Primary anxiety disorders and the development of subsequent alcohol use disorders: a 4-year community study of adolescents and young adults

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ABSTRACT

Background. Cross-sectional findings in community surveys of adults suggest that adolescent anxiety disorders are strong predictors of the subsequent onset of alcohol use, abuse and dependence. However, prospective data that follow a sample of adolescents into adulthood are needed to confirm these associations.

Method. Baseline and 4-year follow-up data from the EDSP-Study, a prospective community survey of 3021 (2548 at follow-up) adolescents and young adults aged 14 to 24 years at baseline carried out in Munich, were used. DSM-IV anxiety disorders, alcohol use and alcohol use disorders were assessed with the Munich-Composite-International-Diagnostic-Interview (M-CIDI). Multiple logistic regression analysis, controlling for age, gender, other mental disorders, substance use disorders and antisocial behaviour was used to study the associations of baseline anxiety disorders with the subsequent onset and course of alcohol use and alcohol disorders.

Results. Baseline social phobia significantly predicts the onsets of regular use and hazardous use and the persistence of dependence. Panic attacks significantly predict the onsets of hazardous use and abuse as well as the persistence of combined abuse/dependence. Panic disorder significantly predicts the persistence of combined abuse/dependence. Other anxiety disorders do not significantly predict any of the outcomes.

Conclusions. Panic and social phobia are predictors of subsequent alcohol problems among adolescents and young adults. Further studies are needed to investigate the underlying mechanisms and the potential value of targeted early treatment of primary panic and social phobia to prevent secondary alcohol use disorders.

INTRODUCTION

Many clinical and epidemiological studies have documented significant cross-sectional relationships between anxiety disorders and alcohol use disorders (Kushner et al. 1990; Regier et al. 1990; Himle & Hill, 1991; Schneier et al. 1992; Allan, 1995; Wittchen et al. 1996; Kessler et al. 1997; Swendsen et al. 1998; Kushner et al. 2000).

Meaning and implication of these associations remain controversial. Discussed mechanisms are: (a) that anxiety disorder provokes alcohol use disorder; (b) alcohol use disorder causes anxiety disorder; and (c) a third shared factor promotes both conditions (Schuckit & Hesselbrock, 1994; Kushner et al. 2000). Analysis of retrospective age-of-onset reports suggests that the anxiety disorders often start at an earlier age than the alcohol disorders (Stockwell et al. 1984; Weiss & Rosenberg, 1985; Wittchen et al. 1991; Magee et al. 1996; Merikangas et al. 1995).
Survival analyses based on these retrospective reports suggest that early anxiety disorders are predictors of the subsequent onset and course of alcohol disorders (Warner et al. 1995; Kessler & Wittchen, 2000; Kessler et al. 2003). It is not clear, however, whether these associations would be confirmed in prospective studies, as the associations in the retrospective studies could be due to systematic recall bias. This is a question of some importance, as the documentation of strong prospective associations would raise the question whether early treatment of primary anxiety disorders might be effective in preventing the onset of secondary alcohol use disorders.

The results of prospective studies of anxiety predicting later alcohol outcomes have been mixed. The vast majority of these studies used dimensional scales of trait anxiety rather than diagnostic assessments of anxiety disorders as the baseline measures (Kammeier et al. 1973; Ensminger et al. 1982; Hagnell et al. 1986; Caspi et al. 1996; Vaillant, 1996; Holahan et al. 2001; Kaplow et al. 2001; Poikolainen et al. 2001; Wennberg et al. 2002). Although most of these studies found that baseline anxiety is significantly associated with elevated levels of subsequent alcohol use, others did not. One reason for this inconsistency might be that different anxiety disorders have different effects on alcohol outcomes (Kushner et al. 1990; Clark & Sayette, 1992; Page & Andrews, 1996). For example, Kaplow et al. (2001) found that a baseline dimensional measure of generalized anxiety was a positive significant predictor of initiation of alcohol use in a 4-year follow-up study of 936 children who were 9, 11, or 13 at baseline, while baseline symptoms of separation anxiety were negative significant predictors of the same outcome.

Two prospective studies have assessed baseline anxiety using diagnostic interviews. Kushner et al. (1999) assessed 454 college students for broadly defined DSM-III anxiety disorders and alcohol use disorders and followed these students 3 and 6 years later to evaluate changes in the same outcomes. Baseline anxiety disorders measured globally (i.e. without distinguishing among the different anxiety disorders) significantly predicted elevated risk of subsequent first-onset alcohol disorders at the follow-ups. Crum & Pratt (2001) evaluated the effects of baseline social phobia on first onset of heavy alcohol use and alcohol use disorders over a 13-year follow-up period among the 1161 adults in the Baltimore ECA follow-up sample. Baseline social phobia did not predict these outcomes, although baseline subclinical social phobia was associated with elevated risk of the onset of all the outcomes.

Neither the Kushner et al. (1999) nor the Crum & Pratt (2001) studies attempted to disaggregate the effects of multiple anxiety disorders to investigate the existence of specificities like those found by Kaplow et al. (2001) and others (Merikangas et al. 1998b). Crum & Pratt (2001) had the added problem of studying respondents in an unrestricted age range even though the retrospective epidemiological data show that the elevated risk of alcohol disorders among people with primary anxiety disorders is limited to adolescence and early adulthood (Christie et al. 1988; Holly & Wittchen, 1998). The current investigation was designed to overcome these limitations by carrying out a disaggregated analysis of the separate effects of individual anxiety disorders in predicting the onset and persistence of alcohol use and alcohol use disorders in a large community epidemiological survey of adolescents and young adults who were assessed at baseline and then reassessed over a 4-year follow-up period.

METHOD
Sample
Data come from the Early Developmental Stages of Psychopathology study (EDSP), a prospective survey of the onset, persistence, and correlates of DSM-IV mental disorders in a representative sample of adolescents and young adults in Munich, Germany. The EDSP consists of a baseline survey and two follow-up surveys. The baseline sample was drawn randomly from the 1994 government registries of all residents in the age range 14–24 in metropolitan Munich and the surrounding counties. As the study was designed as a longitudinal panel with special interest in early developmental stages of psychopathology, 14–15-year-olds were sampled at twice the probability of people 16–21 years of age and 22–24-year-olds were sampled at half the probability of the 16–21-year-olds. Details
about the sampling procedures are presented elsewhere (Wittchen et al. 1998b; Lieb et al. 2000). A total of 3021 respondents were interviewed at baseline (T0) with a response rate of 71%. The first follow-up study (T1) was conducted only for subjects aged 14–17 at baseline, whereas the second follow-up study (T2) was conducted for all subjects. In the first follow-up, an average of 20 months after baseline, a total of 1228 interviews were completed (response rate: 88%). From the 3021 subjects of the baseline study, a total of 2548 interviews were completed at the second follow-up, which was conducted an average of 42 months after baseline (response rate: 84%). Most frequent reasons for non-response at baseline as well as at the second follow-up were refusal (18.2% and 9.2%, respectively), lack of time (3.3% and 1.5%), and failure to contact (3.1% and 2.7%). Respondents who responded in both the baseline (T0) and the T2 reinterview are the focus of the current report. There was no selective attrition due to age, gender, or geographic distribution, anxiety disorders and alcohol outcomes between the baseline and second follow-up investigation. A more detailed discussion of EDSP sample design and field procedures is reported elsewhere (Lieb et al. 2000).

Diagnostic assessment

The diagnostic assessment was based on the computer-assisted version of the Munich-Composite-International-Diagnostic-Interview (DIA-X/M-CIDI) (Wittchen & Pfister, 1997), an updated version of the World Health Organization’s CIDI version 1.2 (WHO, 1990, 1992). The M-CIDI allows for the standardized assessment of symptoms, syndromes and diagnoses of a wide range of DSM-IV disorders along with information about onset, duration and severity (APA, 1994). The M-CIDI has good reliability and validity for all the disorders considered here (Lachner et al. 1998; Reed et al. 1998; Wittchen et al. 1998a). Interviews were administered by highly trained clinical interviewers, most of whom were clinical psychologists. Interviews were carried out face-to-face and mostly in the homes of respondents. At baseline, the M-CIDI was used to assess lifetime and 12-month disorders. The two follow-up surveys administered a modified version of the M-CIDI that covered only the time interval since the last interview.

DSM-IV anxiety disorders assessed in the baseline survey include panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, social phobia, specific phobia, phobia not otherwise specified (phobia NOS) and generalized anxiety disorder (GAD). In addition, results for the DSM-IV-anxiety syndrome panic attack are presented.

DSM-IV alcohol use disorders include alcohol abuse without dependence and alcohol dependence with or without alcohol abuse. As described in more detail elsewhere (Holly & Wittchen, 1998; Lachner et al. 1998; Nelson & Wittchen, 1998) lifetime and 12-month alcohol use status was defined according to four commonly used quantity-frequency categories (Babor et al. 1989; Saunders et al. 1993): (A) ‘Hazardous use’ was defined as an average use of more than 40 g/day (men) or 20 g/day (women) of ethanol in the period of peak lifetime use; (B) ‘Regular use’ was defined as using at least three times a week in the period of peak lifetime use but never meeting criteria specified for ‘hazardous’ use; (C) ‘Occasional use’ was defined as using >12 times a year but <3 times a week in the peak period; (D) ‘No/seldom use’ was defined as either abstinent or use that did not qualify for occasional or higher use categories. The alcohol measures used in the baseline analyses are respondents’ highest lifetime consumption status, lifetime alcohol abuse, lifetime alcohol dependence, and comparable 12-month outcomes. The alcohol measures used in prospective analyses are respondents’ highest consumption status, incident alcohol abuse and dependence during the follow-up period between baseline and the second follow-up wave. For the 14- to 17-year-olds at baseline, the follow-up status is assessed from the aggregation of information obtained from the first and second follow-up interviews. For respondents older than 17 years at baseline, information on the total follow-up-period stems from the second follow-up interview.

Additional baseline disorders that were assessed according to DSM-IV and used as controls in the current analyses include major depressive disorder, dysthymia, bipolar disorder, and illegal substance use disorders. Lifetime antisocial behaviour according to the criteria of DSM-IV antisocial personality disorder was also used as a control variable. It was only...
assessed at second follow-up by means of a self-constructed questionnaire based on the German version of the SKID-II questionnaire and interview concerning antisocial personality disorder (Fydrich et al. 1997). All control variables were selected on the basis of an extensive literature review, where confounding issues of these variables with regard to the association between anxiety and alcohol use disorders are discussed (Schuckit & Hesselbrock, 1994; Merikangas et al. 1998b; Kushner et al. 2000).

Statistical analyses
Baseline associations of lifetime anxiety disorders with lifetime alcohol use and alcohol use disorders were estimated in terms of odds ratios (OR) based on logistic regressions controlling for age and gender. Prospective analyses also used logistic regression to study the associations of baseline anxiety disorders in predicting the onset of regular use, hazardous use and alcohol use disorders in the subsamples of baseline respondents who had never met criteria for these outcomes. Separate logistic regression analyses were used to study the associations of baseline anxiety disorders in predicting the persistence of alcohol use disorders in the subsample of respondents with a history of these disorders at baseline.

The outcomes in the prospective analyses were defined as the highest outcome measures between baseline and the 4-year follow-up period. Cases with alcohol dependence at baseline with partial remission during follow-up were classified as having persistent dependence. The baseline anxiety disorders used in the initial analyses were lifetime disorders as of T0. The effects of the significant anxiety disorders were subsequently disaggregated into the separate estimated effects associated with disorders that were active as of T0 (present in the 12 months before T0) and those that were in remission as of T0 (not existing in the 12 months before T0 among respondents with a lifetime history of the particular anxiety disorder). All prediction equations included controls for age, gender, other anxiety disorders, major depression, dysthymia, bipolar disorders, illegal substance use disorders and antisocial behaviour. In analyses of the predictors of regular and hazardous use, extent of alcohol use at baseline was also controlled. This procedure was done because all variables might be related to anxiety disorders as well as to the alcohol outcomes. Additionally, the effects of the seven anxiety disorders, as a set, were evaluated globally by Wald chi-squared tests based on the concerning logistic regression equation. Differences between active and remitted anxiety were also tested by Wald chi-squared tests for differences in the magnitudes of pairs of coefficients. Based on evidence that the associations of negative affect with adolescent alcohol use might differ by gender (Deykin et al. 1987; Henry et al. 1993; Clark et al. 1997), interactions of all predictors were computed with gender.

The data were weighted to adjust for differential probabilities of selection by age and for differential response rates based on the census population distribution of the cross-classification of age, gender and geographic distribution at baseline (Wittchen et al. 1998b). Drop-out between baseline and follow-up was not markedly related to sex, gender and mental disorders at baseline. All statistical analyses were carried out with the STATA (StataCorp., 2001) software package. The Huber–White sandwich method for weighted data was used to adjust significance tests for the weighting of the data (Royall, 1986). Statistical significance was evaluated using 0.05-level two-sided tests.

RESULTS
Prevalences and incidences
Ten per cent of respondents reported lifetime regular alcohol use and 8.4% reported a lifetime history of hazardous alcohol use at baseline (Table 1). In the past 12 months, 9.2% reported regular alcohol use, while 3.9% reported hazardous use. Lifetime and 12-month prevalences of alcohol use disorders (see Table 1, 15.9% and 10.1%, respectively) are higher than the prevalences of hazardous use, with higher prevalences of abuse without dependence (9.7% lifetime, 5.3% 12-month) than of alcohol dependence (6.2% lifetime, 4.7% 12-month).

The baseline prevalences of having one or more anxiety disorders (see Table 1, 26.9% lifetime, 18.2% 12-month) are considerably higher than the prevalences of baseline alcohol use disorders. There is wide variation in the prevalences of individual baseline anxiety disorders, from a high of 16.2% lifetime and
10.9% 12-month prevalences of specific phobia to a low of 1.6% lifetime and 1.2% prevalences of panic disorder with or without agoraphobia.

First lifetime onset of hazardous use over the follow-up period (see Table 2) was reported by 6.9% of T2 respondents who had no history of hazardous use at T0. Between T0 and T2, 36.7% of baseline hazardous users persisted in their hazardous use. First onset of alcohol abuse over the follow-up period was reported by 11.9% of the T2 respondents who had no history of abuse or dependence as of baseline (Table 2). First onset of alcohol dependence over the follow-up period was reported by 3.5% of the T2 respondents who had no history of dependence as of baseline. Those who met criteria for dependence at the time of the baseline interview, 25.2% of T0 abusers and 70.1% of T0 respondents, persisted in their abuse and dependence, respectively, between T0 and T2.

**Alcohol–anxiety associations at baseline**

All baseline anxiety disorders except for phobia NOS have positive cross-sectional associations
with all the baseline alcohol outcomes (Table 3). Approximately half of the ORs are statistically significant at the 0.05 level, using two-sided tests. ORs are somewhat higher for dependence than for any of the other alcohol measures. The number of significant ORs progresses sequentially from a low of two for regular use and abuse to four for hazardous use and five for dependence. None of the 35 cross-sectional ORs varies significantly with sex.

**Associations between baseline anxiety and the subsequent onset of alcohol outcomes**

The seven lifetime anxiety disorders assessed at baseline, taken as a set, significantly predict the onset of hazardous use ($\chi^2 = 15.07; P = 0.035$) and abuse ($\chi^2 = 14.26; P = 0.047$) and have marginally significant associations with the onset of any alcohol use disorder over the follow-up period ($\chi^2 = 13.64; P = 0.058$) (Table 4). The anxiety disorders are not significant predictors, in comparison, of the onset of regular use or dependence. Four of the 35 ORs in Table 4 are significant. Two of these four involve panic attacks and the other two involve social phobia. All four of these significant ORs are $> 1.0$, indicating that panic attacks and social phobia are associated with an elevated risk of the subsequent onset of the alcohol outcomes.

It is noteworthy that the panic attack ORs are consistently elevated in predicting all the alcohol onset outcomes (1.4–2.7), while the ORs associated with panic disorder are also elevated in predicting four of the five outcomes (1.1–3.7), the exception being regular use. There is no difference between the ORs associated with panic attacks and panic disorder in any of the five equations (with $P$ values in the range 0.109–0.888 using two-sided tests). The social phobia ORs, in comparison, are elevated only in predicting regular use (1.9) and hazardous use (2.1). The sign pattern of the ORs for the remaining four anxiety disorders is statistically random (ten were $> 1.0$, nine were $< 1.0$, and one was equal to 1.0). No differences in any associations were found for gender.

**Associations between baseline anxiety and persistence of alcohol outcomes**

As shown in Table 5, the seven lifetime anxiety disorders assessed at baseline, taken as a set, significantly predict the persistence of any alcohol disorder ($\chi^2 = 25.53; P = 0.001$) and are marginally significant predictors of the persistence of alcohol dependence ($\chi^2 = 12.77; P = 0.078$). The anxiety disorders are not significant predictors, in comparison, of the persistence of regular use, hazardous use, or abuse. In saying that the anxiety disorders do not significantly predict the persistence of these three outcomes, it needs to be noted that the small number of cases involved in the analyses and the skew of

<table>
<thead>
<tr>
<th>Alcohol use</th>
<th>Alcohol use disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least regular use$^\dagger$</td>
<td>Hazardous use$^\ddagger$</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Panic disorder w or w/o agoraphobia</td>
<td>2.1 (0.8–5.3)</td>
</tr>
<tr>
<td>Panic attack</td>
<td>4.2* (2.2–7.7)</td>
</tr>
<tr>
<td>Agoraphobia w/o panic disorder</td>
<td>2.2* (1.0–4.8)</td>
</tr>
<tr>
<td>Social phobia</td>
<td>1.4 (0.9–2.2)</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>1.2 (0.8–1.7)</td>
</tr>
<tr>
<td>Phobia (not otherwise specified)</td>
<td>1.2 (0.6–2.2)</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>1.4 (0.7–2.7)</td>
</tr>
</tbody>
</table>

OR, Odds ratio adjusted for age and gender.

† Reference group for a particular anxiety disorder, without this particular anxiety disorder; reference group for panic attack, without panic attack.

‡ Reference group, no/occasional use.

§ Reference group, not more than regular use.

|| Reference group, no alcohol use disorder.

* Reference group, no dependence.

* $P < 0.05$. 

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Table 3. **Baseline associations (odds ratios) of lifetime DSM-IV Anxiety Disorders with lifetime alcohol use and DSM-IV Alcohol Use Disorders (N = 3021)†**

<table>
<thead>
<tr>
<th>Anxiety Disorder</th>
<th>At least regular use$^\dagger$</th>
<th>Hazardous use$^\ddagger$</th>
<th>Abuse$^|$</th>
<th>Dependence$^|$</th>
<th>Any alcohol use disorder$^|$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panic disorder w or w/o agoraphobia</td>
<td>2.1 (0.8–5.3)</td>
<td>1.7 (0.4–6.1)</td>
<td>1.9 (0.5–6.1)</td>
<td>7.1* (2.4–20.5)</td>
<td>4.1* (1.6–10.1)</td>
</tr>
<tr>
<td>Panic attack</td>
<td>4.2* (2.2–7.7)</td>
<td>3.5* (1.7–6.9)</td>
<td>2.6* (1.2–5.5)</td>
<td>6.2* (3.0–12.6)</td>
<td>4.4* (2.4–8.0)</td>
</tr>
<tr>
<td>Agoraphobia w/o panic disorder</td>
<td>2.2* (1.0–4.8)</td>
<td>5.0* (2.3–10.9)</td>
<td>2.2 (0.9–5.1)</td>
<td>5.0* (1.9–12.8)</td>
<td>3.3* (1.6–6.7)</td>
</tr>
<tr>
<td>Social phobia</td>
<td>1.4 (0.9–2.2)</td>
<td>1.5 (0.8–2.6)</td>
<td>1.2 (0.6–2.2)</td>
<td>2.0* (1.1–3.5)</td>
<td>1.5 (0.9–2.4)</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>1.2 (0.8–1.7)</td>
<td>1.9* (1.3–2.9)</td>
<td>1.6* (1.1–2.4)</td>
<td>2.5* (1.6–3.8)</td>
<td>2.0* (1.4–2.8)</td>
</tr>
<tr>
<td>Phobia (not otherwise specified)</td>
<td>1.2 (0.6–2.2)</td>
<td>1.4 (0.6–2.9)</td>
<td>1.0 (0.4–2.1)</td>
<td>1.6 (0.7–3.5)</td>
<td>1.2 (0.7–2.1)</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>1.4 (0.7–2.7)</td>
<td>2.2* (1.1–4.4)</td>
<td>1.7 (0.7–3.6)</td>
<td>1.6 (0.6–4.0)</td>
<td>1.8 (0.9–3.5)</td>
</tr>
</tbody>
</table>

OR, Odds ratio adjusted for age and gender.

† Reference group for a particular anxiety disorder, without this particular anxiety disorder; reference group for panic attack, without panic attack.

‡ Reference group, no/occasional use.

§ Reference group, not more than regular use.

|| Reference group, no alcohol use disorder.

* Reference group, no dependence.

* $P < 0.05$. 

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P. Zimmermann and others


Table 4. Associations (odds ratios) between baseline lifetime DSM-IV Anxiety Disorders and onset/progression of lifetime alcohol use or DSM-IV Alcohol Use Disorders at follow-up†

<table>
<thead>
<tr>
<th>Anxiety Disorder</th>
<th>Alcohol use</th>
<th>Alcohol use disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Panic disorder w/o agoraphobia</td>
<td>0.6 (0.1–1.9)</td>
<td>1.1 (0.3–3.6)</td>
</tr>
<tr>
<td>Panic attack</td>
<td>1.8 (0.7–4.4)</td>
<td>2.5* (1.1–5.8)</td>
</tr>
<tr>
<td>Agoraphobia w/o panic disorder</td>
<td>0.6 (0.1–1.9)</td>
<td>1.9 (0.6–5.3)</td>
</tr>
<tr>
<td>Social phobia</td>
<td>1.9* (1.0–3.4)</td>
<td>2.1* (1.2–3.8)</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>0.8 (0.5–1.3)</td>
<td>0.9 (0.5–1.4)</td>
</tr>
<tr>
<td>Phobia (not otherwise specified)</td>
<td>0.7 (0.3–1.4)</td>
<td>1.3 (0.6–2.5)</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>1.5 (0.6–3.4)</td>
<td>1.4 (0.5–3.2)</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>$\chi^2_1=10.59$</td>
<td>$\chi^2_1=15.07^*$</td>
</tr>
</tbody>
</table>

* P < 0.05.

Table 5. Associations (odds ratios) between baseline lifetime DSM-IV Anxiety Disorders and persistence of lifetime alcohol use or DSM-IV Alcohol Use Disorders at follow-up‡

<table>
<thead>
<tr>
<th>Anxiety Disorder</th>
<th>Alcohol use</th>
<th>Alcohol use disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Panic disorder w/o agoraphobia</td>
<td>7.8 (0.7–83.34)</td>
<td>11.0 (0.9–123.3)</td>
</tr>
<tr>
<td>Panic attack</td>
<td>1.2 (0.3–4.0)</td>
<td>0.4 (0.0–4.0)</td>
</tr>
<tr>
<td>Agoraphobia w/o panic disorder</td>
<td>0.5 (0.0–3.0)</td>
<td>0.4 (0.0–3.0)</td>
</tr>
<tr>
<td>Social phobia</td>
<td>1.7 (0.6–4.5)</td>
<td>1.5 (0.3–6.0)</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>0.7 (0.2–3.1)</td>
<td>0.5 (0.1–1.4)</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>1.3 (0.4–4.4)</td>
<td>1.6 (0.2–10.1)</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>$\chi^2_1=5.50$</td>
<td>$\chi^2_1=9.15$</td>
</tr>
</tbody>
</table>

‡ P < 0.05.
the outcomes reduce statistical power to detect substantively significant effects. Consistent with this observation, a number of large ORs can be seen in Table 5 that are not statistically significant.

Three of the 35 odds-ratios in Table 5 are significant at the 0.05 level using two-sided tests. One of these involves panic attacks, one panic disorder, and one social phobia. As in Table 4, there is no difference between the ORs associated with panic attacks and panic disorder in any of the five equations (with $P$ values in the range 0.075–0.772). Also consistent with Table 4 is the fact that all three statistically significant ORs are $>1.0$, indicating that panic attacks, panic disorder and social phobia are associated with a elevated risk of the subsequent persistence of the alcohol outcomes. Nine of the ten panic ORs are elevated in predicting the five outcomes (1.2–22.7), the exceptions being panic attacks in predicting the persistence of at least harmful use. Four of the five social phobia ORs are elevated (1.5–19.7), the exception being panic attacks in predicting the persistence of at least harmful use. Four of the five social phobia ORs are elevated (1.5–19.7), the exception being the association between baseline social phobia and the persistence of alcohol use disorders (0.4). The sign pattern of the ORs for the remaining four anxiety disorders is largely negative (12 were $<1.0$ and seven $>1.0$). The examination of interaction with gender of proband revealed only one effect: among probands with phobia NOS, risk for persistence of at least regular use of alcohol was significantly reduced in women but not in men (OR for interaction $=0.0$; 95% CI $=0.0$–0.2; OR for women $=0.0$; 95% CI $=0.0$–0.6; OR for men $=5.1$; 95% CI $=0.8$–30.4).

The differential effects of active and remitted anxiety disorders

Replications of the results in Tables 4 and 5 were carried out that distinguished between cases of lifetime (as of T0) panic and social phobia that were active at the time of the baseline interview and those that were in remission at the time of the baseline interview. (Results not shown, but available on request.) The number of cases was too small to estimate stable coefficients to predict persistence (cell sizes ranged between $N=0$ and $N=29$). However, it was possible to disaggregate the significant effects of panic in predicting the onsets of hazardous use and abuse into components due to active and remitted panic. It was also possible to disaggregate the significant effects of social phobia in predicting the onsets of regular use and hazardous use into components due to active and remitted social phobia. In all of these cases, remitted panic and social phobia were found to be as important as active panic and social phobia in predicting the subsequent alcohol outcomes. For example, the OR of T0 remitted panic attack in predicting the subsequent onset of any alcohol use disorder (i.e. either abuse or dependence) was 2.3 compared to an OR of 1.8 associated with T0 active panic attack. None of the tests comparing the ORs between active and remitted disorders was significant ($\chi^2 = 0.03–2.86, P = 0.091–0.859$). These results suggest that a history of panic and social phobia is the important factor in these predictions rather than the current presence of these disorders at baseline.

**DISCUSSION**

Consistent with numerous previous reports based on cross-sectional data (George et al. 1990; Regier et al. 1990; Himle & Hill, 1991; Kushner & Sher, 1993; Allan, 1995; Kessler et al. 1997; Kushner et al. 2000), significant cross-sectional associations exist between anxiety disorders and alcohol use disorders in the EDSP data. Analysis of the prospective EDSP data, furthermore, document that anxiety disorders are significant predictors of the subsequent onset and persistence of regular and hazardous alcohol use and alcohol use disorders. Panic and social phobia are the only anxiety disorders involved in these predictive associations. As the prospective associations with onset and persistence were carried out in separate subsamples, the effects of panic and social phobia on both sets of outcomes can be seen as an affirmation of the importance of these two anxiety disorders for the development of alcohol problems. It is important to note that these results were obtained in models that controlled for the confounding effects of other anxiety disorders, mood disorders, illegal drug use disorders, antisocial behaviour and demographic variables.

It is not clear what the processes are that create these associations. One possibility is that anxiety disorders are causes of subsequent alcohol use disorders. The most commonly
discussed causal processes of this type are that people with anxiety disorders use alcohol to self-medicate their anxiety (Quittin et al. 1972; Cox et al. 1990; Cowley, 1992; Brady & Lydiard, 1993) or to reduce tension associated with their anxiety (Conger, 1956; Cappel & Herrman, 1972; Levenson et al. 1980; Sayette, 1999) and that these processes lead to hazardous use and alcohol use disorders. Consistent with these possibilities, a high proportion of people with anxiety disorders in community surveys report that they have consciously used alcohol or other substances to manage their anxiety (Kessler et al. 2001). However, if these causal processes are at work, we would expect that active panic and social phobia would be more important than remitted panic and social phobia in predicting alcohol outcomes. We did not find this to be the case in the EDSP. This observation is more consistent with a second interpretation of the results: that unmeasured third variables cause both anxiety disorders and subsequent alcohol use disorders (Maier et al. 1993; Merikangas et al. 1996, 1998). A number of common causes have also been suggested (Clark & Sayette, 1992; Kendler et al. 1995; Merikangas et al. 1996; Kushner et al. 2000; Holahan et al. 2001). The results of family aggregation studies reported by Merikangas et al. (1998b) are consistent with the self-medication hypothesis being a more plausible explanation in the case of social phobia and shared etiology more plausible in the case of panic disorder. Note, that our results are not contrary to the possibility that alcohol use disorders can also be risk factors for subsequent anxiety disorders. To clarify this, separate prospective analyses for testing the effect of primary alcohol use disorder on the onset and persistence of subsequent anxiety disorders are needed (e.g. Kushner et al. 1999).

Although in our sample anxiety disorders are more prevalent in young women than in men and alcohol consumption and alcohol use disorders are more prevalent in young men than in women (Holly & Wittchen, 1998; Wittchen et al. 1998c), no evidence of consistently significant gender differences was found in our analyses concerning the associations between anxiety disorders and alcohol outcomes. Kaplow and colleagues (2001), in the only other prospective study of adolescents to examine gender differences, also failed to find evidence of gender differences in the associations between baseline anxiety and alcohol outcomes in young adulthood. This finding is superficially inconsistent with the repeated finding in adult cross-sectional epidemiological surveys that the co-morbidity of anxiety disorders with alcoholism is far more common among women than men (Cooper et al. 1992; Merikangas et al. 1996, 1998b). However, the latter finding does not adjust for the fact that anxiety disorders are significantly more common among women than men. When this adjustment is made and the focus is on relative odds rather than on prevalences, the evidence of a gender difference in the associations between anxiety disorders and substance disorders among adults becomes less strong (Kessler, 1997). It is nonetheless possible that gender differences in these associations become larger with age, a possibility that cannot be evaluated in the EDSP data due to the truncated upper age range of the sample.

Interpreting our results we have to consider that legal access to alcoholic beverages in Germany begins at age 16 and is accompanied by a relatively widespread acceptance of alcohol use at this age. In accordance with this, we found high rates of regular use and hazardous use among the 14- to 24-year-olds. Despite its legal prohibition already 26% of the 14- to 15-year-olds in Germany consumed alcohol 1 to 2 times a week (Holly & Wittchen, 1998). This is in contrast, for example, to the United States, where the legal age for purchasing alcoholic beverages is 21 years and sales to under-age consumers are significantly sanctioned. So, findings from this German sample, are possibly not generalizable to such populations.

A number of substance abuse researchers have proposed that outreach and intervention programs aimed at treating adolescent anxiety disorders might be cost-effective in preventing substance use disorders (Kushner et al. 1999; Crum & Pratt, 2001; Kessler et al. 2003). This proposal is predicated on the assumption that anxiety disorders are causal risk factors rather than non-causal markers. This assumption can be called into question based on the finding in the EDSP data that remitted panic and social phobia are as important as active panic and social phobia in predicting alcohol outcomes. However, it is important to appreciate that this finding is not definitive. In particular, it might
be that recurrence of these anxiety disorders subsequent to the baseline assessment promoted the subsequent outcomes in the subsample of respondents who were classified as having remitted panic and social phobia at baseline. Statistical analyses aimed at investigating this possibility were attempted but could not be carried out because of the small number of respondents with baseline remitted panic or social phobia. Resolution of this uncertainty will require replication and extension in a larger sample or over a longer follow-up period.

If this uncertainty is resolved in favor of a causal interpretation, there would be a number of practical advantages of early intervention programmes aimed at the treatment of adolescent anxiety in order to prevent secondary substance disorders in comparison to more conventional preventive interventions (Kessler & Price, 1993). These programmes would allow prevention researchers to include proven treatment technologies, including pharmacological and cognitive-behavioral interventions. They would increase the social warrant for preventive interventions with critical community constituencies and professional groups because the programmes would be targeted at youth with existing disorders. Recipients would be more open to accepting the interventions than the recipients of most preventive interventions because these recipients would already be experiencing significant distress. These advantages are sufficiently compelling that they argue strongly for other researchers with access to relevant naturalistic data to carry out parallel studies to see if adolescent panic and social phobia are, in fact, reliable predictors of alcohol problems in early adulthood and, if so, whether there is evidence to suggest that these associations are causal.

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Primary anxiety disorders predicting alcohol use/disorders


