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Family history of alcohol use disorders among adults with panic disorder in the community

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ABSTRACT

Objective: Clinical studies suggest a familial association between panic disorder and alcohol use disorders but this relationship has not been examined in a representative community sample. The objective of this study is to examine the familial association between panic disorder and alcohol use disorders among adults in the community.

Method: Data were drawn from the NESARC, a nationally representative sample of over 43,000 adults in the United States. Rates of alcohol use disorders were examined using the family history method in first-degree relatives (FDRs) of adults with panic disorder. Analyses were adjusted for demographics, alcohol use disorders in the proband, and anxiety disorders in the FDRs.

Results: First-degree relatives of adults with panic disorder have significantly higher odds of alcohol use disorders, compared with FDRs of adults without panic disorder. These associations persist after adjusting for demographic characteristics, alcohol use disorders in the proband, and anxiety disorders in the FDR's.

Conclusions: Consistent with findings from clinical studies, this is the first population-based study to show a familial link between panic disorder and alcohol use disorders. This association appears independent of the influence of comorbidity of alcohol use disorders and anxiety disorders, suggesting a potential familial and/or genetic pathway. Future longitudinal studies will be needed to further understand the mechanism of this observed association.

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1. Introduction

In recent years, there has been growing interest in the comorbidity of anxiety disorders and alcohol use disorders. While it was once thought that alcohol and other substance use disorders were more commonly comorbid only with depression and other mood disorders, research has increasingly shown strong and significant links between anxiety disorders and alcohol use problems (Zimmermann et al., 2003; Abram et al., 2007; Moss et al., 2010). Panic disorder has emerged as an anxiety disorder strongly linked with alcohol use disorders; population-based studies have shown that over 37% of adults with panic disorder have lifetime alcohol abuse or dependence (Kessler et al., 2006), and several community and clinically-sampled studies have reported similar findings (e.g., Joyce et al., 1989; Jacobi et al., 2004).

The reason for the observed link between panic disorder and alcohol use disorders is not known. The three main possibilities include: alcohol use disorders lead to the onset of panic disorder; panic disorder leads to onset of alcohol use problems, possibly via self-medication, or that there are common risk factors for the co-occurrence of both alcohol use problems and panic disorder. One possibility is that the observed comorbidity of panic disorder and alcohol use problems results from a shared familial vulnerability to both panic disorder and alcohol use problems. Several family studies have found increased rates of alcohol use problems in the first-degree relatives of panic disorder (PD) probands as compared to controls (Noyes et al., 1978; Crowe et al., 1983; Maier et al., 1993a,b; Goldstein et al., 1994; Merikangas et al., 1994, 1998). As such, evidence consistently suggests a familial link between PD and alcohol use disorders. Yet, several methodological features of previous studies leave questions unanswered. Specifically, with few exceptions (Maier et al., 1993a,b; Katerndahl and Realini, 1999), the study designs of previous investigations have not considered the potentially confounding role of comorbid alcoholism in the PD

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proband. As alcohol use disorders have a familial component, it therefore remains unclear whether the observed increases reflect a familial association between alcoholism and PD, or are attributable to proband alcohol comorbidity. In addition, all previous studies have examined these relationships in clinical and specifically recruited treatment samples. As such, it is not clear whether findings are generalizable to those with alcohol use disorders and panic disorder in the community. As rates of PD are higher among females in the community, and alcohol use disorders are more common among males, the degree to which these patterns are gender specific in terms of familial vulnerability is unclear as this has been difficult to examine in clinical samples due to smaller sample size.

Against this background, the goal of the current study is to investigate the familial association between PD and alcohol use disorders among adults in the community. First, the study will examine whether there are higher rates of alcohol use problems among first-degree relatives of adults with panic disorder as compared to relatives of non-PD controls. Second, the study will examine the degree to which the familial link between PD and alcohol use disorders is explained by comorbid mental disorders or demographic differences. Third, the study will examine whether the familial link between PD and alcohol use problems differs by gender, as a previous clinical study (e.g., Goodwin et al., 2006) found significantly higher rates of alcohol use disorders in males, but not females, of PD probands though the patterns were similar so it was unclear whether this is a meaningful sex difference or due to smaller sample size. Based on clinical findings (Noyes et al., 1978; Crowe et al., 1983; Maier et al., 1993a,b; Goldstein et al., 1994; Merikangas et al., 1994, 1998; Goodwin et al., 2006), we hypothesized that there would be an elevated risk of alcohol use disorders among first-degree relatives of adults with PD. We predicted that this link would persist after adjusting for both alcohol use disorders in the proband, and other comorbid mental disorders.

2. Method

2.1. Sample

The cross-sectional sample was drawn from participants in the 2001–2002 National Epidemiologic Survey of Alcohol and Related Conditions (NESARC), a nationally representative United States survey of 43,093 civilian non-institutionalized participants aged 18 and older. Details of the sampling frame are described elsewhere (Grant et al., 2003a,b, 2004a,b; Compton et al., 2004). The National Institute on Alcohol Abuse and Alcoholism (NIAAA) sponsored the study and supervised the fieldwork, conducted by the U.S. Bureau of the Census. Young adults, Hispanics, and African-Americans were over sampled, and the study achieved an overall response rate of 81%. To adjust for non-response and selection probability, the sample was weighted and adjusted to reflect the U.S. population from the 2000 Decennial Census in terms of age, race, sex, and ethnicity. The research protocol, including informed consent procedures, received full ethical review and approval from the U.S. Census Bureau and U.S. Office of Management and Budget.

2.2. Interviewers, training, and field quality control

Interviews were conducted by 1800 professional interviewers from the Census Bureau using computer-assisted software with built-in skip, logic, and consistency checks. All interviewers had experience with other national health-related surveys with an average of five years of experience, and were further trained for 10 days under the direction of NIAAA. Verification of the interviewer was conducted by regional supervisors who re-contacted a random 10% of all respondents for quality control purposes.

2.3. Measures

2.3.1. Alcohol dependence

The Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS-IV) (Grant et al., 2001), a state-of-the-art structured diagnostic interview, was administered to the NESARC participants. This instrument was specifically designed for experienced lay interviewers and was developed to advance measurement of substance use and mental disorders in large-scale surveys. The AUDADIS-IV used an extensive list of over 40 questions to assess alcohol abuse and dependence. Diagnoses were indicated according to the DSM-IV (American Psychiatric Association, 1994); at least 3 of 7 criteria are necessary for alcohol dependence. Withdrawal syndromes were also assessed according to DSM-IV criteria; the presence of at least 2 symptoms out of 8 plus distress is necessary for a withdrawal diagnosis. Time frames for diagnosis included the previous 12-month period and prior to the previous 12-month period, combined to create a 'lifetime' diagnosis.

The reliability and validity of alcohol dependence diagnosis has been extensively documented in the U.S. and abroad. The reliability of the alcohol dependence diagnosis has achieved a minimum kappa of 0.74 (Fyer et al., 1995; Swendsen et al., 1998; Katerndahl and Realini, 1999; Kushner et al., 2000). The validity of the diagnosis has been documented in numerous studies including the World Health Organization/National Institutes of Health Reliability and Validity Study and others (Hasin et al., 1997a,b,c,d; Canino et al., 1999; Hasin and Paykin, 1999; Hasin and Grant, 2004). Further, the symptom items have been validated using clinical reappraisals conducted by psychiatrists (Canino et al., 1999).

2.4. Panic disorder

An episode of PD was diagnosed when recurrent unexpected panic attacks occurred and at least one attack was followed by at least one month of persistent concern about having additional attacks, worry about the implications/consequences of the attacks, or a significant change in behavior related to the attacks. In the AUDADIS-IV, panic attacks were operationalized as discrete periods of intense fear/discomfort in which at least 4 of the 13 panic attack symptoms developed abruptly and reached a peak within 10 min.

2.5. Other psychiatric disorders

Dichotomous measures of lifetime any mood, any anxiety disorder, and any personality disorder were included as covariates in modeling (Grant et al., 2004a,b). Any mood disorder was coded as positive for individuals who met DSM-IV criteria for any of the following: major depression, dysthymia, mania, or hypomania. Anxiety disorders were included as separate covariates of: social phobia, specific phobia, or generalized anxiety disorder. Diagnoses of eight independently measured personality disorders were combined into one measure. The derivation and psychometric properties of these measures have been described elsewhere (Grant et al., 2004a,b, 2005, 2006).

2.6. Family history

Family history of alcohol problems included respondent report of any first-degree relative with an alcohol problem (i.e., parent or sibling). Participants were provided definitions of various examples of symptoms that are included in the alcohol and drug diagnostic criteria, and then asked whether relatives (in each category) had experienced the problem as described. The definitions read to respondents included observable manifestations, as these are most likely to be known to family informants and sensitivity is a key

Table 1
Proportion of probands with a positive first-degree family history of alcohol use problems.

	Proband with no PD, no ALC	Proband with PD, no ALC	Proband with ALC, no PD	Proband with PD, ALC	Chi-square, df, p-value
	36745	1567	4232	549	
All first-degree relatives	27.8 (0.5)	43.7 (1.5)	49.9 (0.9)	64.7 (2.5)	146.5, 3, <0.0001
Female relatives	8.8 (0.3)	16.9 (1.1)	20.1 (0.7)	33.1 (2.3)	131.9, 3, <0.0001
Male relatives	24.0 (0.5)	37.2 (1.5)	44.5 (1.0)	58.4 (2.6)	146.4, 3, <0.0001

issue in family history information (Andreasen et al., 1977; Zimmerman et al., 1988; Slutske et al., 1996; Goodwin et al., 2006). The reliability of family history measures indicated good reliability for first-degree relatives (ICCs from 0.72 to 0.87, Grant et al., 2003a,b).

2.7. Statistical analyses

Analyses were conducted using SUDAAN (2002) to derive standard errors that account for the complex sampling scheme of the dataset. Cross-tabulations were used to estimate the proportion of probands with a family history of alcohol problems in four groups: those with no PD or alcohol dependence (ALC), those with PD but not ALC, those with ALC but not PD, and those with both. A proband was considered to be positive for family history of alcohol use disorder if he/she reported any first-degree relative with alcohol problems. Analyses were then stratified by male relatives and female relatives. Differences among the groups were tested bivariate using chi-square. We also used logistic regression to determine the odds of positive family history of alcohol problems based on the main predictor: proband diagnosis. The first models adjusted for demographic variables of sex, race/ethnicity, age, marital status and education. A second model included demographics as well as comorbid proband mood disorder, personality disorder, and drug disorder. The final model included aforementioned covariates along with any other anxiety disorder in the proband, included as separate covariates of social phobia, specific phobia, and generalized anxiety disorder (GAD).

3. Results

3.1. Alcohol use disorders in first-degree relatives of probands with panic disorder

Results of bivariate chi-square tests showed that there were significant differences in rates of alcohol use disorders among FDRs of probands with PD and alcohol use disorder, compared with those

without (see Table 1). This pattern appeared fairly consistent among male and female FDRs.

3.2. Alcohol use disorders in first-degree relatives of probands with panic disorder, adjusted for potentially confounding factors

Adjusted analyses revealed that FDR's of probands with PD who did not have alcohol use disorders had significantly higher odds of alcohol use disorders, compared with FDRs of probands with neither panic disorder nor alcohol use disorders (see Table 2). These associations remained significant after additionally adjusting for demographic differences, comorbid mood disorders, drug use disorders, personality disorders, and other anxiety disorders in the FDR. The odds of alcohol use disorders in relatives of probands with PD and alcohol use disorders were even greater, compared with those with neither. These associations remained strong even after adjusting for demographics, and other mental disorders. When the FDRs were stratified by gender, it appeared that there was an association between PD in the proband and likelihood of alcohol use disorders in female FDRs, yet this link was no longer significant after adjusting for mood, personality, and drug use disorders. The associations remained significant among males. We note, however, that the interaction between gender and proband status was not statistically significant ($F = 0.17$, $df = 3$, $p = 0.91$), indicating little evidence for a difference in the effect of proband disorder on relative disorder by gender of the relative.

4. Discussion

Consistent with findings from clinical studies, the results of this population-based study indicate a familial link between PD and alcohol use disorders. This association appears independent of the influence of proband comorbidity for alcohol use disorders and anxiety disorders. Future longitudinal studies will be needed to further understand the mechanism of this observed association.

These results suggest that one possible explanation for the comorbidity of alcohol dependence and PD is a common familial

Table 2
Odds of positive first-degree family history of alcohol use problems based on proband diagnosis.

		Proband with no PD, no ALC	Proband with PD, no ALC	Proband with ALC, no PD	Proband with PD, ALC
		36745	1567	4232	549
All first-degree relatives	AOR1*	1.00	1.72 (1.51–1.96)	2.73 (2.50–2.99)	4.33 (3.43–5.45)
	AOR2**	1.00	1.24 (1.08–1.41)	2.14 (1.95–2.35)	2.25 (1.77–2.86)
	AOR3***	1.00	1.20 (1.05–1.37)	2.13 (1.94–2.34)	2.17 (1.70–2.76)
Female relatives	AOR1*	1.00	1.71 (1.44–2.03)	2.67 (2.38–2.99)	4.61 (3.71–5.72)
	AOR2**	1.00	1.17 (0.98–1.41)	1.99 (1.76–2.24)	2.29 (1.82–2.87)
	AOR3***	1.00	1.14 (0.94–1.39)	1.98 (1.76–2.23)	2.22 (1.77–2.80)
Male relatives	AOR1*	1.00	1.62 (1.42–1.86)	2.68 (2.45–2.94)	4.09 (3.28–5.10)
	AOR2**	1.00	1.20 (1.04–1.38)	2.16 (1.96–2.37)	2.30 (1.83–2.88)
	AOR3***	1.00	1.17 (1.01–1.34)	2.14 (1.95–2.36)	2.22 (1.77–2.79)

* AOR1 covariates: sex, race, age, marital status, and education.

** AOR2 covariates: sex, race, age, marital status, education, any mood disorder, any personality disorder, any drug disorder.

*** AOR3 covariates: sex, race, age, marital status, education, any mood disorder, any personality disorder, any drug disorder, social phobia, specific phobia, and GAD.

vulnerability. It cannot be determined from this study whether the pathway is genetic, or through some other (e.g., familial, environmental) mechanism. It is conceivable that exposure to common risk factors for both alcohol use disorders and PD (e.g., traumatic life events) may increase vulnerability to both alcohol use disorders and PD within the individual and within families. The possibility that the association is due to sampling bias or uncontrolled confounding factors (e.g., lower socioeconomic status (SES)) is decreased by our use of a population sample and adjustment for these potentially confounding demographic factors. Yet, confounding due to low SES in childhood could still contribute to this observed association. Since childhood and adulthood SES are related this seems fairly unlikely to be the sole explanation as adjusting for adult SES does not explain the association. Still, future studies that can investigate this possibility would be worthwhile.

Our findings are also consistent with the possibility of a common genetic vulnerability for both panic and alcohol use disorders, though this cannot be tested in the current study. While there is consistent evidence of a genetic contribution to both panic (e.g., Hamilton, 2009) and alcohol use disorders (e.g., Kendler et al., 2010), to our knowledge no genetic studies have specifically examined the potential genetic contribution to comorbidity of panic and alcohol use disorders. Although the panic-alcohol link has not been examined in genetic studies, Kendler et al. (2003) found that the association of common psychopathology such as mood and anxiety disorders—and substance use disorders—was largely explained by genetic and not environmental factors (Kendler et al., 2003). The cumulative evidence suggests future studies in this area could yield fruitful results in advancing our understanding of the mechanisms underlying the co-occurrence of panic and alcohol use disorders both within individuals and families, as well as shedding new light on the etiology of each.

A causal relationship between panic and alcohol use disorders, in either direction, is also possible. Yet, recent evidence from a prospective longitudinal study showed a link between anxiety disorders and the subsequent development of alcohol dependence became non-significant after adjusting for a range of social, family, and environmental factors (Goodwin et al., 2004). This suggests that the relationship was due to confounding/mediating factors, but is not causal. While theories about self-medication and alcohol inducing panic via neurobiological mechanisms have been postulated, to our knowledge no studies to date have demonstrated a causal link between the two.

Limitations of this study should be considered when interpreting results. First, there was no assessment of anxiety disorders in the relatives. Therefore it is conceivable that increased risk of alcohol use disorders observed in relatives was related to comorbid anxiety disorders. It would be of interest to know whether PD transmits alcohol dependence in the absence of PD or any other anxiety disorder in the relative. Future studies that measure both anxiety disorders and alcohol use disorders in relatives will be needed to do this. Second, information on disorders in relatives was done by proband report, which is vulnerable to report bias (Chapman et al., 1994). Replication of these results in a study using direct interview of both probands and relatives will be needed next. Third, lifetime diagnoses of PD and alcohol use disorders were used, and therefore may be vulnerable to both report bias and limited in reliable assessment of comorbidity (Kraemer et al., 2006). These findings should be replicated using prospective data on family members to examine these relationships.

Contributors

Drs. Renee Goodwin, Joshua Lipsitz and Abby Fyer conceived of the study idea and planned analyses. Dr. Goodwin wrote the first

draft of the paper, and Drs Lipsitz, Fyer and Galea made critical revisions and assisted with interpretation of results. Katherine Keyes performed the statistical analyses.

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Conflict of interest

The authors have no conflict of interest to report.

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