depression-related characteristics</i>											
Duration	.4 (.4)	.5 (.4)	1.10	.50–2.44	.81	1.41	.96–2.08	.08	1.34	.53–3.37	.54
Severity ^c	22.6 (14.7)	29.2 (13.0)	.96	.64–1.45	.86	.93	.77–1.13	.49	.84	.53–1.35	.48

AD = Alcohol dependence.

^a Based on multivariable multinomial logistic regression analyses, including all variables that had a p < .10 in univariable analyses.^b Based on multivariable logistic regression analyses, including all variables that had a p < .10 in univariable multinomial logistic regression analyses.^c OR per SD increase: neuroticism: SD = 8.1; extraversion: SD = 7.0; openness to experience: SD = 5.4; agreeableness: SD = 5.3; conscientiousness: SD = 6.1; loneliness: SD = 3.7; severity of symptoms: SD = 13.4.

addition, we found that comorbid alcohol dependence was more likely to be secondary than primary to anxiety or depressive disorders. Considerable variation in characteristics exists in persons with primary alcohol dependence (more often male and more extravert) versus secondary alcohol dependence (more neurotic, more often single and more lonely).

Since alcohol dependence is a severely impairing condition (Hasin et al., 2007; Rae et al., 2002) that negatively affects the course of anxiety and depressive disorders (Bruce et al., 2005; Hasin et al., 1996), identification of these problems through screening may greatly enhance mental health care. Our study shows that risk indicators that have previously been associated with pure alcohol dependence in general population studies (male gender, addiction-related characteristics and specific vulnerability factors [family history of alcohol dependence, personality factors, being single and childhood trauma]; Grant et al., 2004; Hasin et al., 2007; Krueger and Markon, 2006; Marquenie et al., 2007; Nurnberger Jr. et al., 2004; Sartor et al., 2008), are also important independent risk indicators for comorbid alcohol dependence among a high-risk group of anxious and/or depressed persons. In contrast, characteristics of anxiety/depression and vulnerability factors often associated with anxiety/depression, such as neuroticism and introversion, were in general less predictive of comorbid alcohol dependence. This is somewhat in contrast with previous studies that did show higher severity of anxiety and depressive symptoms among persons with comorbid alcohol dependence (Rae et al., 2002; Schade et al., 2004). However, most of these anxiety/depression factors have not been previously examined in relation to comorbid alcohol dependence. Our results suggest that factors associated with anxiety or depressive disorders are less important in determining heightened risk for alcohol dependence in anxious and/or depressed persons, but in fact the same factors that have been related to addiction in the general population are. Nevertheless, persons with comorbid alcohol dependence appear to be a distinct subgroup of anxious and/or depressed persons, and screening for alcohol dependence might be based on the presence of addiction-related and vulnerability factors.

Consistent with previous reports (Merikangas et al., 1998), comorbid alcohol dependence was more likely to be secondary than primary in this sample of anxious and/or depressed persons. Furthermore, in persons with primary alcohol dependence the onset of anxiety and depressive disorders was rather late (34 years in persons without alcohol dependence) while in persons with secondary alcohol dependence it was rather early (16 years). Thus temporal sequencing did not solely reflect which disorder happened to occur first, but the actual ages of onset of alcohol dependence differed significantly. Among anxiety disorders, the age of onset of social phobia (18 years) was lower compared to other anxiety disorders (26 years) and this may partly explain our finding that alcohol dependence was more likely to be secondary to social phobia than to other anxiety disorders. On the other hand, alcohol dependence was more likely to be secondary to dysthymia than to major depressive disorders, whereas the age of onset of these depressive disorders did not differ (29 versus 28 years, respectively). These different patterns in findings suggest a distinct etiology

of primary and secondary alcohol dependence in relation to specific anxiety and depressive disorders and emphasize the importance of taking into account temporal sequencing of disorders during treatment. However, prospective studies are necessary to clarify the different pathways to comorbidity.

This study is unique in directly comparing anxious and/or depressed persons with primary versus secondary alcohol dependence on an extensive set of potential risk indicators. The results show that persons with secondary alcohol dependence were characterized by high neuroticism, more loneliness and having no partner – all risk indicators that have also been related to anxiety or depressive disorders (e.g. Grant et al., 2009; de Graaf et al., 2002a,b), although being single has also been associated with alcohol dependence (Hasin et al., 2007). Despite our finding that male gender was an overall risk indicator for comorbid alcohol dependence, relatively more women had secondary alcohol dependence compared with primary alcohol dependence. Female gender is also a well-known risk indicator for anxiety and depressive disorders (e.g. Grant et al., 2009; de Graaf et al., 2002a,b). In contrast, male gender and extraversion, more often associated with addiction (Hasin et al., 2007; Prescott et al., 1997), appeared to be important indicators of primary alcohol dependence. Hence, persons with comorbid alcohol dependence tend to present more typical characteristics of their first-emerging disorder. This may imply a causal model of comorbidity in which the presence of the anxiety and/or depressive disorder may predispose to the development of alcohol dependence and the presence of alcohol dependence may predispose to anxiety/depression. For instance, the “self-medication” hypothesis (Quitkin et al., 1972) suggests that anxious and/or depressed persons misuse alcohol to reduce their distressing symptoms, which is corroborated by more recent research (Bolton et al., 2006, 2008). It may be likely that distressing circumstances such as having no partner and feelings of loneliness in combination with a neurotic personality may increase a person's desire to reduce distress with alcohol. On the other hand, anxiety and depressive disorders may be consequences of (chronic) alcohol intoxication and/or withdrawal in primary alcohol dependence (Falk et al., 2008; Hasin and Grant, 2002; Wang and Patten, 2002).

In line with two large general population studies in the US (Kessler et al., 1997; Hasin et al., 2007), this study shows that alcohol dependence, but not abuse, is more prevalent in anxious and/or depressed persons. Consistent with most previous studies, persons in our study were only considered having alcohol abuse if alcohol dependence was not present. This suggests that alcohol abuse symptoms may be important in the context of alcohol dependence, but not in the absence of alcohol dependence. This also raises the question whether alcohol abuse should in fact be considered a genuine psychiatric disorder. Previous studies have shown that diagnostic classification of alcohol dependence is highly reliable and valid, but not for the classification of alcohol abuse when diagnosed hierarchically (Hasin, 2003). Besides, alcohol abuse and dependence criteria appear to form a single latent dimension with abuse and dependence criteria interspersed across an underlying severity spectrum (Kahler and Strong, 2006; Saha et al., 2006; Hasin and Beseler, 2009). In preparation of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V; www.dsm5.org).

org), the Work Group has therefore proposed to combine all alcohol abuse and dependence criteria into one diagnosis of an alcohol-use disorder.

Methodological strengths of our study are that we analyzed a large sample of persons with a psychiatric diagnosis of anxiety and/or depressive disorder as well as alcohol abuse and alcohol dependence. In addition, extensive information about potential risk indicators was available. However, there are some limitations to be recognized. Persons with a primary diagnosis of a severe substance use disorder were excluded from this study. Therefore, reported comorbidity rates of alcohol abuse and alcohol dependence with anxiety/depressive disorders are likely to be underestimates and found risk indicators may not be generalized to severe alcohol use disorders. However, in general, found risk indicators for alcohol dependence in our sample were comparable to those found in the general population, suggesting that sampling frame might not have a very significant influence. Furthermore, causal inferences about associations between risk indicators and the disorders studied are precluded since results were based on cross-sectional data. Prospective data are necessary to further clarify causality in the pathways to comorbidity. Also, the temporal sequencing of disorders was based on the relative age of disorder onset, which might have introduced recall bias. The reported age of onset of some anxiety and depressive disorders (see also Lamers, 2011) differs slightly from other studies such as the Dunedin study (e.g., Jaffee et al., 2002), which is probably due to the fact that data were collected prospectively in the Dunedin study and, therefore, may yield more reliable estimates since there is no recall bias. Besides, the mean age of study participants differs since the Dunedin birth cohort had assessments from the age of 11 to 32 years, whereas the mean age of NESDA participants was 41.9 years.

In conclusion, alcohol dependence, but not alcohol abuse, is more common among anxious and/or depressed persons. The prevalence of lifetime alcohol dependence is as high as 20.3% in persons with combined lifetime anxiety and depressive disorder. Anxious and/or depressed persons with comorbid alcohol dependence are distinct from those without alcohol dependence in their addiction-related habits (smoking and illicit drug use) and typical addiction-related vulnerability (e.g. male gender, family history of alcohol dependence, openness to experience and low conscientiousness), rather than in anxiety or depression severity or duration indicators. However, characteristics identifying persons with comorbid alcohol dependence may vary depending on the temporal sequencing of disorders, which emphasizes the importance to consider primary and secondary alcohol dependence separately. This knowledge may help to identify those anxious and/or depressed patients in clinical practice who are likely to have or to develop alcohol dependence and offers potential for more suitable therapy for those suffering from this severely impairing comorbid condition.

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Conflict of interest

None of the authors report competing interest.

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