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# Mental disorders and cardiovascular disease among adults in the United States

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## Abstract

*Objective:* Numerous population-based studies have found an association between major depression and CVD, though these studies did not assess anxiety disorders. Patient samples have shown associations between anxiety disorders and cardiovascular disease (CVD), but without consideration of depressive disorders. Therefore, it remains unclear whether: (a) both anxiety and depressive disorder are associated with CVD; (b) these associations are generalizable to adults in the community.

*Materials and Methods:* Data were drawn from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a nationally representative sample of 43,093 civilian non-institutionalized participants aged 18 and older.

*Results:* CVD (total prevalence 3.3%) was associated with increased likelihood of any anxiety disorder (OR = 1.43, (1.20, 1.71)), after adjusting for depressive disorders, as well as Generalized Anxiety Disorder (OR = 1.48 (1.09, 2.01)), Panic disorder (OR = 1.46 (1.12, 1.91)), and specific phobia (OR = 1.29 (1.04, 1.59)). CVD was significantly associated with any mood disorder (OR = 1.34 (1.13, 1.58)) after adjusting for anxiety disorders, though neither the link with major depression, nor other specific mood disorders remained significant after adjustment.

*Conclusions:* Our findings suggest that anxiety disorders, mood disorders, and CVD are highly comorbid among adults in the United States, and demonstrate the importance of including anxiety disorder assessment in studies of mental and physical comorbidity. These results reveal how the lack of investigation into specific relationships between CVD and the range of mental disorders in population-based studies of risk factors for CVD may obscure important relationships.

In recent years, several studies have documented a link between mood and anxiety disorders and cardiovascular disease (CVD) incidence, course, and recurrence in clinical samples (Strik et al., 2003; Birkhofer et al., 2005; Todaro et al., 2007; Davidson et al., 2006). While there is mounting evidence of an important link between mental health and CVD outcomes in clinical settings, relatively little is known about this association in randomly-selected, population-based samples with state-of-the-art Axis I disorder diagnoses. Specifically, several studies have examined psychological symptoms as risk factors for CVD among adults in population-based studies (Jonas et al., 1997; Ferketich et al., 2000; Wulsin et al., 2005), but comprehensive assessment of the range of mental disorders has not been available in a single study using a representative sample of the general population.

A number of studies have also found links between anxiety symptoms (Kawachi et al., 1994; Coryell et al., 1986), panic disorder, and CVD (Weissman et al., 1990) as well as Generalized Anxiety Disorder (GAD) and CVD (Barger and Snyderman, 2005). Studies have also shown an association between major depression (MDD) and CVD among adults in various community samples

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(e.g. Musselman et al., 1998), but although excellent methodology has been used and socioeconomic status (SES) has been adjusted for, these studies have not adjusted for anxiety disorders. As such, it remains unclear whether and to what degree anxiety and major depressive disorders have independent comorbidity with CVD. Therefore, the specific associations between CVD and the full range of mood and anxiety disorders in the general population have not been determined. Yet, the identification and understanding of these relationships has substantial implications for our understanding of community health.

Another dimension of the association that remains unclear is the potential role of comorbid alcohol and substance use disorders in the link between mood and anxiety disorders and CVD in the general population. These disorders are both highly comorbid with mood and anxiety disorders and are strongly associated with increased risk of CVD. Behaviors such as cigarette smoking, illicit drug use, and problematic alcohol use are significantly more common among adults with mental disorders than those without (Grant et al., 2003a; Davidson et al., 2001). These same behaviors (i.e. smoking, alcohol abuse, and drug use) are also primary risk factors for CVD and for poorer outcomes among those with CVD (Urbano-Marquez et al., 1995; Rogacheva et al., 2007). Since the extent of drug and alcohol misuse is strongly associated with risk of adverse outcomes (Smoller et al., 2003, 2007; Joynt et al., 2003; Sawchuk et al., 2005), a more fine-grained analysis of the role of these disorders should improve our understanding of the relationship between mood and anxiety disorders and CVD.

Against this background, the present study was performed to address some of these knowledge gaps. The current study investigated the comorbidity of mood and anxiety disorders and CVD among adults in the United States, and examined the role of demographic factors, cigarette, alcohol, and illicit drug use disorders in the association between mood and anxiety disorders and CVD. We hypothesized that mood and anxiety disorders would be significantly associated with CVD among adults in the community, and that some of this association would be explained by demographic characteristics, nicotine, alcohol and drug dependence.

## 1. Materials and methods

### 1.1. 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., 2003b, 2004a; Compton et al., 2004). The National Institute on Alcohol Abuse and Alcoholism (NIAAA)

sponsored the study and supervised the fieldwork, conducted by the US Bureau of the Census. Young adults, Hispanics, and African–Americans were oversampled, 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 US 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 US Census Bureau and US Office of Management and Budget. Demographic characteristics of the NESARC sample has been described elsewhere (Grant et al., 2004a,b).

### 1.2. Interviewers, training, and field quality control

One thousand eight hundred professional interviewers from the Census Bureau using computer-assisted software conducting built-in skip, logic, and consistency checks conducted interviewing. All of the 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. In addition, a randomly-selected subset of respondents was re-interviewed with 1–3 complete sections of the AUDADIS-IV. This served as a test–retest reliability study of NESARC measures (Grant et al., 2003a). In the few cases when accuracy was uncertain, the data were discarded and a supervising interviewer repeated the interview.

### 1.3. Measures

The NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV (AUDADIS-IV) was used to assess independent mood and anxiety disorders as well as alcohol and drug use disorders according to DSM-IV criteria. This instrument was specifically designed for experienced lay interviewers and was developed to advance measurement of substance use disorders and other mental disorders in large-scale surveys.

### 1.4. Mood and anxiety disorders

Mood and anxiety disorders assessed by the AUDADIS-IV included primary major depression, dysthymia, bipolar disorder, generalized anxiety disorder, panic disorder with or without agoraphobia, social phobia, and specific phobia. Diagnoses were assessed in two timeframes: last 12 months and prior to the last 12 months. These were combined to create "lifetime" diagnoses for the present analysis. Diagnoses included a requirement of distress and/or social or occupational dysfunction (as per DSM-IV requirement). Rule outs included substance-induced disorders or those due to bereavement. The reliability and

validity of mood and anxiety disorder diagnoses and symptom items were fair to good (kappas 0.42–0.64) (Grant et al., 1995, 2003a; Canino et al.,1999), including test–retest and clinical re-appraisal studies. Each mood and anxiety disorder has been further validated by showing highly significant associations with disability (Grant et al.,2004a,b,c, 2005a). Details of the generalized anxiety (Grant et al., 2005a), depression (Hasin et al., 2005), bipolar (Grant et al., 2005b), social anxiety (Grant et al., 2006), and panic (Grant et al., 2006) diagnoses have been described in detail elsewhere.

### 1.5. Substance use disorders

DSM-IV abuse and dependence diagnoses for substance use disorders were assessed for alcohol and for 10 classes of drugs: sedatives, tranquilizers, opiates (other than heroin or methadone), stimulants, hallucinogens, cannabis, cocaine (including crack cocaine), inhalants/solvents, heroin, and other drugs. Diagnoses were assessed using a set of over 40 questions. As per DSM-IV criteria, at least one of four criteria was required for a DSM-IV diagnosis of alcohol or drug abuse. At least three of seven criteria were required for DSM-IV alcohol or drug dependence diagnoses either in the 12 months preceding the interview or previously. For prior diagnoses of dependence, at least three criteria must have occurred within a 1-year period, following DSM-IV. The reliability and validity of substance diagnoses and symptom items have been examined via test–retest reliability studies, clinical reappraisals conducted by psychiatrists and other designs (Canino et al., 1999). These had excellent reliability in US and international clinical and general population samples, with alcohol diagnoses having a minimum kappa of 0.74 and drug diagnoses having a minimum kappa of 0.79 (Hasin et al., 1997b; Grant et al., 1995, 2003a; Canino et al.,1999). Validity was also demonstrated in numerous studies including the World Health Organization/National Institutes of Health and Reliability and Validity Study among others (Grant and Harford, 1988, 1990; Grant et al., 1992; Hasin and Grant, 1994; Grant, 1996; Hasin and Paykin, 1999; Hasin et al., 1997a,c,d).

Nicotine dependence is assessed in a unique module separate from the assessment of other substance use. Respondents are considered to have ever used cigarettes if they have smoked 100 or more cigarettes during their lifetime. Four other modes of nicotine use are assessed as well: pipe, cigar, snuff, and chewing tobacco use. The test–retest reliability of the nicotine use variables and well as other AUDADIS-IV nicotine use measures (e.g. frequency and duration of use), were excellent, with interclass correlation coefficients of 0.83–0.84. Diagnosis of nicotine dependence was made according to DSM-IV guidelines such that three of seven criteria were needed for a diagnosis. The reliability and validity of this diagnosis has been documented as good ($k = 0.63$), and the diagnosis has been validated against disability measures.

### 1.6. Cardiovascular disease

The cardiovascular disease measure was developed from a section of the AUDADIS-IV assessing medical conditions. Respondents were asked a series of questions about possible medical conditions. A respondent was considered a possible candidate for cardiovascular disease if they reported that they had a heart attack or any other form of cardiovascular disease in the last 12 months. Responses were only considered positive for CVD if a physician had confirmed the diagnosis, which was asked in a separate question immediately after each possible medical diagnosis.

### 1.7. Statistical analysis

Analyses were conducted using SUDAAN (RTI, 2004) to derive standard errors that account for the complex sampling scheme of the dataset. Weighted percentages were obtained to describe the demographic characteristics of those with and without a cardiovascular disease diagnosis. Statistical associations with demographic characteristics were tested using chi-square. Odds ratios (ORs) were derived to establish the association between lifetime mental disorders (predictor) and current cardiovascular disease (outcome), controlling for demographic characteristics, as well as any other mood, anxiety, personality, or substance disorder.

## 2. Results

### 2.1. Socio-demographic characteristics and behavioral factors associated with CVD

The prevalence of heart disease varies across socio-demographic and clinical characteristics. Specifically, individuals who are older, Native American or White, widowed/separated/divorced, have less than a high school education, have low personal income, and have a history of nicotine dependence have a higher prevalence of CVD (see Table 1).

### 2.2. Comorbidity of CVD and mental disorders

All of the mental disorders were significantly comorbid with CVD prevalence in unadjusted logistic regression models (see Table 2). However, after adjusting for differences in demographic characteristics, substance disorders, and comorbid mental disorders, only any mood disorder, any anxiety disorder, GAD, panic disorder, and specific phobia remained significantly associated with CVD (see Table 2). Further, Table 2 indicates that each additional psychiatric disorder results in a 20% increase in the odds of comorbid CVD. The associations between CVD and bipolar disorder as well as social phobia were no longer significant after control for comorbid nicotine dependence, and the association between CVD and major depression as well as dysthymia was no longer significant after

Table 1
Prevalence of cardiovascular disease by demographic characteristics

| | | | Heart disease | Chi-square, df, p-value |
|---|---|---|---|---|
| | | N | 1548 | |
| Total | | 43,093 | 3.3 (0.1) | |
| **Sex** | | | | |
| | Male | 18,518 | 3.4 (0.2) | 1.2, 1, 0.29 |
| | Female | 24,575 | 3.2 (0.2) | |
| **Age** | | | | |
| | 18–29 | 8666 | 0.6 (0.1) | 123.2, 2, <0.01 |
| | 30–44 | 13,382 | 1.0 (0.1) | |
| | 45–64 | 12,840 | 3.8 (0.2) | |
| | 65+ | 8205 | 10.5 (0.4) | |
| **Race** | | | | |
| | White | | 3.7 (0.1) | 43.7, 4, <0.01 |
| | Black | | 3.0 (0.2) | |
| | Native American | | 4.6 (1.3) | |
| | Asian or Pacific Islander | 1332 | 1.8 (1.0) | |
| | Hispanic | 8308 | 1.5 (0.2) | |
| **Marital status** | | | | |
| | Married or living with someone as if married | 22,081 | 3.2 (0.2) | 115.8, 2, <0.01 |
| | Widowed, separated, or divorced | 11,117 | 6.3 (0.3) | |
| | Never married | 9895 | 1.1 (0.1) | |
| **Education** | | | | |
| | Less than high school | 7849 | 5.6 (0.4) | 70.3, 2, <0.01 |
| | High school | 12,547 | 3.4 (0.2) | |
| | Some college or higher | 22,697 | 2.6 (0.1) | |
| **Personal income** | | | | |
| | 0–19,999 | 21,075 | 4.2 (0.2) | 60.3, 3, <0.01 |
| | 20,000–34,999 | 9999 | 3.2 (0.2) | |
| | 35,000–69,999 | 9031 | 2.0 (0.2) | |
| | >70,000 | 2988 | 2.2 (0.3) | |
| **Urbanicity** | | | | |
| | Urban | 35,297 | 3.2 (0.1) | 1.1, 1, 0.29 |
| | Rural | 7796 | 3.9 (0.3) | |
| **Region** | | | | |
| | Northeast | 8209 | 3.5 (0.2) | 2.3, 3, 0.52 |
| | Midwest | 8991 | 3.2 (0.2) | |
| | South | 16,156 | 3.5 (0.2) | |
| | West | 9737 | 3.0 (0.4) | |
| **Drug dependence** | | | | |
| | Yes | 1045 | 3.2 (0.7) | 0.0, 1, 0.84 |
| | No | 42,048 | 3.3 (0.1) | |
| **Alcohol dependence** | | | | |
| | Yes | 4781 | 3.1 (0.3) | 0.4, 1, 0.52 |
| | No | 38,312 | 3.3 (0.1) | |
| **Nicotine dependence** | | | | |
| | Yes | 6937 | 4.0 (0.3) | 7.8, 1, 0.007 |
| | No | 36,156 | 3.2 (0.1) | |

simultaneous control for substance disorders as well as other comorbid psychiatric conditions.

## 3. Discussion

The majority of studies on the mental health predictors, correlates and outcomes associated with CVD focus on major depression, and subclinical measures of depression symptoms. Epidemiologic studies with state of the art sampling and measurement of CVD typically include only depression symptom scales, and sometimes structured interviews used to identify diagnoses of depression, but do not usually assess anxiety disorders (Haines et al., 1987; Barlow, 1988; Stansfeld and Marmot, 2002; Kubzansky et al., 2006). The current data suggest that anxiety disorders are strongly and significantly associated with CVD

Table 2
Association between CVD and mental disorders among adults in the community

| Psychiatric disorder | % (SE) of heart disease among those with psychiatric disorder (in lifetime timeframe) | % (SE) of heart disease among those without psychiatric disorder (in lifetime timeframe) (reference group) | OR (95% CI) unadjusted | OR (95% CI) adjusted for demographics[a] | OR (95% CI) adjusted for nicotine dependence | OR (95% CI) any personality disorder | OR (95% CI) adjusted for any alcohol or drug dependence | OR (95% CI) adjusted for all variables | OR (95% CI) adjusted for all variables (including other disorders) |
|---|---|---|---|---|---|---|---|---|---|
| *Any mood disorder* | 4.0 (0.3) | 3.2 (0.1) | *1.27 (1.09–1.47)* | *1.74 (1.48–2.03)* | *1.22 (1.05–1.41)* | *1.19 (1.02–1.38)* | *1.30 (1.11–1.52)* | *1.44 (1.22–1.70)* | *1.34 (1.13–1.58)* |
| Major depression | 4.0 (0.3) | 3.2 (0.1) | *1.28 (1.08–1.50)* | *1.69 (1.42–2.01)* | *1.23 (1.04–1.44)* | *1.20 (1.01–1.41)* | *1.30 (1.10–1.54)* | *1.40 (1.17–1.68)* | 1.22 (1.00–1.48) |
| Bipolar disorder | 4.1 (0.6) | 3.3 (0.1) | 1.33 (0.99–1.78) | *2.40 (1.76–3.28)* | 1.25 (0.92–1.69) | 1.17 (0.86–1.59) | *1.37 (1.01–1.86)* | *1.72 (1.23–2.41)* | 1.44 (1.00–2.06) |
| Dysthymia | 5.0 (0.6) | 3.2 (0.1) | *1.58 (1.22–2.06)* | *1.80 (1.36–2.37)* | *1.51 (1.15–1.97)* | *1.46 (1.11–1.91)* | *1.62 (1.24–2.12)* | *1.41 (1.06–1.88)* | 1.13 (0.84–1.52) |
| *Any anxiety disorder* | 4.5 (0.3) | 3.1 (0.1) | *1.47 (1.26–1.73)* | *1.82 (1.54–2.16)* | *1.43 (1.21–1.68)* | *1.40 (1.19–1.64)* | *1.50 (1.27–1.78)* | *1.52 (1.27–1.82)* | *1.43 (1.20–1.71)* |
| GAD | 6.1 (0.7) | 3.2 (0.1) | *1.97 (1.51–2.55)* | *2.30(1.76–3.00)* | *1.89 (1.45–2.46)* | *1.82(1.40–2.37)* | *2.01 (1.54–2.62)* | *1.83(1.39–2.39)* | *1.48 (1.09–2.01)* |
| Panic disorder | 5.5 (0.6) | 3.2 (0.1) | *1.75 (1.40–2.19)* | *2.16 (1.69–2.76)* | *1.67 (1.33–2.09)* | *1.63 (1.30–2.05)* | *1.79 (1.42–2.26)* | *1.72 (1.34–2.21)* | *1.46 (1.12–1.91)* |
| Social phobia | 4.1 (0.5) | 3.3 (0.1) | 1.27 (0.97–1.66) | *1.53 (1.16–2.01)* | 1.22 (0.93–1.60) | 1.13 (0.86–1.50) | 1.29 (0.98–1.70) | 1.14 (0.84–1.54) | 0.90 (0.66–1.23) |
| Specific phobia | 4.4 (0.4) | 3.2 (0.1) | *1.37 (1.13–1.67)* | *1.72 (1.40–2.10)* | *1.32 (1.08–1.61)* | *1.29 (1.07–1.56)* | *1.39 (1.14–1.70)* | *1.43 (1.16–1.75)* | 1.29 (1.04–1.59) |
| Number of psychiatric disorders | 0.8 (0.1) | 0.6 (0.0) | *1.12 (1.07–1.17)* | *1.28 (1.22–1.34)* | *1.10 (1.05–1.16)* | *1.10 (1.04–1.16)* | *1.19 (1.12–1.26)* | *1.22 (1.15–1.31)* | – |

[a] Adjusted for sex, age, ethnicity, marital status, education, urbanicity.

among adults in the United States, and that this relationship persists independent of the influence of depressive disorders. As such, our results provide preliminary evidence suggesting that a range of mental disorders, including anxiety disorders, should be assessed when attempting to understand the role of depression in CVD prevalence, incidence, and recurrence. Our results also suggest that there is a significant relationship between having any mood disorder and CVD among adults in the community, which persists after adjusting for anxiety disorders. Yet, the link between major depression specifically and CVD, or other specific mood disorders, was no longer significant after adjusting for anxiety disorders, suggesting that failure to evaluate both mood and anxiety disorders when examining the relationship between mental disorders and CVD may obscure potentially important relationships.

These data have limitations in the assessment of CVD. Specifically, CVD diagnosis is by self-report of a physician diagnosis. Sensitivity (98%) and specificity (99.3%) has recently been reported for the comparison of self-report of myocardial infarction (MI) to verified hospital records (Meisinger et al., 2004). Further, where patients mis-reported an MI, they most typically had a documented cardiovascular event, and so would still meet our case definition. Similarly, in Minnesota Heart Health participants, documentation of MIs existed for 60% of those reporting a physician diagnosis of MI, and almost half of the other 40% had cardiac hospitalizations (for congestive heart failure, cardiac procedures, and coronary insufficiency) (Rosamond et al., 1995). Thus, a self-report of CVD physician diagnosis is ideal for epidemiological studies of over 40,000 persons, but does not provide much detail in terms of severity or specific type of event, and still leaves report bias a possibility. As anxiety and depression are associated with over-reporting of medical symptoms (Katon et al., 2007), there is potential confounding in our study. We acknowledge this limitation in our large epidemiologic study but do not believe that sensitivity and specificity would fall to unacceptable levels because of selective reporting by anxious patients.

Whether anxiety disorders are implicated in the incidence or recurrence of CVD is currently unknown, as most previous studies testing this association employ self-reported subclinical anxiety symptoms, rather than anxiety disorder diagnoses (Haines et al., 1987; Barlow, 1988; Paterniti et al., 2001; Stansfeld and Marmot, 2002). Whether or to what degree our positive association between anxiety disorders and CVD suggests that adjustment for anxiety disorders in previous associations found between depression and CVD incidence and recurrence would alter their conclusions is also not known (Kapfhammer, 2006). Without studies that use state-of-the-art, diagnostic measures for both physical and mental health problems in the same population-based study, it will not be possible to answer these questions. As the disparity between our results and the majority of previous studies of major depression and CVD indicates, funding gold standard measures for only

one part of an association could result in erroneous conclusions.

Even very recently published studies of the association of anxiety and CVD incidence/recurrence continue to employ self-report measures of anxiety symptoms such as MMPI or MMPI-2 scores, rather than anxiety disorder diagnostic assessments (Kubzansky et al., 2006; Rothenbacher et al., 2007; Shen et al., 2008). Interestingly, in all three of these smaller, but prospective studies, anxiety symptoms uniquely predict CVD incidence or recurrence, over conventional factors and depressive symptoms. What remains to be answered is if the same unique CVD contribution exists for anxiety disorders, over depressive disorders, when these and CVD are assessed by gold standard measures.

### Conflicts of Contributors

Renee Goodwin and Karina Davidson conceptualized the study question, reviewed literature and designed the analytic strategy. Katherine Keyes conducted the statistical analysis. All authors contributed to and have approved the final manuscript.

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None declared.

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