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The Laboratory of Epidemiology and Biometry (LEB) develops, designs, implements, and directs a large multidisciplinary epidemiologic research program of national scope and complexity. In addition to the design, collection, cleaning and dissemination of large-scale, nationally representative survey data on alcohol use and its related conditions, the Laboratory's mission entails: (1) national surveillance activities to collect and analyze alcohol-related program data through various information systems, including the Alcohol Epidemiologic Data System (AEDS); (2) analysis of epidemiologic data on alcohol use, abuse, and dependence, and associated disabilities, and preparation of scientific reports and manuscripts for publication in peer-reviewed journals; (3) adaptation of state-of-the-art statistical methodology to the alcohol field; (4) collaboration with other agencies and organizations to promote the application of epidemiologic research nationally and internationally; (5) maintenance of national statistics on alcohol use disorders and their related conditions and consequences; (6) sponsorship and development of, and participation in, scientific conferences, meetings, workshops, and symposia to exchange information and disseminate new knowledge; (7) collaboration with other National Institutes of Health as well as other government agencies to foster shared interests and goals; and (8) provision of support for a full range of interagency agreements and contracts.

The current focus of the Laboratory's work is on Waves 1 and 2 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Designed to measure a broad range of substance use and other mental disorders based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* (DSM-IV), the NESARC is the largest longitudinal psychiatric epidemiology survey conducted to date. Wave 1 was fielded in 2001-2002, and Wave 2 was conducted in 2004-2005. The target population of the NESARC is the noninstitutionalized population, 18 years and older, residing in households and noninstitutional group quarters (boarding houses, rooming houses, nontransient hotels and motels, shelters, facilities for housing workers, college quarters, and group homes) in the United States, including the District of Columbia, Alaska, and Hawaii. Blacks, Hispanics, and young adults 18 to 24 years of age were oversampled; the total sample size of the NESARC is 43,093 respondents. Using the Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS) for DSM-IV, the Wave 1 NESARC collected comprehensive, detailed data on alcohol consumption, use of 10 categories of drugs, and symptoms of alcohol and specific drug use disorders, as well as mood (major depression, dysthymia, bipolar I, and bipolar II), anxiety (panic with and without

agoraphobia, generalized anxiety, social and specific phobias) and personality disorders. All disorders were assessed in well-defined time frames, current (past 12 months) and prior to the past 12 months. In addition to diagnostic criteria, the interview assessed indicators of impairment and distress due to each disorder, as well as disorder-specific treatment and help seeking. Respondents were also asked to self-report stressful life events occurring in the year preceding interview as well as a range of general medical conditions and measures of health-related quality of life. The Wave 2 AUDADIS introduced an extensive new battery of risk factors, including race-ethnic orientation, acculturation, perceived discrimination, perceived stress, interpersonal support and social networks, alcoholism stigma, childhood abuse, intimate partner violence, and sexual orientation, attraction, and preference, and included new measures of posttraumatic stress disorder and attention deficit-hyperactivity disorder.

Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol use disorders in the United States

A major paper based on the Wave 1 NESARC represents the most authoritative source of information on the prevalence (12-month abuse, 4.7%; dependence, 3.8%), correlates, disability, and comorbidity of DSM-IV AUDs in the U.S. published since 1994. This study was the first to demonstrate that disability associated with DSM-IV alcohol dependence, controlling for sociodemographic characteristics and comorbidity, was similar to impairment levels for drug abuse and mood and personality disorders. The results revealed the severe impairment accompanying AUDs, especially dependence. When alcohol dependence goes untreated, impaired functioning may diminish life chances and increase stressful life conditions even after alcohol dependence remits, raising the subsequent risk for other psychiatric disorders such as major depressive disorder (MDD). These NESARC findings on disability underscore the seriousness of DSM-IV alcohol dependence, for which the majority of affected individuals never receive treatment. Moreover, compared to those documented in 1991-1992 using the earlier NIAAA National Longitudinal Alcohol Epidemiologic Survey (NLAES), current treatment rates for AUDs revealed a disappointing lack of progress.

Due to its size, the NESARC provided more precise information on the risk of AUDs among race-ethnic groups than any other data source. The findings indicated a higher risk of alcohol dependence among Native Americans and a lower risk of alcohol abuse and dependence among Blacks and Asians than among non-Hispanic Whites. NESARC findings of lower risk of alcohol abuse and dependence among Hispanics contributed new information. Determining risk and protective factors for AUDs among minorities is of interest, both to understand the overall etiology of AUDs, and to develop targeted prevention and intervention programs.

This study also changed the way future research will examine comorbidity, by controlling for other comorbid psychiatric disorders when examining associations between alcohol abuse and dependence and other psychiatric conditions. Controlling for all other substance use and psychiatric disorders addresses the fact that tests of association controlling only for sociodemographic characteristics do not yield information on the unique relationships of alcohol abuse and dependence with other disorders, which are also highly comorbid with one another. This study found that associations with drug and nicotine use disorders and Antisocial Personality Disorder (ASPD) were reduced, but remained strong and significant, after adjustment for all comorbid disorders. The drop in magnitude is analogous to results obtained from family, twin, and genetic study designs and suggests common causal factors underlying alcohol and other substance use disorders. However, remaining associations of alcohol dependence with

these other disorders after controlling for comorbidity suggest unique factors leading to the disorder-specific associations, for example, that the specific factors underlying the association between alcohol dependence and nicotine dependence are not necessarily the same as the specific factors underlying the associations between AUDs and illicit drug use disorders. With control for additional comorbidity, significant though considerably reduced associations remained also between alcohol dependence and bipolar I, bipolar II, specific phobia, and histrionic and ASPDs. Thus, while some unique disorder-specific associations were found, much of the association of alcohol dependence with other mood, anxiety, and personality disorders appears to be due to factors common to these other disorders. Taken together, these findings suggest continued investigation of both common and specific factors leading to associations between AUDs and other psychiatric disorders, especially other substance use disorders.

Representative publication:

Hasin DS, Stinson FS, Ogburn E, Grant BF. Prevalence, correlates, disability and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions.

Arch Gen Psychiat 64:830-42, 2007.

Prevalence, correlates, disability, comorbidity, and changes over time of DSM-IV drug use disorders

Although extensive data on drug use in the U.S. population have been available on an ongoing basis, epidemiologic data on the prevalence, correlates, and disability of drug use disorders (DUDs) among the U.S. adult population are less routinely collected. Prior to the publication of this major LEB study, it had been over 16 years since such comprehensive information on DUDs in the general U.S. population had been reported. This study showed that DUDs are prevalent (12-month abuse, 1.4%; dependence, 0.6%; lifetime abuse, 7.7%; dependence, 2.6%), highly disabling, and often go untreated. The onsets in adolescence or young adulthood of drug abuse (19.9 years) and dependence (21.7 years) revealed critical windows of opportunity for prevention efforts.

This study also highlighted the high rates of DUDs among Native Americans, individuals 18 to 24 years old, and those of never married, widowed, separated, or divorced marital status, of lower socioeconomic status as defined by income and education, and with residence in the Western region of the U.S. In addition, associations of DUDs with other substance use disorders, most mood disorders, and antisocial PD were reduced, but remained strong and significant, once other comorbid psychiatric disorders were controlled in the analyses. Consistent with results of genetically informed research, these findings indicate that both common and unique factors underlie these disorder-specific associations. In addition, the present findings underscore the need for continued research on common and specific factors underlying the comorbidity of drug abuse and dependence and the need for comprehensive assessment and treatment of the disorders most highly comorbid with DUDs.

Representative publication:

Compton WM, Thomas YF, Stinson FS, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions.

Sociodemographic and psychopathologic predictors of first incidence of DSM-IV substance use, mood, and anxiety disorders in the United States

The importance of longitudinal epidemiologic research in psychiatry cannot be overestimated. Information on risk factors for first onsets of specific psychiatric disorders can inform the development of evidence-based prevention and education programs targeting sociodemographic and psychopathologic precursors. Knowledge of psychopathologic risk factors can also guide etiologic investigations of common and unique genetic and environmental influences underlying comorbidity, and provide more etiologically derived phenotypes for genetic research. Accordingly, this LEB study was based on the three-year prospective follow-up of the 2001-2002 NESARC. The goals of this study were to: (1) estimate, for the first time in a national study, the annual (one-year) first incidence rates for specific major DSM-IV substance use, mood, and anxiety disorders in a sample large enough to produce stable estimates; (2) provide information on an expanded range of sociodemographic risk factors; and (3) provide estimates of the risks posed by specific Axis I and Axis II psychiatric disorders for subsequent onsets of other disorders.

One-year incidence rates of DSM-IV substance use, mood, and anxiety disorders were highest for alcohol abuse (1.02), alcohol dependence (1.70), MDD (1.51) and Generalized Anxiety Disorder (GAD) (1.12). Incidence rates were significantly greater among men for substance use disorders and greater among women for mood and anxiety disorders except bipolar disorders and social phobia. Age was inversely related to the incidence of all disorders. Black individuals were at decreased risk of incident alcohol abuse and Hispanic individuals were at decreased risk of GAD compared with non-Hispanic Whites. This study also identified other sociodemographic risk factors for DSM-IV disorders not generally reported in prior research due to limitations in sample size. Incidences of alcohol and drug abuse and dependence, MDD, and GAD were greater among individuals who were separated, divorced, or widowed, a result that extended to never-married individuals for alcohol abuse and dependence. While these findings do not entirely clarify the causal relationship between marital status and psychopathology, they indicate that the relationship is not due solely to unmarried status resulting from preexisting psychopathology.

Among the most interesting findings of this study were the reciprocal temporal relationships between MDD and GAD, and between GAD and panic disorder. These findings suggest the existence of strong common causes underlying those disorders, stronger than the common factors characterizing comorbidity among other disorders except for alcohol abuse and dependence. The observed reciprocal relationship between MDD and GAD is consistent with results of twin studies showing these disorders to share joint genetic susceptibility. Findings on the relationship between GAD and panic disorder show GAD to be etiologically distinct from panic disorder, but more recent studies support a shared diathesis between GAD and panic disorder or additive genetic influences common to GAD and panic disorder in the presence of a nonadditive genetic contribution specific to panic disorder. The present results suggest that genetic research be expanded to encompass MDD, GAD, and panic disorder, along with other mood and anxiety disorders, for the purpose of unraveling common and unique genetic and environmental influences underlying comorbidity.

Taken together, the findings of this study call for more research in the rapidly growing field of psychiatric genetics, which has begun to expand phenotypic definitions beyond the study of a single disorder or trait to a range of phenotypes that show a high degree of comorbidity. Work in this area is beginning to identify latent genetic risk factors that indicate shared genetic susceptibility across a range of diagnostic phenotypes. Information on sociodemographic and psychopathologic risk factors prospectively identified in this study may also begin to inform a new class of interventions aimed at prevention of comorbidity (i.e., the prevention of the first onset of a second disorder or set of disorders). With regard to clinical implications, clearer data about the risks of future disorders posed by chronologically primary disorders can increase efficiency of treatment planning and provide important information to patients at risk of developing secondary disorders. Primary prevention of secondary disorders would be feasible even when the comorbid conditions share common causes. The onset of the secondary disorder is not inevitable because common causes often have modifiable mediators.

Representative publication:

Grant BF, Goldstein RB, Chou SP, Huang B, Stinson FS, Dawson DA, Saha TD, Smith SM, Pulay AJ, Pickering RP, Ruan WJ, Compton WM. Sociodemographic and psychopathologic predictors of first incidence of DSM-IV substance use, mood, and anxiety disorders: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. *Mol Psychiat* Epub ahead of print, 2008.

Prospectively ascertained consequences of risk drinking

NIAAA guidelines define low-risk drinking as no more than 14 drinks per week or 4 drinks on any given day for men and no more than 7 drinks per week or 4 drinks on any given day for women. Although numerous cross-sectional studies exist that document adverse correlates of exceeding the daily drinking guidelines, including many based on the Wave 1 NESARC data, their design precludes causal attribution. Data from Wave 2 of the NESARC provided the first opportunity to derive nationally representative estimates of the prospective harms associated with frequency of risk drinking (i.e., of exceeding the daily drinking limits). After controlling for differences in sociodemographic characteristics, psychopathology, other aspects of consumption and duration of drinking, daily or near daily risk drinking was associated with a seven-fold increase in the incidence of dependence and a three-fold increase in the incidence of abuse only. Smaller but significantly increased risks of AUD incidence were observed at lower frequencies as well.

Initiation of tobacco use and incidence of nicotine dependence were also increased at all frequencies of risk drinking, showing a fairly linear pattern of increase. Frequency of risk drinking did not show an independent association with the incidence of mood or anxiety disorders, CHD, arteriosclerosis, hypertension, gastric disease or arthritis, but the likelihood of developing liver disease was almost five times as high among daily/near daily risk drinkers as among drinkers who never exceeded the daily drinking limits. Daily/near daily risk drinkers were also at increased risk of marital disruption, spouse abuse and other forms of violent behavior, and rates of driver's license revocation rose steadily with increasing frequencies of risk drinking.

This study, through its application of successive levels of adjustment for sociodemographic characteristics, psychopathology and other substance use, and other aspects of alcohol

consumption, demonstrated that much of the excess incidence of harm among risk drinkers is attributable to factors other than risk drinking per se. However, it also provided clear evidence of the adverse effects solely attributable to exceeding the recommended daily drinking limits, highlighting the importance of addressing this behavior even before it develops into alcohol abuse or dependence.

Representative publication:

Dawson DA, Li TK, Grant BF. A prospective study of risk drinking: At risk for what?
Drug Alcohol Depend 93:21-9, 2008.

Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder in the United States

Although borderline PD is among the most frequently studied PDs in clinical settings, little is known about its prevalence, correlates, disability, and comorbidity in general population samples. This LEB study was designed to address these gaps in the literature by providing comprehensive and current information on borderline PD. This study found that borderline PD was more prevalent in the general population than previously recognized, with no differences in prevalence between men and women. Borderline PD was associated with considerable disability, especially among women. Rates of borderline PD were also higher among Native American men, younger and separated, divorced, and widowed adults, and those with lower incomes and less education. Lower risk of borderline PD was found among Hispanic men and women and Asian women than in their non-Hispanic White counterparts. Although borderline PD was inversely related to age, the greatest decline in rates occurred after age 44 years, indicating that borderline PD may not be as chronic as previously believed.

After adjustment for sociodemographic characteristics and other psychiatric disorders, associations of borderline PD with bipolar I and II disorders and narcissistic and schizotypal PDs were reduced, but remained strong and significant, indicating that both common and unique factors underlie these disorder-specific associations. Significant, but weaker, associations remained with alcohol dependence, MDD, social phobia, GAD, and posttraumatic stress disorder (PTSD), suggesting that much of the comorbidity of borderline PD with these disorders appears to reflect common factors. Subtle sex differences in the rates and associations of borderline PD can inform more focused, hypothesis-driven investigations.

Representative publication:

Grant BF, Chou SP, Goldstein RB, Huang B, Stinson FS, Saha TD, Smith SM, Dawson DA, Pulay AJ, Pickering RP, Ruan WJ. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions.
J Clin Psychiat 69:533-45, 2008.

Overweight, obesity, and psychopathology

The physical health risks associated with overweight and obesity are well known, but there has been far less research into the relationship between obesity and psychopathology. Data from the Wave 1 NESARC revealed that obesity and overweight were far more strongly associated with

sociodemographic factors, including age, gender, race-ethnicity, education, and income, than with psychopathology. AUDs did not demonstrate any significant associations with overweight or obesity, but illicit drug dependence was associated with a reduced risk of obesity in the population as a whole and for both men and women. Nicotine dependence showed a strong inverse dose-response relationship with BMI, reducing the likelihood of overweight, obesity and extreme obesity for the population as a whole and for men, but the negative associations fell short of significance among women. In addition, MDD was associated with a reduced risk of overweight among all adults, but this association was not significant for either men or women in gender-specific analyses.

In terms of positive associations, panic disorder was associated with an increased risk of overweight among men only, possibly signaling symptom overlap with undiagnosed cardiovascular disease or diabetes mellitus, type II. Most positive associations were limited to women, including those between GAD and the odds of overweight and obesity and between bipolar I and the odds of obesity and extreme obesity. In addition, the likelihood of extreme obesity was increased among women with avoidant and antisocial PDs, and the likelihood of overweight was increased among women with ASPD.

A second study based on the NESARC found that positive associations with overweight and obesity among women extended to the wider range of antisocial behavioral syndromes, including “CD only” and AABS. These data were suggestive of stronger associations among women with childhood symptomatology (CD alone or as part of ASPD) than among women whose antisocial behavior were restricted to adulthood. This unexpected finding suggests that the optimal ordering of antisocial behavioral syndromes along continua of externalizing disorder severity may differ by outcome, gender, or both. Future research will address this issue, in addition to investigating possible causal mechanisms underlying the associations observed between the full range of mental disorders and overweight and obesity.

Representative publications:

Pickering RP, Grant BF, Chou SP, Compton WM. Are overweight, obesity and extreme obesity associated with psychopathology? Results from a national survey.

J Clin Psychiat 68:998-1009, 2007.

Goldstein RB, Dawson DA, Saha TD, Ruan WJ, Compton WM, Grant BF. Antisocial behavioral syndromes and DSM-IV alcohol use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions.

Alcohol Clin Exp Res 31:814-28, 2007.

Violent behavior and DSM-IV psychiatric disorders

High rates of psychopathology among jail and prison inmates, combined with elevated risks of violent behavior among individuals with some Axis I and Axis II disorders, may lead to unwarranted stigmatization of the mentally ill as responsible for the majority of violent behavior. Data from the Wave 1 NESARC were used to look beyond patterns of association in a unique analysis that investigated the proportion of violent behavior accounted for by individuals with different types of DSM-IV disorders.

This study found that individuals with pure disorders of any type had lower rates of violent behavior both before and since age 15 than those with comorbid conditions. However, the

disparity in rates far underestimated the burden of violence associated with comorbidity, because comorbid conditions were also more common than pure disorders. Thus, while the prevalence of violent behavior was two to three times higher for individuals with comorbid compared to pure alcohol dependence, the comorbid group accounted for more than ten times as many violent individuals. After standardization for age, sex, and race-ethnicity, this approach revealed that individuals with only anxiety disorders accounted for just 1.33% of all violent persons in the population; those with only anxiety or mood disorders accounted for 5.27%; and those with only anxiety, mood or personality disorders accounted for 10.81%. Even individuals whose disorders were limited to all of those listed above plus nicotine dependence and pathological gambling accounted for less than one fifth of the violent population. When AUDs and DUDs were included, this estimate rose dramatically to 93.07% of all violent individuals. That is, individuals with AUDs and DUDs, rather than those who only had other mental disorders, were the primary source of violence in the U.S. population.

These findings extended the range of disorders known to have a significant association with violent behavior. More importantly, these results demonstrated that population estimates of violence are dependent not only on the relative risks of violence for different psychiatric disorders, but also the base rates of those disorders in the population. When both components of population estimates were considered, this study found that the burden of violence in the U.S. was not equally shared across the spectrum of psychiatric disorders. Future research will focus on the interplay of risk factors for violence in order to identify subgroups of individuals with psychiatric disorders who are particularly prone to violent behavior, with the goal of developing more effective violence prevention strategies.

Representative publication:

Pulay AJ, Dawson DA, Hasin DS, Goldstein RB, Ruan WJ, Pickering RP, Huang B, Chou SP, Grant BF. Violent behavior and DSM-IV psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions.
J Clin Psychiat 69:12-22, 2008.

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