Depressive and Anxiety Disorders Predicting First Incidence of Alcohol Use Disorders: Results of the Netherlands Study of Depression and Anxiety (NESDA)

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ABSTRACT

Introduction: Depressive and anxiety disorders may predict first incidence of alcohol abuse and alcohol dependence. This study aims to identify those persons who are at an increased risk of developing alcohol abuse or alcohol dependence by considering the heterogeneity of depressive and anxiety disorders and exploring the role of other risk factors.

Method: In a large sample of persons with and without baseline *DSM-IV* depressive or anxiety disorders (n = 2,676; 18–65 years; assessed in 2004–2007), the first incidences of *DSM-IV* alcohol abuse and alcohol dependence during a 4-year follow-up were considered as primary outcomes. Status (remitted or current disorder), severity, and type (specific disorders) of depressive and anxiety disorders were assessed, as well as other risk factors, such as sociodemographic, vulnerability, and addiction-related factors.

Results: Cumulative first-incidence rates of alcohol abuse and alcohol dependence were 2.0% and 3.0%, respectively. Persons with current, but not remitted, depressive or anxiety disorders were at an increased risk of a first incidence of alcohol dependence (hazard ratio [HR] = 2.69; 95% CI, 1.37–5.29), but not first incidence of alcohol abuse (HR = 0.55; 95% CI, 0.28–1.09). Although this association was not conditional on the type of disorder, first-incidence rates of alcohol dependence gradually increased with the number of depressive and anxiety disorders (HR per SD increase = 1.65; 95% CI, 1.37–2.00). Subthreshold alcohol problems especially ($P < .001$), but also recent negative life events ($P = .06$), were additional independent predictors of first incidence of alcohol dependence.

Conclusion: Current depressive disorder, anxiety disorder, or both significantly predicted first incidence of alcohol dependence, which stresses the importance of addiction prevention strategies for depressed and anxious patients in mental health settings. Subthreshold alcohol problems and recent negative life events may help to identify persons at an increased risk for developing alcohol dependence.

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The comorbidity of depressive/anxiety disorders (ie, depressive disorder, anxiety disorder, or both) with alcohol use disorders (alcohol abuse and alcohol dependence) has been extensively documented in cross-sectional studies in the general population[1–4] as well as in clinical[5] and mixed[6] samples. Persons with depressive/anxiety disorders have a 2- to 4-fold increased risk of alcohol dependence, whereas no associations have been found for alcohol abuse.[1,4,6] Since comorbid alcohol dependence negatively affects the natural course of depressive/anxiety disorders[7] and is associated with more severe impairments[2] and suicidality,[8] prevention and treatment strategies for alcohol use disorders in depressed/anxious persons have the potential to greatly enhance mental health care.

Retrospective studies based on the age at onset of disorders have shown that depressive/anxiety disorders often precede alcohol use disorders,[6,9,10] suggesting that alcohol use disorders may be caused by or develop in the course of depressive/anxiety disorders. Prospective studies examining first incidence of alcohol use disorders are needed to verify the temporal relationship as an essential step toward understanding causality. However, findings of first-incidence studies are conflicting, resulting in significant,[11] nonsignificant,[12,13] or mixed results for depressive/anxiety disorders.[14–20] These inconsistent findings may be partly explained by the heterogeneity of depressive/anxiety disorders across previous studies. In addition, sociodemographic, vulnerability, and addiction-related factors have been shown to be related to the cross-sectional association between depressive/anxiety disorders and alcohol use disorders[4,6,11] and may also play an important role in this prospective association.

The present study separately examines first incidence of alcohol abuse and alcohol dependence in a large sample of healthy controls and persons with depressive/anxiety disorders. We will explicitly examine the role of status, severity, and type of depressive/anxiety disorders in predicting first incidence of alcohol abuse and alcohol dependence, and we will additionally take into account the role of other risk factors (ie, sociodemographic, vulnerability, and addiction-related factors).

METHOD

Study Sample

Data were derived from the Netherlands Study of Depression and Anxiety (NESDA),[21] 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. A total of 2,981 persons were included for the baseline assessment in 2004–2007, consisting of healthy controls (22%) and persons with depressive/anxiety disorders (78%). To represent various settings and stages of psychopathology, persons were recruited from the community (19%), primary care (54%), and outpatient mental

health care services (27%). Community-based participants had previously been identified in a population-based study; primary care participants were identified through a 3-stage screening procedure (involving the Kessler-10[22] and the short-form Composite International Diagnostic Interview [CIDI][23] by phone) conducted among a random sample of patients of 65 general practitioners; and mental health care participants were recruited consecutively when newly enrolled at 1 of the 17 participating mental health organization locations. Persons with insufficient command of the Dutch language were initially excluded from this sample. An additional exclusion criterion involved the presence of a primary clinical diagnosis of severe substance use disorder, bipolar disorder, obsessive-compulsive disorder, posttraumatic stress disorder, psychotic disorder, or organic psychiatric disorder that would need a specific intervention, such as a specialized addiction treatment strategy. Information about these disorders was provided by mental health practitioners or was based on self-report by the participants. A detailed description of the NESDA study design, sampling procedures, and initial response rates can be found elsewhere.[21] The research protocol was approved by the ethics committee of participating universities and all participants provided written informed consent.

The baseline assessment included a face-to-face appraisal of demographic and personal characteristics as well as a standardized diagnostic psychiatric interview. Face-to-face follow-up assessments, including the same standardized diagnostic interview, were conducted after 2-year follow-up (response: n = 2,596; 87.1%)[24] and 4-year follow-up (response: n = 2,402; 80.6%). For the present study, we selected persons with complete diagnostic interview data at the 2-year, 4-year, or both follow-up assessments (n = 2,676; 89.8%). Nonresponders were significantly less educated ($P < .001$) and more often had a current depressive/anxiety disorder ($P < .001$) compared to responders, whereas gender ($P = .75$), age ($P = .17$), remitted depressive/anxiety disorder ($P = .69$), and severity of alcohol problems ($P = .12$) were not associated with nonresponse. To examine first incidence of alcohol abuse during 4-year follow-up, we excluded all persons with a lifetime alcohol use disorder at baseline (n = 714) or with a first incidence of alcohol dependence during 4-year follow-up (n = 52), leaving a sample of 1,910 persons. In the analyses on first incidence of alcohol dependence, we excluded all persons with lifetime alcohol dependence at baseline (n = 405), leaving a sample of 2,271 persons.

Measures

Diagnostic assessment. Diagnoses of psychiatric disorders were established with the CIDI, version 2.1, which classifies diagnoses according to *DSM-IV* criteria. The CIDI is highly reliable and valid in assessing psychiatric disorders[23] and was administered by specially trained research staff. Lifetime diagnoses of depressive disorders (major depressive disorder and dysthymia), anxiety disorders (generalized anxiety disorder, social phobia, panic disorder, and agoraphobia), and alcohol use disorders (alcohol abuse and alcohol dependence) were established at the baseline interview, which included recency questions to determine when persons most recently experienced these psychiatric disorders. At the 2-year and 4-year follow-up assessments, diagnoses were established over the period since the last interview.

First incidence of alcohol abuse and alcohol dependence during 4-year follow-up. First incidence of alcohol abuse and alcohol dependence (primary outcome) was based on the presence of a CIDI diagnosis of alcohol abuse and alcohol dependence at the 2-year or 4-year follow-up assessment. Specific CIDI questions regarding the onset of psychiatric disorders were used to determine the time until first incidence of alcohol abuse or alcohol dependence (ie, years since the baseline assessment). The CIDI hierarchy criteria for diagnosing alcohol use disorders were based on the *DSM-IV* and excluded the possibility of a diagnosis of alcohol abuse when a lifetime diagnosis of alcohol dependence was present at the baseline, 2-year, or 4-year follow-up assessment.

Depressive/anxiety disorders at baseline. Various measures of baseline depressive/anxiety disorders were assessed. Status of depressive/anxiety disorders distinguished persons with no lifetime disorders as well as disorders that were present in the 6 months prior to the baseline interview (current disorder) and before this period of time (remitted disorder). We also assessed the severity of depressive/anxiety disorders, defined by the number of depressive and anxiety disorders present at baseline, a method that has been used previously by others.[25] To assess the robustness of these findings, we additionally examined the role of baseline severity of depressive symptoms (based on the 30-item self-report Inventory of Depressive Symptoms[26]) and anxiety symptoms (based on the 21-item self-report Beck Anxiety Inventory[27]) in predicting first incidence of alcohol use disorders. We also considered specific depressive/anxiety disorders by separately examining whether specific types of disorders predicted the first incidence of alcohol use disorders.

Other risk factors. An extensive set of potential risk factors for first incidence of alcohol abuse or alcohol dependence was a priori selected on the basis of previously reported associations with alcohol abuse or alcohol dependence.[4,6,11] Sociodemographic factors included gender, age (in years), education (in years), and partner status at baseline. Vulnerability factors consisted of family history, childhood trauma, recent negative life events, and personality. A positive family history of depressive/anxiety disorders and alcohol dependence was assessed separately by using the family tree

Clinical Points

- Patients with a current depressive/anxiety disorder have an increased risk of developing alcohol dependence compared to persons without a depressive/anxiety disorder.
- Subthreshold alcohol problems and recent negative life events are additional, independent risk factors for alcohol dependence.
- The first incidence of alcohol abuse is not related to the presence of depressive/anxiety disorders.

method,[28] which obtains information on the presence of psychiatric disorders among first-degree relatives (not including offspring). Consistent with a previous study,[29] a cumulative childhood trauma index was constructed based on the Childhood Trauma Inventory (available from L.B. upon request) that considered the frequency of emotional neglect, psychological abuse, physical abuse, and sexual abuse before the age of 16 years.

To determine the number of recent (ie, past-year) negative life events, we used the total count of the 12-item Brugha's List of Threatening Experiences.[30] Personality was assessed by using the Neuroticism-Extraversion-Openness Personality Inventory,[31] a 60-item instrument measuring 5 personality domains: neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness. Addiction-related factors included subthreshold alcohol problems, drug use, and smoking status. Severity of subthreshold alcohol problems was assessed with the 10-item Alcohol Use Disorder Identification Test (AUDIT),[32] developed by the World Health Organization. As an indication for addiction to substances other than alcohol, we obtained information about illicit drug use (ie, cannabis, ecstasy, speed, cocaine, heroin, or lysergic acid diethylamide [LSD]) in the past month as well as smoking status (ie, never smoked, former smoker, and current smoker).

Statistical Analyses

Analyses were conducted using SPSS version 15.0 statistical software (SPSS Inc, Chicago, Illinois). The first incidence of alcohol abuse and alcohol dependence, relative to either the number of persons at risk or the number of person-years at risk, was assessed. To examine whether baseline characteristics predicted the time to first incidence of alcohol abuse and alcohol dependence during 4-year follow-up, we used Cox regression analyses. So that associations could be compared across all continuous factors, hazard ratios (HRs) were expressed per standard deviation (SD) increase.

First, we examined whether groups based on the status of depressive/anxiety disorders (ie, no lifetime [= reference], remitted, and current disorder) differed in first incidence of alcohol use disorders. Then, we determined whether the severity of depressive/anxiety disorders, as indicated by the number of disorders as well as severity of depressive and anxiety symptoms, predicted first incidence of alcohol use disorders. Next, we examined whether the associations were conditional on the type of depressive/anxiety disorders by separately considering the effects for specific depressive/anxiety disorders. To determine whether predictive variance of specific depressive or anxiety disorders was unique versus redundant for the severity of depressive/anxiety disorders, we tested models in which each specific disorder was entered simultaneously with the number of disorders. Univariate Cox regression analyses were performed with baseline sociodemographic, vulnerability, and addiction-

Table 1. Sample Characteristics

Characteristic	Sample for Analyses on Alcohol Abuse (n = 1,910)	Sample for Analyses on Alcohol Dependence (n = 2,271)
Measures for depression and anxiety		
Status of depressive/anxiety disorder, n (%)		
No lifetime disorder	494 (25.9)	581 (25.6)
Remitted disorder	444 (23.2)	513 (22.6)
Current disorder	972 (50.9)	1,177 (51.8)
Severity of current depressive/anxiety disorders, mean (SD)		
No. of depressive/anxiety disorders	1.1 (1.4)	1.1 (1.4)
IDS score	19.7 (13.6)	19.9 (13.6)
BAI score	11.0 (10.1)	11.1 (10.1)
Type of current depressive/anxiety disorder, n (%)		
Major depressive disorder	623 (32.6)	753 (33.2)
Dysthymia	153 (8.0)	191 (8.4)
Generalized anxiety disorder	249 (13.0)	303 (13.3)
Social phobia	361 (18.9)	441 (19.4)
Panic disorder	370 (19.4)	450 (19.8)
Agoraphobia	351 (18.4)	417 (18.4)
Sociodemographics		
Male gender, n (%)	503 (26.3)	707 (31.1)
Age, mean (SD), y	42.4 (13.1)	42.1 (13.2)
Education, mean (SD), y	12.3 (3.2)	12.3 (3.3)
No partner, n (%)	553 (29.0)	665 (29.3)
Vulnerability factors		
Family history, n (%)		
Depressive/anxiety disorder	1,508 (79.0)	1,795 (79.0)
Alcohol dependence	411 (21.5)	485 (21.4)
Childhood trauma severity		
CTI score, mean (SD)	1.5 (2.0)	1.5 (2.0)
No. of recent negative life events		
List of Threatening Experiences score, mean (SD)	0.8 (1.0)	0.8 (1.0)
Neuroticism-Extraversion-Openness Personality Inventory score, mean (SD)		
Neuroticism	35.2 (9.3)	35.3 (9.3)
Extraversion	37.4 (7.2)	37.4 (7.2)
Openness to experience	31.1 (5.2)	31.2 (5.3)
Agreeableness	44.6 (5.0)	44.2 (5.1)
Conscientiousness	38.2 (5.9)	37.9 (6.0)
Addiction-related factors		
Severity of subthreshold alcohol problems		
AUDIT score, mean (SD)	3.5 (3.1)	4.0 (3.6)
Illicit drug use, n (%)	89 (4.7)	134 (5.9)
Smoking status, n (%)		
Never	654 (34.2)	726 (32.0)
Former	663 (34.7)	788 (34.7)
Current	593 (31.0)	757 (33.3)
First incidence of alcohol use disorders (outcome)		
Cumulative incidence alcohol abuse (relative to persons at risk), n (%)	39 (2.0)	…
Incidence rate alcohol abuse (relative to 1,000 person years at risk), n (%)	39 (5.4)	…
Cumulative incidence alcohol dependence (relative to persons at risk), n (%)	…	67 (3.0)
Incidence rate alcohol dependence (relative to 1,000 person years at risk), n (%)	…	67 (7.9)

Abbreviations: AUDIT = Alcohol Use Disorder Identification Test, BAI = Beck Anxiety Inventory, CTI = Childhood Trauma Inventory, IDS = Inventory of Depressive Symptoms.

Table 2. Risk of a First Incidence of Alcohol Abuse and Alcohol Dependence According to Measures for Depressive and Anxiety Disorders

	First Incidence of Alcohol Abuse Univariate[a]			First Incidence Alcohol Dependence Univariate[a]		
Baseline Predictor	HR	95% CI	*P*	HR	95% CI	*P*
Status of depressive/anxiety disorder						
No lifetime disorder		Reference			Reference	
Remitted disorder	0.42	0.16–1.07	.07	0.45	0.14–1.44	.18
Current disorder	0.55	0.28–1.09	.08	2.69	1.37–5.29	.004
Severity of current depressive/anxiety disorders						
No. of depressive/anxiety disorders[b]	0.99	0.72–1.36	.94	1.65	1.37–2.00	<.001
Severity of depressive symptoms[b]	1.16	0.86–1.57	.33	1.62	1.30–2.01	<.001
Severity of anxiety symptoms[b]	1.15	0.85–1.54	.63	1.49	1.23–1.80	<.001
Type of current depressive/anxiety disorder						
Major depressive disorder	1.31	0.69–2.50	.41	2.14	1.32–3.45	.002
Dysthymia	0.31	0.04–2.23	.24	2.96	1.64–5.34	<.001
Generalized anxiety disorder	1.49	0.66–3.37	.34	2.26	1.31–3.92	.004
Social phobia	0.78	0.33–1.86	.58	2.19	1.32–3.63	.002
Panic disorder	0.76	0.32–1.82	.54	2.30	1.40–3.79	.001
Agoraphobia	0.99	0.44–2.24	.98	2.55	1.55–4.20	<.001

[a]Based on univariable Cox regression analyses.
[b]Hazard ratio per SD increase.
Abbreviation: HR = hazard ratio.

related characteristics to explore whether these factors predicted first incidence of alcohol use disorders. Finally, all factors with a $P < .15$ in the univariate analyses were entered into a multivariate model to identify independent predictors of first incidence of alcohol use disorders.

RESULTS

First Incidence of Alcohol Abuse

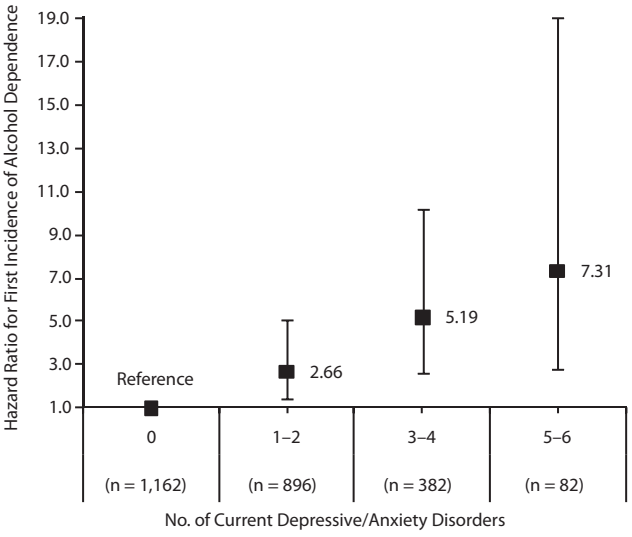
Table 1 shows the characteristics of the sample for the analyses on the first incidence of alcohol abuse (n = 1,910). The cumulative first incidence of alcohol abuse during 4-year follow-up was 2.0%, and the incidence was 5.4% per 1,000 person-years. Table 2 shows that none of the measures for depressive/anxiety disorders were significant predictors of first-incident alcohol abuse. Therefore, no further analyses on first incidence of alcohol abuse were conducted.

First Incidence of Alcohol Dependence

Table 1 shows the characteristics of the sample for the analyses on first incidence of alcohol dependence (n = 2,271). The cumulative first incidence of alcohol dependence during 4-year follow-up was 3.0%, and the incidence was 7.9% per 1,000 person-years.

Status of disorder. Persons with current (< 6 months) depressive/anxiety disorders, but not remitted disorders, had an increased risk of first incidence of alcohol dependence compared to persons with no lifetime depressive/anxiety disorder (see Table 2). Additional analyses showed that the incidence of alcohol dependence was increased only in persons with a recent depressive/anxiety disorder (ie, HR = 2.83 for < 1 month; HR = 2.03 for 1–6 months) but not for persons with disorders that were only present earlier in life (HR = 0.93 for 6–12 months; HR = 0.39 for > 12 months). As only current disorders were associated with the first incidence of alcohol dependence, further analyses only explored the role of severity and type of current depressive/anxiety disorders in predicting first incidence of alcohol dependence.

Figure 1. Risk of a First Incidence of Alcohol Dependence According to the Number of Current Depressive/Anxiety Disorders



Severity of disorder. The number of current depressive/anxiety disorders was a significant predictor of first incidence of alcohol dependence (HR per SD increase = 1.65; 95% CI, 1.37–2.00; $P < .001$; see Table 2), indicating that first-incidence rates gradually increased with the severity of depressive/anxiety disorders (Figure 1). Similar associations were observed for participants recruited from the community (HR per SD increase = 1.76; 95% CI, 0.99–3.12; $P = .05$), primary care (HR per SD increase = 1.66; 95% CI, 1.22–2.27; $P = .001$), and outpatient mental health organizations (HR per SD increase = 1.49; 95% CI, 1.04–2.12; $P = .03$). Sensitivity analyses supported our findings regarding the number of depressive/anxiety disorders, as

Table 3. Factors Predicting First Incidence of Alcohol Dependence

	First Incidence of Alcohol Dependence Univariate[a]			First Incidence of Alcohol Dependence Multivariate[b]		
Baseline Predictor	HR	95% CI	*P*	HR	95% CI	*P*
Measure for depressive/anxiety disorder						
No. of current depressive/anxiety disorders[c]	1.65	1.37–2.00	<.001	1.42	1.11–1.83	.006
Sociodemographics						
Male gender	2.17	1.35–3.51	.001	1.37	0.78–2.40	.28
Age[c]	0.96	0.76–1.22	.75	…	…	…
Education[c]	1.00	0.78–1.27	.97	…	…	…
No partner	1.18	0.71–1.97	.51	…	…	…
Vulnerability factors						
Family history						
Depressive/anxiety disorder (yes)	1.11	0.60–2.03	.74	…	…	…
Alcohol dependence (yes)	0.97	0.54–1.75	.92	…	…	…
Childhood trauma						
Severity of childhood trauma[c]	1.30	1.06–1.59	.01	1.17	0.93–1.47	.19
Life events						
No. of recent negative life events[c]	1.30	1.08–1.56	.006	1.20	0.99–1.44	.06
Personality						
Neuroticism[c]	1.77	1.37–2.29	<.001	1.30	0.91–1.87	.15
Extraversion[c]	0.84	0.66–1.07	.16	…	…	…
Openness to experience[c]	1.22	0.97–1.54	.09	1.08	0.87–1.35	.48
Agreeableness[c]	0.62	0.49–0.78	<.001	0.91	0.70–1.19	.51
Conscientiousness[c]	0.65	0.52–0.83	<.001	1.06	0.81–1.39	.66
Addiction-related factors						
Severity of subthreshold alcohol problems[c]	1.91	1.71–2.14	<.001	1.84	1.59–2.12	<.001
Illicit drug use (yes)	2.20	1.05–4.60	.04	0.89	0.40–1.99	.78
Smoking status						
Never		Reference			Reference	
Former	1.29	0.63–2.63	.49	0.99	0.48–2.05	.98
Current	2.73	1.45–5.14	.002	1.30	0.66–2.54	.45

[a]Based on univariate Cox regression analyses.
[b]Based on multivariate Cox regression analyses, including all variables that had a $P < .15$ in the univariate analyses.
[c]Hazard ratio per SD increase.
Abbreviation: HR = hazard ratio.

both severity of depressive symptoms (HR per SD increase in Inventory of Depressive Symptoms score = 1.62; 95% CI, 1.30–2.01; $P < .001$) and severity of anxiety symptoms (HR per SD increase in Beck Anxiety Inventory score = 1.49; 95% CI, 1.23–1.80; $P < .001$) significantly predicted first incidence of alcohol dependence.

Type of disorder. Next, we examined whether the association with first incidence of alcohol dependence was conditional on the type of current depressive/anxiety disorders by testing the specific disorders separately (see Table 2). All current depressive/anxiety disorders were significant predictors and had similar hazard ratios and large overlap in CIs. However, none of the specific disorders remained a significant predictor (eg, dysthymia [= strongest association]: HR = 1.33, [95% CI, 0.65–2.70], $P = .44$; panic disorder [= weakest association]: HR = 0.89, [95% CI, 0.45–1.76], $P = .73$; not tabulated) after adjustment for the number of depressive/anxiety disorders, indicating that the association with first incidence of alcohol dependence was conditional on the severity, but not the type, of disorders.

Independent risk factors. Finally, we examined the role of other potential risk factors in predicting the first incidence of alcohol dependence (Table 3). Univariate Cox regression analyses showed that male gender was the only sociodemographic factor that showed a significant association with the first incidence of alcohol dependence. In addition, severity of childhood trauma, number of recent negative life events, high neuroticism, low agreeableness, and low conscientiousness were significant vulnerability risk factors, whereas severity of subthreshold alcohol problems, illicit drug use, and current smoking were significant addiction-related risk factors. To determine whether the number of current depressive/anxiety disorders (as the most informative measure for depressive/anxiety disorders) and other factors independently predicted the first incidence of alcohol dependence, we used multivariate Cox regression analyses, including all characteristics that had a $P < .15$ in the univariate analyses. The number of current depressive/anxiety disorders and severity of subthreshold alcohol problems remained significant, which indicates that they are independent risk factors. The number of recent negative life events was borderline significant ($P = .06$).

DISCUSSION

Main Findings

To our knowledge, this is the first large study explicitly examining the role of status, type, and severity of depressive/anxiety disorders as risk factors for first incidence of alcohol abuse and alcohol dependence. Persons with a current, but not remitted, depressive/anxiety disorder had an almost 3-fold

increased risk of developing alcohol dependence during 4 years, compared to healthy controls. Although we found consistent associations across types of current depressive/anxiety disorders, first-incidence rates of alcohol dependence gradually increased with the severity of current disorders, even after taking into account the effects of other risk factors for alcohol dependence. Subthreshold alcohol problems, but also recent negative life events, especially appeared to be additional independent risk factors for first incidence of alcohol dependence. Depressive/anxiety disorders were not related to first incidence of alcohol abuse.

Characteristics of Depressive and Anxiety Disorders

Previous studies on first incidence of alcohol dependence reported on significant,[11] nonsignificant,[12,13] and mixed results[14–20] for depressive/anxiety disorders. Our study demonstrated that current depressive/anxiety disorders predicted first incidence of alcohol dependence, whereas remitted disorders did not. This combination of findings may partly explain the previous inconsistencies in the literature, as studies reporting on exclusively significant associations were based on current disorders,[11] whereas studies reporting on nonsignificant associations were based on lifetime disorders.[12,13] We additionally found that all types of depressive/anxiety disorders showed similar associations (ie, HRs ranging from 2.1 to 3.0) with the first incidence of alcohol dependence, which corresponds with associations observed in another large study considering the impact of several depressive and anxiety disorder (ie, ORs ranging from 1.9 to 2.7).[20] Our study further showed that the risk of first incidence of alcohol dependence increased with the severity of depressive/anxiety disorders but was not conditional on the type of disorder. This corroborates the findings of a recent cross-sectional study[25] in a large US community sample relating type and severity of depressive/anxiety disorders to the prevalence of alcohol dependence.

Models to Comorbidity

Our study demonstrated that only current depressive/anxiety disorders, but not remitted disorders, predicted the first incidence of alcohol dependence, supporting a causal model in which depressive/anxiety disorders induce the onset of alcohol dependence. A shared vulnerability model in which common risk factors independently cause the onset of depressive/anxiety disorders as well as alcohol dependence is less likely, as we did not find significant results for remitted depressive/anxiety disorders. This outcome is also supported by our finding that the severity of current depressive/anxiety disorders was an independent predictor of first incidence of alcohol dependence, even after taking into account the effects of other important risk factors for depressive/anxiety disorders and alcohol dependence. The "self-medication hypothesis"[33] might be an underlying mechanism, as it suggests that depressed persons, anxious persons, or both misuse alcohol to reduce their distressing symptoms and, therefore, have an increased risk of developing alcohol dependence. This is supported by previous studies showing that 10%–20% of depressed or anxious persons reported using alcohol to improve mood or reduce fears.[34,35] In addition, recent prospective studies demonstrated that self-medication predicted the first incidence of alcohol dependence in depressed[36] and anxious[37] patients. However, more prospective studies are needed to unravel the exact mechanisms underlying the onset of depressive/anxiety disorders as well as alcohol dependence. For example, our study showed that both depressive/anxiety disorders and subthreshold alcohol problems were independent risk factors of the first incidence of alcohol dependence, but we could not determine whether the onset of these alcohol problems preceded or followed the onset of depressive/anxiety disorders.

Clinical Implications

Of those persons with severe current depressive/anxiety disorders (ie, persons having 5 or 6 disorders), 9.0% developed a first incidence of alcohol dependence during follow-up. Prevention strategies for alcohol dependence could easily be implemented in this high-risk group, since a large proportion of depressed/anxious persons are under supervision of a health care professional in the Netherlands (ie, 63.8% and 40.5% for mood and anxiety disorders, respectively).[38] This approach has the potential to greatly improve health care, as only 17.5% of persons with alcohol use disorders receive any form of treatment.[38] Assessing subthreshold alcohol problems and recent negative life events may be helpful, as these factors demonstrated to be important risk factors for first incidence alcohol dependence. Time-efficient screening instruments such as the AUDIT[32] could be helpful in identifying depressed/anxious persons at an increased risk for developing alcohol dependence. The AUDIT has been shown to be accurate in detecting alcohol dependence in depressed or anxious persons.[39] This screening method has the potential to be highly effective as in our study, 66% of persons with first incidence of alcohol dependence during follow-up already had subthreshold alcohol problems at the baseline assessment (ie, AUDIT total score ≥ 9 for men and ≥ 6 for women). In addition, we showed that recent negative life events were independently linked to first incidence of alcohol dependence. This supports the findings of previous studies hypothesizing that persons turn to alcohol as a coping mechanism when their adaptive resources are challenged.[40] A clinician should, therefore, be alert when depressed or anxious patients, especially those with subthreshold alcohol problems, are faced with negative life events.

Alcohol Abuse Versus Alcohol Dependence

This study showed that depressive/anxiety disorders predicted first incidence of alcohol dependence but not first-incident alcohol abuse. A similar pattern of results was found in other studies reporting that alcohol dependence was more prevalent in depressed/anxious persons, whereas alcohol abuse was not.[1,4,6] In addition, alcohol dependence, in contrast to alcohol abuse, has a negative effect on the course of depressive/anxiety disorders.[7] Since others have

found that the reliability and validity were excellent for the diagnosis of alcohol dependence, but not for alcohol abuse,[41,42] the question arises as to whether alcohol abuse, as diagnosed by the current diagnostic criteria of *DSM-IV* (ie, hierarchical assessed based on 1 or more criteria), should be considered a genuine psychiatric disorder. Recent studies[43–46] have shown that the individual criteria of alcohol abuse and alcohol dependence are reliable and valid and represent a single latent dimension with alcohol abuse and alcohol dependence criteria interspersed across an underlying severity spectrum. Together, these findings have motivated the *DSM-5* Work Group to propose 1 diagnosis of an alcohol use disorder that is based on alcohol abuse as well as alcohol dependence criteria.

Strengths and Limitations

Our study has both strengths and limitations. One methodological strength is that we prospectively examined whether different measures of *DSM-IV* depressive/anxiety disorders predicted first incidence of alcohol abuse and alcohol dependence during a 4-year follow-up. In addition, we used a very large sample (n = 2,676), including healthy controls as well as persons with current or remitted depressive/anxiety disorders. Consequently, the sample was much larger than some of the previous studies on this topic.[11–14,16,17] Despite the large sample size, a limitation of our study is the small number of persons with first incidence of alcohol dependence (n = 67) and, especially, first incidence of alcohol abuse (n = 39). This may be a consequence of our sample consisting of adults with a mean age of 42 years, since alcohol use disorders, especially in persons with a genetic vulnerability, typically develop at an earlier stage in life (ie, 15–30 years).[4,47] In our study, first incidence of alcohol use disorders should, therefore, be mainly considered as late-onset alcohol use disorders and may differ from alcohol use disorders that develop earlier in life. Moreover, risk factors for late-onset alcohol use disorders may be different from risk factors for alcohol use disorders with an early onset. This possibility may also explain our finding that a positive family history of alcohol dependence was not related to first-incident alcohol dependence, whereas our group previously showed a strong cross-sectional association.[6] Future studies including both younger and older participants are necessary to determine whether etiologic pathways for the development of early- versus late-onset alcohol use disorders indeed differ. In addition, our study focuses on primary depressive/anxiety disorders and, consequently, excluded persons with other clinical disorders (eg, substance use disorder, bipolar disorder, and posttraumatic stress disorder). Our sample may therefore be not fully representative for all depressed/anxious persons, and reported associations between depressive/anxiety disorders and the first incidence of alcohol dependence may be underestimates, as previous studies have shown that these disorders are strongly related to alcohol dependence.[16,48] More research is needed to explore the role of these and other disorders (eg, conduct disorder and antisocial personality disorder) in the association between depressive/anxiety disorders and first incidence of alcohol dependence.

CONCLUSION

In conclusion, severity of current depressive and anxiety disorders strongly predicts first incidence of alcohol dependence, but not alcohol abuse, even after taking into account other important risk factors. Subthreshold alcohol problems and recent negative life events were additional independent predictors of first incidence of alcohol dependence. These findings stress the importance of addiction prevention strategies for depressed or anxious patients in mental health services, especially in those persons with subthreshold alcohol problems who are faced with stressful life events.

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