Psychological Medicine (2009), **39**, 1365–1377. © 2008 Cambridge University Press
doi:10.1017/S0033291708004510 Printed in the United Kingdom

ORIGINAL ARTICLE

Mental disorders as risk factors for later substance dependence: estimates of optimal prevention and treatment benefits

M. D. Glantz[1]*, J. C. Anthony[2], P. A. Berglund[3], L. Degenhardt[4], L. Dierker[5], A. Kalaydjian[6], K. R. Merikangas[6], A. M. Ruscio[7], J. Swendsen[8] and R. C. Kessler[9]

[1] *Division of Epidemiology, Services and Prevention Research, National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD, USA*
[2] *Department of Epidemiology and Biostatistics, Michigan State University School of Medicine, East Lansing, MI, USA*
[3] *Institute for Social Research, University of Michigan, Ann Arbor, MI, USA*
[4] *National Drug and Alcohol Research Centre, University of New South Wales, Randwick, Australia*
[5] *Department of Psychology, Wesleyan University, Middletown, CT, USA*
[6] *National Institute of Mental Health, Bethesda, MD, USA*
[7] *Department of Psychology, University of Pennsylvania, Philadelphia, PA, USA*
[8] *National Scientific Research Center* (*CNRS 5231*), *Bordeaux, France*
[9] *Department of Health Care Policy, Harvard Medical School, Boston, MA, USA*

Background. Although mental disorders have been shown to predict subsequent substance disorders, it is not known whether substance disorders could be cost-effectively prevented by large-scale interventions aimed at prior mental disorders. Although experimental intervention is the only way to resolve this uncertainty, a logically prior question is whether the associations of mental disorders with subsequent substance disorders are strong enough to justify mounting such an intervention. We investigated this question in this study using simulations to estimate the number of substance disorders that might be prevented under several hypothetical intervention scenarios focused on mental disorders.

Method. Data came from the National Comorbidity Survey Replication (NCS-R), a nationally representative US household survey that retrospectively assessed lifetime history and age of onset of DSM-IV mental and substance disorders. Survival analysis using retrospective age-of-onset reports was used to estimate associations of mental disorders with subsequent substance dependence. Simulations based on the models estimated effect sizes in several hypothetical intervention scenarios.

Results. Although successful intervention aimed at mental disorders might prevent some proportion of substance dependence, the number of cases of mental disorder that would have to be treated to prevent a single case of substance dependence is estimated to be so high that this would not be a cost-effective way to prevent substance dependence (in the range 76–177 for anxiety-mood disorders and 40–47 for externalizing disorders).

Conclusions. Treatment of prior mental disorders would not be a cost-effective way to prevent substance dependence. However, prevention of substance dependence might be considered an important secondary outcome of interventions for early-onset mental disorders.

Received 11 June 2008; Revised 18 August 2008; Accepted 21 August 2008; First published online 2 December 2008

Key words: Mental disorders, prevention, substance dependence, treatment.

Introduction

A large proportion of people with alcohol and other drug disorders have a history of mental disorders (Allan, 1995; Kessler *et al*. 1996; Armstrong & Costello, 2002; Grant *et al*. 2004*a*; Chan *et al*. 2008). This has significant implications, as co-morbid cases often require more intensive treatment and have a poorer clinical course than other cases (Brooner *et al*. 1997; Swendsen & Merikangas, 2000; White *et al*. 2001). The reasons for this co-morbidity are unclear (Kessler, 1995; Waldman & Slutske, 2000; Willoughby *et al*. 2004). Although some studies suggest that substance disorders possibly precipitate mental disorders (e.g. Crum *et al*. 2005; Lukassen & Beaudet, 2005; Semple *et al*. 2005), reports of the reverse order predominate, with mental disorders typically found to begin at earlier ages than substance disorders (Merikangas

* Address for correspondence: Dr M. D. Glantz, 6001 Executive Boulevard, Suite 5185, MSC 9589 Bethesda, MD 20892, USA.
(Email: mglantz@nida.nih.gov)

et al. 1998; Costello *et al*. 1999; Kessler, 2004; Falk *et al*. 2008) and to predict subsequent onset of substance disorders (Armstrong & Costello, 2002; King *et al*. 2004; Cohen *et al*. 2007; Pardini *et al*. 2007; Wilens *et al*. 2008). The variability in findings probably reflects variability in temporal order, strength and pattern of association of particular mental disorders with substance disorders (Weinberg & Glantz, 1999; Compton *et al*. 2000; Zilberman *et al*. 2003; Sung *et al*. 2004; Jane-Llopis & Matytsina, 2006; Costello, 2007), as externalizing disorders and early-onset anxiety disorders typically precede and predict substance disorders, whereas the temporal-predictive relationships of substance disorders with mood disorders are more variable (Glantz, 2002).

To the extent that mental disorders have a causal influence on later substance disorders, prevention or early successful treatment of mental disorders might reduce subsequent substance disorders (Glantz & Leshner, 2000; White *et al*. 2001; Kendall & Kessler, 2002). Such an impact would presumably be greatest for youth, as the risk of severe secondary substance disorders is highest when mental disorders begin during childhood/adolescence (Kessler *et al*. 2001). It is unknown, however, how large a proportion of substance disorders might be prevented in this way. Randomized controlled trials could be used to answer this question, akin to studies of effects of school-based randomized prevention trials for primary prevention of socially maladaptive behavior problems on subsequent drug use (e.g. Kellam & Anthony, 1998; Furr-Holden *et al*. 2004). Given the enormous difficulty and expense of carrying out such interventions, however, a prudent first step is to estimate likely effects with non-experimental data. Preliminary estimates of this sort are routinely calculated in public policy research prior to implementing broad policy-based interventions (e.g. Jeffery, 1989; Dube *et al*. 2001; Wilson *et al*. 2002; Cook *et al*. 2005) to assess whether the intervention might be cost-effective.

To this end, the current report presents estimates of the possible effects of intervening to treat mental disorders on prevention of secondary substance dependence. We focus on dependence rather than abuse because mental disorders are known to predict the dependence more strongly than abuse (Roberts *et al*. 2007). The estimates reported here are not intended to be realistic estimates of intervention effects, as the latter can be obtained only from intervention studies, but upper-bound estimates. As described below, these estimates are based on simulations that use survival models from a general population survey on the associations of temporally primary mental disorders with subsequent nicotine dependence, alcohol dependence, and dependence syndromes involving cannabis, cocaine and other internationally regulated drugs (hereinafter, 'substance dependence'). A series of predicted prevalence estimates of substance dependence was generated from the model based on different hypothetical scenarios where we assumed one or more mental disorders could either be prevented or cured. Comparisons of prevalence estimates across scenarios were used to estimate possible treatment effects.

Method

Sample

The data came from the National Comorbidity Survey Replication (NCS-R; Kessler & Merikangas, 2004), a nationally representative face-to-face survey of people aged $\geqslant$18 years in the US household population interviewed between February 2001 and April 2003. The response rate was 70.9%. The current analysis focuses on respondents aged 18–44 years for reasons described below. The interview was in two parts. Part I included a core diagnostic assessment administered to all respondents ($n=9282$). Part II included questions about correlates and additional disorders administered to all Part I respondents with any lifetime core disorder plus a probability subsample of other Part I respondents ($n=5692$). Externalizing disorders that typically begin in childhood, including attention deficit hyperactivity disorder (ADHD), oppositional-defiant disorder (ODD) and conduct disorder (CD), were assessed only among Part II respondents in the age range 18–44 years ($n=3199$) because of concern about long-term recall bias among older respondents. In addition, there were major secular changes in illegal drug use and dependence after the 1950s. Consequently, only Part II respondents aged 18–44 are included in the current report. This subsample was weighted to adjust for differential probabilities of selection, oversampling of Part I cases, and residual discrepancies between the sample and the population. More details on NCS-R weighting are reported elsewhere (Kessler *et al*. 2004).

Assessment

DSM-IV mental and substance disorders were assessed with the World Health Organization (WHO) Composite International Diagnostic Interview Version 3.0 (CIDI; Kessler & Üstün, 2004). In addition to nicotine, alcohol and other drug dependence, the CIDI assessed anxiety disorders [panic disorder, generalized anxiety disorder (GAD), phobias, post-traumatic stress disorder (PTSD)], mood disorders (major depressive disorder, bipolar disorder, dysthymic disorder), and the externalizing disorders noted above in

addition to intermittent explosive disorder (IED). In addition to lifetime history, retrospective age-of-onset (AOO) reports obtained for each disorder were used to establish temporal order in the sequencing of disorder onset.

In the CIDI substance use module, respondents were asked if they ever used: alcohol, tobacco (cigarettes, cigars or pipes), cannabis (marijuana, hashish), cocaine, prescription drugs (sedatives, tranquilizers, painkillers, stimulants) either without the recommendation of a health professional or for any reason other than what a health professional said they should be used, and any other illegal drugs (heroin, opium, glue, LSD, peyote, or other substances). In the case of tobacco use, the CIDI then went on to assess features of smoking history (e.g. age of first use, age of first regular use, number of years used, etc.) and DSM-IV criteria for lifetime dependence. AOO was assessed for the first symptom of dependence, not the full dependence syndrome. In the case of alcohol and other drugs, questions were asked about smoking history and lifetime history of substance abuse. Abuse was assessed only once for illegal drugs, not separately for each type of illegal drug used. AOO was assessed for the first symptom of abuse. Respondents who reported any lifetime symptom of abuse were then assessed for history of dependence, but no additional questions were asked about AOO of dependence symptoms.

Respondents who denied any history of abuse, in comparison, were not assessed for dependence. This approach to the assessment of dependence only among respondents with a history of abuse focuses attention on dependence syndromes that have clinical significance in the form of a socially maladaptive or hazard-laden pattern of use. This approach undercounts mild alcohol dependence cases (Grant *et al*. 2004*a*; Degenhardt *et al*. 2007*a*), but does not seem to appreciably undercount dependence on illegal drugs (Degenhardt *et al*. 2007*b*, 2008). Moreover, satisfactory concordance was found in NCS-R methodological research that compared dependence diagnoses based on blinded clinical reappraisal interviews using the Structured Clinical Interview for DSM-IV (SCID; First *et al*. 2002)) with those based on the CIDI (Haro *et al*. 2006).

As retrospective AOO reports played an important part in these analyses, it should be noted that previous research has shown aggregate AOO distributions of lifetime DSM disorders in community surveys to have an implausible shape that seems to be generated by AOO being reported as occurring more recently than it actually did (Simon & Von Korff, 1992, 1995). Analysis of question-wording experiments has shown that this problem of 'telescoping' AOO reports can be corrected using AOO question probes that make respondents aware that AOO questions are difficult to answer accurately, encourages respondents to think carefully before answering, and accepts upper-bound estimates (i.e. the earliest age the respondent feels confident in saying that an episode occurred) when exact AOO cannot be recalled (Knauper *et al*. 1999). This sophisticated AOO question-probing strategy was used in the NCS-R to improve the accuracy of AOO reports.

Sociodemographic correlates

Six sociodemographic controls were included in the analyses. Three were time invariant: age at interview (cohort), gender and race-ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Other). The other three were time varying, which means that we coded them at different values in different years of each respondent's life: person-year (each year of life of each person in the sample), education (the respondent's level of educational attainment to date at each year of risk) and marital status (whether the respondent was never married, married, or previously married at each year of risk).

Analysis methods

Associations of mental disorders with substance dependence were examined in four stages. First, we calculated odds ratios (ORs) of cross-sectional associations between lifetime mental disorders and lifetime substance dependence to obtain basic descriptive information.

Second, we compared AOO reports of mental and substance disorders among respondents with a history of both to assess typical temporal sequencing.

Third, we used discrete-time survival analysis (Efron, 1988) to examine associations of mental disorders (which were treated as time-varying predictors) with subsequent first onset of substance dependence. Mental disorders were defined as temporally primary only if their AOOs were reported to be earlier than the AOO of the respondent's first substance problem. The limitations of this approach to assessing AOO sequencing are discussed below. A dummy predictor variable for *active* presence of each mental disorder was coded (A), beginning at the reported AOO of that disorder to the age of most recently having the disorder. A separate dummy predictor variable for each *remitted* mental disorder (R) was created for the years after offset of the most recent episode. Comparison of survival coefficient for active *versus* remitted cases in a multivariate model that included all disorders as predictors along with basic

sociodemographic controls was used to make provisional inferences about the potential effects of successfully treating mental disorders.

Fourth, we carried out simulations to estimate the potential effects of both prevention and successful treatment of mental disorders in reducing subsequent substance dependence. The simulations, described below, evaluated the extent to which the estimated (based on the survival models) prevalence of substance dependence would decrease if one or more mental disorders were either prevented or successfully treated. These simulation results implicitly assumed that the survival coefficients represent causal effects of mental disorders. To the extent that this assumption is incorrect, the simulated effect estimates will tend to have an upward bias.

We simulated three scenarios. Scenario 1 was the case of no mental disorders ever occurring. The rationale for this was that it represents a best-case scenario. This simulation was implemented by setting the prevalence estimates of all the mental disorders in the model to zero. Scenario 2 was the case of remission of all mental disorders that had onsets during the school years (i.e. prior to age 18) within 2 years of onset. The rationale for this was that a 2-year treatment-recovery period was considered a best-case scenario for timely detection, treatment and cure. This simulation was implemented by recoding all active mental disorders with onsets prior to age 18 as remitted 2 years after onset. Scenario 3 was the case of remission of all mental disorders within 3 years of onset no matter what their AOO. The rationale for this was that a 3-year treatment-recovery period was considered a best-case scenario for timely detection, treatment and cure of mental disorders in the absence of ongoing monitoring during the school years. This simulation was implemented by recoding all active mental disorders as remitted 3 years after onset.

There were a total of 100 069 person-years in the lives of the 3199 18- to 44-year-old Part II NCS-R respondents (an average of 31 years of life per respondent). Each survival analysis used person-year as the unit of analysis and focused on the subset that began with the year of first use of the substance in question and continued up to and including either (i) the year of interview for respondents who never had dependence or (ii) the year of first onset of dependence for respondents who had dependence. The year of onset of dependence was coded 1 and all earlier years 0 on the dependent variable. Each person-year included information about time-invariant characteristics (gender, race-ethnicity, age at interview) and time-varying characteristics (age, education, and marital status at that time in the respondent's life; and history of mental disorders as of that time in the respondent's life). Dummy variables were included for each active and remitted mental disorder assessed in the survey.

Simulation results were summarized by two descriptive statistics: the Population Attributable Risk Proportion (PARP; Walter, 1978) and the Number Needed to Treat (NNT; McQuay & Moore, 1997). PARP is the proportion of observed cases of substance dependence estimated not to occur in the absence of the disorders included in the simulation based on the assumption that the coefficients in the model are due to causal effects of the disorders. NNT is the number of mental disorders that would be needed to prevent or treat in order to prevent one case of secondary substance dependence. Standard formulas exist to calculate both PARP (Walter, 1978) and NNT (McQuay & Moore, 1997). We needed to examine both PARP and NNT because there is no one-to-one relationship between the two measures. PARP is a population-level measure whereas NNT is an individual-level measure. NNT will be larger in a situation where the predictor is highly prevalent and the survival coefficient is relatively weak than in a situation that generates the same PARP based on a smaller proportion of the population having the predictor and the survival coefficient being stronger.

The simulations were carried out by using the coefficients in the final survival equations to generate a conditional probability of first onset of each outcome for each year of life of each respondent using the actual values of the predictor variables for each person-year. The actuarial method (Halli *et al*. 1992) was used to cumulate these conditional probabilities across the lifespan of each respondent using the formula

$$\mathrm{CuP}_{t+1} = \mathrm{CuP}_t + (1 - \mathrm{CuP}_t)\ \mathrm{CoP}_{t+1},$$

where CuP_{t+1} is the cumulative probability of having a first onset of the disorder up to the end of year $t+1$ and CoP_{t+1} is the conditional probability of having a first onset in year $t+1$ among people with no history of the disorder as of year t. The mean of CuP for respondents as of their age at interview was then calculated to estimate the proportion of respondents expected to have the outcome based on the actual data. The process of calculating CoP_t for each person-year and then cumulating these estimates for person-level estimates of CP was repeated three more times, each time using the same survival coefficients but modifying the input data to impose simulated scenario constraints. In scenario 1, all values of A and R for all mental disorders were recoded N. In scenario 2, all values of A were recoded R after the first 2 years of onset when the mental disorder occurred before age 18. In scenario 3, all values of A were recoded R after the first 3 years of onset.

Because the NCS-R sample design used weighting and clustering, all analyses were carried out using the design-based Taylor series linearization method (Wolter, 1985) implemented in the SAS software system (SAS Institute, 2002). Multivariate significance was estimated in logistic regression equations using Wald χ^2 tests based on design-corrected coefficient variance–covariance matrices. Statistical significance was evaluated using two-sided 0.05 level tests.

Results

Prevalence and co-morbidity

Lifetime prevalence estimates of DSM-IV substance dependence among respondents in the 18–44 age range were 7.9% for nicotine, 15.5% for alcohol and 11.6% for other drugs (Table 1). Substance dependence is strongly associated with mental disorders. All 39 bivariate ORs of the 13 DSM-IV mental disorders with the three types of substance dependence are statistically significant. Across mental disorders, the ORs are lower for DSM-IV nicotine dependence than other types of dependence. Across substances, the ORs are highest for externalizing disorders and lowest for anxiety disorders.

Temporal order

AOO distributions show that first symptoms of substance disorders typically occur in young adulthood, with medians (25th–75th percentiles) of 21 (19–32) for nicotine, 21 (18–28) for alcohol and 28 (20–40) for other drugs (Kessler *et al*. 2005). Comparison of AOO reports for individual mental–substance pairs (Table 2) shows that externalizing disorders are most likely to precede nicotine dependence (91.6%), alcohol dependence (92.8%) and other drug dependence (90.9%). Anxiety disorders are also highly likely to precede nicotine dependence (81.5%), alcohol dependence (80%) and illegal drug dependence (81.7%). Mood disorders, in comparison, are only slightly more likely to precede nicotine dependence (56.5%) than the reverse and somewhat less likely to precede alcohol dependence (46%) and other drug dependence (45.9%) than the reverse.

Active and remitted mental disorders predicting onset of substance dependence

Several different multivariate models were tested to arrive at a final model to predict each type of dependence. Only summary results are reported here (detailed results available on request). We began by estimating multivariate models that distinguished the predictive effects of the 13 active [$\chi^2(13) = 265.9$–628.7, $p < 0.001$] *versus* remitted [$\chi^2(10$–$11) = 38.0$–148.7, $p < 0.001$] mental disorders. The number of coefficients in the models for remitted disorders varied across outcomes because sparse data made it impossible to estimate coefficients for some less common remitted disorders for some outcomes. Disorder-specific comparison showed that the survival coefficients for active *versus* remitted mental disorders did not differ from each other as a set in a global test in predicting nicotine dependence [$\chi^2(11) = 17.5$, $p = 0.095$], but did differ in predicting alcohol [$\chi^2(9) = 52.7$, $p < 0.001$] and other drug [$\chi^2(10) = 60.1$, $p < 0.001$] dependence. Individual disorders differed significantly in their prediction of nicotine dependence once active and remitted disorders were combined [$\chi^2(12) = 56.0$, $p < 0.001$]. There were also differences among active [$\chi^2(12) = 161.5$, $p < 0.001$] but not remitted [$\chi^2(9) = 15.3$, $p = 0.083$) disorders in predicting alcohol dependence, and among both active [$\chi^2(12) = 437.2$, $p < 0.001$] and remitted [$\chi^2(9) = 32.8$, $p < 0.001$] disorders in predicting other drug dependence. Again, the number of coefficients in the models varied because we were unable to estimate coefficients for some less common disorders in all models.

The final trimmed models retained only mental disorders with statistically significant or substantively meaningful (i.e. OR $\geqslant 1.5$) survival coefficients. All retained predictors were either active disorders or combinations of active and remitted disorders (Table 3). Externalizing disorders were both the strongest and most consistent predictors in these final models. The coefficients did not differ, as a set, either by respondent gender [$\chi^2(5$–$7) = 6.9$–10.6, $p = 0.439$–0.155] or life stage [defined in terms of person-years 1–19, 20–29, 30–44; $\chi^2(10$–$14) = 7.9$–230, $p = 0.794$–0.060].

Estimated effects of mental disorders on substance dependence

Simulations based on the coefficients in the final trimmed survival models generated PARP estimates for the first scenario (i.e. prevention of all mental disorders) of 31.3% for nicotine dependence, 20.5% for alcohol dependence, and 21.6% for other drug dependence (Table 4). The second and third scenarios were simulated only for alcohol and illegal drug dependence based on the fact that active and remitted mental disorders did not differ in predicting onset of nicotine dependence. PARP estimates for the second scenario were 10.1% for alcohol and 12.8% for illegal drugs, and those for the third scenario were 11.3% for alcohol and 14.0% for illegal drugs. NNT was calculated only for scenarios 2 and 3, as scenario 1 involves prevention rather than treatment. NNT was in the range 19–44 for anxiety-mood disorders and 10–12 for

Table 1. *Lifetime co-morbidity (odds ratios) between DSM-IV substance dependence and DSM-IV mental disorders among Part II NCS-R respondents aged 18–44 (n = 3199)*[a]

	Dependence in the total sample						Dependence among lifetime users					
	Nicotine		Alcohol		Any illegal		Nicotine		Alcohol		Any illegal	
Lifetime prevalence	7.9[b]	(0.5)	15.5[b]	(0.8)	11.6[b]	(0.7)	17.0[b]	(1.1)	16.6[b]	(0.9)	20.2[b]	(1.1)
I. Mood disorders												
Major depression	2.5*	(1.8–3.5)	2.3*	(1.9–2.8)	1.9*	(1.6–2.3)	2.2*	(1.5–3.3)	2.2*	(1.8–2.7)	1.5*	(1.2–1.9)
Bipolar disorder	3.4*	(2.0–5.9)	5.6*	(4.1–7.7)	5.8*	(4.3–8.0)	2.1*	(1.2–3.7)	5.3*	(3.8–7.4)	4.9*	(3.5–7.0)
Dysthymia	4.2*	(2.6–6.6)	3.9*	(2.9–5.2)	3.9*	(2.7–5.7)	3.0*	(1.9–4.6)	4.0*	(2.9–5.4)	3.2*	(2.1–4.9)
II. Anxiety disorders												
Panic disorder	2.4*	(1.6–3.5)	3.6*	(2.5–5.2)	2.9*	(2.0–4.2)	1.8*	(1.2–2.8)	3.5*	(2.4–5.1)	2.1*	(1.5–2.9)
Social phobia	2.6*	(1.8–3.6)	2.8*	(2.2–3.4)	3.0*	(2.4–3.8)	2.3*	(1.5–3.3)	2.8*	(2.2–3.5)	2.4*	(1.8–3.1)
Specific phobia	1.9*	(1.4–2.7)	2.0*	(1.5–2.6)	2.1*	(1.5–2.9)	1.8*	(1.3–2.5)	2.0*	(1.5–2.6)	1.9*	(1.4–2.6)
GAD	1.9*	(1.3–2.8)	2.5*	(1.9–3.4)	2.5*	(1.8–3.5)	1.5*	(1.0–2.2)	2.4*	(1.8–3.2)	2.0*	(1.4–2.9)
PTSD	2.4*	(1.5–3.9)	3.0*	(2.1–4.2)	3.6*	(2.5–5.3)	1.8*	(1.1–3.0)	2.8*	(2.0–4.0)	2.5*	(1.7–3.7)
Agoraphobia	3.1*	(1.8–5.6)	3.4*	(2.0–5.9)	3.4*	(2.2–5.2)	2.0*	(1.0–3.9)	3.6*	(2.1–6.1)	2.8*	(1.8–4.4)
III. Externalizing disorders												
IED	2.5*	(1.9–3.4)	3.2*	(2.5–4.2)	2.9*	(2.2–3.8)	1.9*	(1.3–2.7)	3.1*	(2.4–4.1)	2.2*	(1.6–2.9)
ODD	3.1*	(2.1–4.5)	4.8*	(3.7–6.3)	6.0*	(4.3–8.4)	1.8*	(1.3–2.7)	4.7*	(3.6–6.1)	4.4*	(3.1–6.2)
CD	4.0*	(2.8–5.7)	5.3*	(3.9–7.2)	6.4*	(4.7–8.7)	2.5*	(1.9–3.4)	5.0*	(3.7–6.9)	4.3*	(3.1–6.0)
ADHD	4.4*	(3.1–6.4)	3.0*	(2.2–4.1)	4.0	(2.9–5.7)	3.2*	(2.3–4.5)	2.9*	(2.2–4.0)	3.1*	(2.1–4.5)
IV. Any disorder												
Any mood disorder	3.5*	(2.5–4.8)	3.6*	(3.0–4.3)	3.3*	(2.7–4.0)	2.7*	(2.0–3.6)	3.5*	(2.9–4.2)	2.6*	(2.1–3.3)
Any anxiety disorder	2.5*	(1.8–3.4)	2.7*	(1.3–3.3)	2.9*	(2.4–3.6)	2.1*	(1.5–3.0)	2.7*	(2.2–3.3)	2.3*	(1.8–3.0)
Any externalizing disorder	4.1*	(3.0–5.5)	4.3*	(3.4–5.3)	4.9*	(3.9–6.0)	2.7*	(2.0–3.6)	4.1*	(3.3–5.1)	3.4*	(2.7–4.3)
Any disorder	3.9*	(2.8–5.6)	4.1*	(3.2–5.3)	4.9*	(3.8–6.4)	3.0*	(2.1–4.3)	3.9*	(3.0–5.1)	3.6*	(2.7–4.9)
V. Number of mental disorders												
0	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–
1	2.3*	(1.6–3.2)	2.0*	(1.4–2.9)	2.7*	(1.8–4.1)	2.0*	(1.4–2.9)	1.9*	(1.3–2.8)	2.3*	(1.4–3.5)
2	3.2*	(2.0–5.0)	3.7*	(2.6–5.1)	3.9*	(2.8–5.4)	2.5*	(1.6–4.1)	3.6*	(2.5–5.2)	2.8*	(1.9–4.0)
⩾3	6.7*	(4.3–10.3)	8.1*	(6.3–10.4)	9.1*	(7.1–11.9)	4.1*	(2.6–6.4)	7.8*	(6.0–10.0)	6.0*	(4.5–8.0)

GAD, Generalized anxiety disorder; PTSD, post-traumatic stress disorder; IED, intermittent explosive disorder; ODD, oppositional-defiant disorder; CD, conduct disorder; ADHD, attention deficit hyperactivity disorder.

Values are given as % (standard error) or odds ratio (95% confidence interval).

[a] Controlling for age, gender and race-ethnicity.

[b] Lifetime prevalence of DSM-IV substance dependence among Part II respondents aged 18–44 years.

* Significant at the 0.05 level, two-sided test.

Table 2. *Temporal priority of DSM-IV mental disorders in relation to first onset of either substance use or DSM-IV substance dependence among Part II NCS-R respondents aged 18–44 with specific mental–substance co-morbidities*[a]

	Mental disorder occurred before use					Mental disorder occurred before dependence		
	Tobacco	Alcohol	Cannabis	Cocaine	Any illegal	Nicotine	Alcohol	Any illegal
I. Mood disorders								
Major depression	16.6 (1.6)	17.4 (1.5)	32.2 (2.2)	52.4 (2.5)	31.6 (2.2)	55.2 (3.0)	43.7 (3.8)	44.2 (4.5)
Bipolar disorder	21.3 (3.0)	18.3 (2.0)	37.7 (3.2)	51.8 (5.1)	34.8 (3.3)	52.9 (5.2)	45.6 (4.5)	44.0 (3.9)
Dysthymia	17.2 (3.7)	21.9 (2.3)	36.8 (3.6)	54.5 (4.2)	36.1 (3.2)	51.7 (5.5)	47.5 (4.8)	46.3 (6.1)
II. Anxiety disorders								
Panic disorder	23.4 (2.3)	26.8 (2.1)	36.3 (2.4)	52.4 (4.0)	31.3 (2.8)	60.3 (3.7)	50.8 (4.4)	49.9 (4.7)
Social phobia	60.0 (2.0)	67.7 (1.6)	81.1 (1.8)	90.3 (1.7)	80.6 (1.8)	88.1 (1.8)	90.3 (1.6)	87.8 (2.3)
Specific phobia	83.3 (2.2)	81.9 (1.2)	92.5 (1.2)	92.6 (1.8)	89.0 (1.4)	91.7 (2.0)	92.7 (1.6)	94.2 (1.6)
GAD	19.9 (2.5)	21.3 (2.0)	38.7 (2.6)	51.1 (5.6)	37.6 (2.5)	53.7 (7.5)	44.3 (4.2	47.9 (3.2)
PTSD	23.6 (2.2)	30.3 (2.3)	41.7 (2.6)	59.5 (7.7)	40.6 (2.6)	48.9 (4.2)	43.0 (3.2)	46.0 (3.9)
Agoraphobia	45.1 (4.0)	44.5 (3.3)	61.4 (4.6)	66.1 (7.1)	56.7 (4.4)	68.3 (4.4)	57.5 (5.5)	62.2 (5.3)
III. Externalizing disorders								
IED	42.6 (2.2)	46.9 (2.3)	67.0 (2.3)	86.3 (2.2)	66.4 (2.5)	86.2 (1.9)	81.4 (2.0)	74.9 (3.3)
ODD	55.9 (3.6)	61.1 (3.9)	80.6 (2.1)	95.7 (1.6)	79.5 (2.3)	94.7 (3.0)	92.5 (1.9)	91.1 (2.0)
CD	44.7 (2.8)	45.2 (2.8)	64.3 (3.2)	96.1 (1.0)	63.8 (3.2)	95.3 (1.6)	94.2 (1.7)	88.7 (3.4)
ADHD	89.6 (2.1)	86.4 (2.4)	98.0 (0.7)	99.5 (0.5)	98.1 (0.8)	98.2 (1.8)	99.4 (0.6)	99.3 (0.7)
IV. Any disorder								
Any mood disorder	18.5 (1.4)	18.8 (1.6)	34.7 (1.7)	54.4 (2.7)	33.5 (1.7)	56.5 (2.9)	46.0 (2.4)	45.9 (3.9)
Any anxiety disorder	60.9 (1.6)	64.0 (1.2)	73.4 (1.6)	82.9 (1.6)	72.8 (1.6)	81.5 (1.7)	80.0 (0.9)	81.7 (2.3)
Any externalizing disorder	59.5 (1.6)	62.7 (1.8)	80.4 (1.6)	95.6 (0.8)	80.2 (1.4)	91.6 (1.4)	92.8 (0.0)	90.9 (2.9)
Any disorder	58.0 (1.2)	59.7 (0.9)	73.6 (1.3)	89.1 (1.0)	73.0 (1.1)	82.9 (1.7)	83.1 (1.5)	84.6 (1.3)

GAD, Generalized anxiety disorder; PTSD, post-traumatic stress disorder; IED, intermittent explosive disorder; ODD, oppositional-defiant disorder; CD, conduct disorder; ADHD, attention deficit hyperactivity disorder.

[a] Each entry to the table is based on the subsample of respondents with lifetime co-morbidity of the mental disorder in the row and the substance use or dependence in the column. Values are given as % (standard error), where % represents the percentage of respondents in the cell who reported that first onset of the mental disorder occurred at an earlier age than first onset of substance use or first symptom of substance dependence.

Table 3. *Survival coefficients of temporally primary DSM-IV mental disorders predicting the subsequent first onset of substance dependence among Part II NCS-R respondents aged 18–44 (n = 3199)*[a]

	Nicotine			Alcohol			Any illegal		
	OR	(95% CI)	A/R	OR	(95% CI)	A/R[2]	OR	(95% CI)	A/R
I. Mood disorders									
Major depression	2.3*	(1.6–3.2)	A + R	2.0*	(1.5–2.6)	A	1.7*	(1.2–2.2)	A
Bipolar disorder	1.6	(0.7–3.9)	A + R	2.7*	(1.8–4.0)	A	2.3*	(1.4–3.8)	A
II. Anxiety disorders									
Panic disorder	–	–	–	1.5	(0.9–2.4)	A	–	–	–
Social phobia	–	–	–	1.5*	(1.2–1.9)	A + R	1.5*	(1.1–1.9)	A + R
Specific phobia	–	–	–	–	–		1.3*	(1.0–1.8)	A
III. Externalizing disorders									
IED	1.5*	(1.1–2.2)	A + R	1.6*	(1.2–2.1)	A + R	–	–	–
ODD	–	–	–	2.0*	(1.6–2.6)	A + R	2.3*	(1.7–3.0)	A + R
CD	2.3*	(1.7–3.2)	A + R	3.8*	(2.9–5.1)	A	4.0*	(3.0–5.4)	A
ADHD	2.4*	(1.6–3.4)	A + R	–	–	–	1.3*	(0.9–1.9)	A + R

IED, Intermittent explosive disorder; ODD, oppositional-defiant disorder; CD, conduct disorder; ADHD, attention deficit hyperactivity disorder; OR, odds ratio; CI, confidence interval; A, the predictor is the active mental disorder; R, the remitted mental disorder; A + R, the predictor is a combination of either the active or the remitted mental disorder.

[a] Based on multivariate equations including all mental disorders to predict dependence, controlling for person-year, age, gender and race-ethnicity.

* Significant at the 0.05 level, two-sided test.

externalizing disorders in these two scenarios respectively.

Discussion

Several study limitations should be noted. First, the analyses used retrospective AOO reports to reconstruct temporal order. Differential recall error could bias results. Second, we excluded respondents without a history of abuse from a diagnosis of dependence, leading to a restriction in the coverage of dependence to those with socially maladaptive or hazardous use. However, this restriction is likely to be small (Degenhardt *et al*. 2007*b*, 2008). Third, the only AOO information recorded was AOO of first symptom of abuse (alcohol, illegal drugs) or dependence (nicotine). To the extent that mental disorders that begin subsequent to these first symptoms predict subsequent progression to dependence, we will have underestimated the overall predictive effects of these disorders in our analysis. Fourth, as we focused only on time-lagged predictive associations, we also underestimated the predictive effects of mental disorders on subsequent onset of substance dependence in the year of onset of the mental disorders.

Within the context of these limitations, the lifetime prevalence estimates of DSM-IV substance dependence reported here are broadly consistent with other general population surveys (Helzer *et al*. 1990; Kessler *et al*. 1994; Grant *et al*. 2004*b*). The strong associations of many mental disorders with lifetime substance dependence are also consistent with previous studies (Regier *et al*. 1990; Kessler *et al*. 1994; Grant & Harford, 1995; Grant *et al*. 2004*a*). The finding that temporally primary mental disorders significantly predict subsequent substance dependence, with the greatest risk associated with externalizing disorders, is also consistent with previous epidemiological studies based on both retrospective (Kessler *et al*. 2001, 2003) and prospective (Lewis *et al*. 1983; Dembo *et al*. 1985; Schuckit & Hesselbrock, 1994; Kranzler *et al*. 1996; Kushner *et al*. 1999) data. The finding that the weakest predictive relationships are with mood disorders is also consistent with previous research (e.g. Patton *et al*. 2002; Degenhardt *et al*. 2003).

The simulated PARP estimates are broadly consistent with those in the one earlier simulation study of this type ever undertaken, in a series of cross-national WHO surveys (Kessler *et al*. 2001). These earlier estimates, however, focused exclusively on active disorders and considered a narrower range of externalizing disorders than the NCS-R.

It is important to recognize that the PARP and NNT estimates are based on two unrealistic assumptions: that the observed associations between mental disorders and later substance dependence are entirely

Table 4. *Population Attributable Risk Proportions (PARP) of lifetime substance dependence associated with temporally primary mental disorders based on three simulation scenarios*

	Nicotine (%)	Alcohol (%)	Any illegal (%)
I. Scenario 1			
Mood-anxiety	11.8	7.0	6.5
Externalizing	23.6	14.3	16.3
All mental disorders	31.3	20.5	21.6
II. Scenario 2			
Mood-anxiety	–	4.1	5.6
Externalizing	–	5.8	7.3
All mental disorders	–	10.1	12.8
III. Scenario 3			
Mood-anxiety	–	5.0	6.1
Externalizing	–	6.2	8.2
All mental disorders	–	11.3	14.0

Scenario 1: The estimated effects of preventing any of the mental disorders from ever occurring. Scenario 2: The estimated effects of recovery/successfully treating within 2 years of onset all mental disorders with onsets prior to age 18. Scenario 3: The estimated effects of recovery/successfully treating within 3 years all mental disorders irrespective of their age of onset. In each of the three scenarios, separate simulations were carried out for preventing or treating only mood and anxiety disorders, only externalizing disorders, and all three types of mental disorders.

due to causal effects of mental disorders; and that it would be possible to prevent or cure all of these mental disorders with treatment. The first assumption is unrealistic in that mental and substance dependence are almost certainly influenced by common causes (Glantz *et al*. 2005; Krueger *et al*. 2007). The second assumption is unrealistic because no intervention for mental disorders approaches 100% effectiveness (Connor *et al*. 2006; Sartorius *et al*. 2007; Gilchrist & Arnold, 2008; Nelson, 2008).

We might have attempted to estimate the latter effect, as we have information on age of first seeking treatment for mental disorders. However, cases that seek treatment are typically more severe than those that do not, often leading treatment to be associated with *increased* rather than *decreased* risk of subsequent persistence, severity and onset of secondary disorders. Because of this problem, we made no attempt to estimate the extent to which treatment of mental disorders predicted subsequent risk of substance dependence.

In light of the above considerations, the actual effects of real treatment of primary mental disorders would probably be smaller than the upper-bound estimates reported here. For example, if only half the mental disorders treated were cured (a reasonable upper bound based on the results of published treatment effectiveness studies) and if only half the predictive effects of mental disorders on later substance dependence are causal, then the actual PARP associated with real-world interventions might be no more than 25% as large as the PARP estimates reported here and the NNT would be four times as large as the NNT estimates reported here. NNT is the most important statistic here, as cost-effectiveness is judged in terms of costs per effectively treated case. Based on reasonable best-case assumptions, NNT would be in the range 76–177 for anxiety-mood disorders and 40–47 for externalizing disorders. Numbers of this size are well outside the range considered cost-effective to prevent a single case of substance dependence. Therefore, even though we found that mental disorders significantly predict subsequent substance dependence, we cannot conclude that prevention or early successful treatment of mental disorders would have a cost-effective impact in preventing subsequent substance dependence in the general population.

At the same time, the NCS-R data show clearly that people with mental disorders have a meaningfully elevated risk of substance dependence. This means that information about mental disorders might be useful as part of a risk formula to target preventive interventions even if the focus of the interventions was on risk factors other than on the mental disorders themselves. Externalizing disorders might be especially important risk markers in this regard (Hicks *et al*. 2004; Glantz *et al*. 2005; Verona & Sachs-Ericsson, 2005), as they are the most strongly predictive of later substance dependence and the only class of disorders for which no difference was found in the magnitude of survival coefficients associated with active and remitted disorders.

It is also noteworthy that the effects of mental disorder treatment interventions in preventing onset of secondary substance dependence, although too small to provide a primary justification for these interventions, might be considered important secondary outcomes in evaluating such interventions. Follow-up over a period of several years might be needed to detect these effects, so the addition of a long-term follow-up component to experimental interventions to treat mental disorders could be valuable in documenting secondary benefits such as this (Kessler *et al*. 2008). Furthermore, even if interventions to treat mental disorders would not completely avert cases of substance dependence, they might mitigate the severity,

course or collateral problems associated with substance dependence and, in particular, cases of comorbidity.

Conclusions

The estimates reported here suggest that interventions to prevent or treat temporally primary mental disorders would, even under optimistic assumptions, have effects in preventing subsequent substance dependence that are apt to be too small to justify these interventions primarily on the grounds of preventing substance dependence. Thus, although the development of early intervention programs for mental disorders remains an important goal in its own right, the role of such interventions in preventing secondary substance dependence should be considered a potential side-benefit rather than a primary rationale. At the same time, it might prove valuable to use information about mental disorders to help target high-risk groups for substance abuse preventive interventions aimed at common underlying causes of both mental disorders and substance use disorders.

Acknowledgments

The National Comorbidity Survey Replication (NCS-R) is supported by the National Institute of Mental Health (NIMH) (U01-MH60220) with supplemental support from the National Institute on Drug Abuse (NIDA) (J.C.A.: K05DA015799; R01DA016558; R.C.K.: R01DA011121), the Substance Abuse and Mental Health Services Administration (SAMHSA), the Robert Wood Johnson Foundation (RWJF; Grant 044780), and the John W. Alden Trust. Collaborating NCS-R investigators include Ronald C. Kessler (Principal Investigator, Harvard Medical School), Kathleen Merikangas (Co-Principal Investigator, NIMH), James Anthony (Michigan State University), William Eaton (The Johns Hopkins University), Meyer Glantz (NIDA), Doreen Koretz (Harvard University), Jane McLeod (Indiana University), Mark Olfson (New York State Psychiatric Institute, College of Physicians and Surgeons of Columbia University), Harold Pincus (University of Pittsburgh), Greg Simon (Group Health Cooperative), Michael Von Korff (Group Health Cooperative), Philip Wang (Harvard Medical School), Kenneth Wells (UCLA), Elaine Wethington (Cornell University), and Hans-Ulrich Wittchen (Max Planck Institute of Psychiatry, Technical University of Dresden). The views and opinions expressed in this report are those of the authors and should not be construed to represent the views of any of the sponsoring organizations, agencies, or the U.S. Government. A complete list of NCS publications and the full text of all NCS-R instruments can be found at www.hcp.med.harvard.edu/ncs. Send correspondence to ncs@hcp.med.harvard.edu.

The NCS-R is carried out in conjunction with the World Health Organization (WHO) World Mental Health (WMH) Survey Initiative. We thank the staff of the WMH Data Collection and Data Analysis Coordination Centres for assistance with instrumentation, fieldwork and consultation on data analysis. These activities were supported by the NIMH Health (R01 MH070884), the John D. and Catherine T. MacArthur Foundation, the Pfizer Foundation, the US Public Health Service (R13-MH066849, R01-MH069864, and R01 DA016558), the Fogarty International Center (FIRCA R03-TW006481), the Pan American Health Organization, Eli Lilly and Company, Ortho-McNeil Pharmaceutical Inc., GlaxoSmithKline, and Bristol–Myers Squibb. A complete list of WMH publications can be found at www.hcp.med.harvard.edu/wmh/.

The viewpoints expressed in this article do not necessarily represent those of the National Institutes of Health or the United States Department of Health and Human Services.

Declaration of Interest

Professor Kessler has been a consultant for GlaxoSmithKline Inc., Pfizer Inc., Wyeth–Ayerst, Sanofi-Aventis, Kaiser Permanente, and Shire Pharmaceuticals; has served on advisory boards for Eli Lilly & Company and Wyeth–Ayerst; and has had research support for his epidemiological studies from Eli Lilly & Company, Pfizer Inc., Ortho-McNeil Pharmaceuticals Inc., and Bristol–Myers Squibb.

References

Allan CA (1995). Alcohol problems and anxiety disorders – a critical review. *Alcohol and Alcoholism* **30**, 145–151.

Armstrong TD, Costello EJ (2002). Community studies on adolescent substance use, abuse, or dependence and psychiatric comorbidity. *Journal of Consulting and Clinical Psychology* **70**, 1224–1239.

Brooner RK, King VL, Kidorf M, Schmidt Jr. CW, Bigelow GE (1997). Psychiatric and substance use comorbidity among treatment-seeking opioid abusers. *Archives of General Psychiatry* **54**, 71–80.

Chan YF, Dennis ML, Funk RR (2008). Prevalence and comorbidity of major internalizing and externalizing problems among adolescents and adults presenting to substance abuse treatment. *Journal of Substance Abuse Treatment* **34**, 14–24.

Cohen P, Chen H, Crawford TN, Brook JS, Gordon K (2007). Personality disorders in early adolescence and the development of later substance use disorders in the general

population. *Drug and Alcohol Dependence* **88** (Suppl. 1), S71–S84.

Compton WM 3rd, Cottler LB, Phelps DL, Ben Abdallah A, Spitznagel EL (2000). Psychiatric disorders among drug dependent subjects: are they primary or secondary? *American Journal on Addictions* **9**, 126–134.

Connor DF, Carlson GA, Chang KD, Daniolos PT, Ferziger R, Findling RL, Hutchinson JG, Malone RP, Halperin JM, Plattner B, Post RM, Reynolds DL, Rogers KM, Saxena K, Steiner H (2006). Juvenile maladaptive aggression: a review of prevention, treatment, and service configuration and a proposed research agenda. *Journal of Clinical Psychiatry* **67**, 808–820.

Cook PJ, Ludwig J, Braga AA (2005). Criminal records of homicide offenders. *Journal of the American Medical Association* **294**, 598–601.

Costello EJ (2007). Psychiatric predictors of adolescent and young adult drug use and abuse: what have we learned? *Drug and Alcohol Dependence* **88** (Suppl. 1), S97–S99.

Costello EJ, Erkanli A, Federman E, Angold A (1999). Development of psychiatric comorbidity with substance abuse in adolescents: effects of timing and sex. *Journal of Clinical Child Psychology* **28**, 298–311.

Crum RM, Storr CL, Chan YF (2005). Depression syndromes with risk of alcohol dependence in adulthood: a latent class analysis. *Drug and Alcohol Dependence* **79**, 71–81.

Degenhardt L, Bohnert KM, Anthony JC (2007*a*). Case ascertainment of alcohol dependence in general population surveys: 'gated' versus 'ungated' approaches. *International Journal of Methods in Psychiatric Research* **16**, 111–123.

Degenhardt L, Bohnert KM, Anthony JC (2008). Assessment of cocaine and other drug dependence in the general population: 'gated' versus 'ungated' approaches. *Drug and Alcohol Dependence* **93**, 227–232.

Degenhardt L, Cheng H, Anthony JC (2007*b*). Assessing cannabis dependence in community surveys: methodological issues. *International Journal of Methods in Psychiatric Research* **16**, 43–51.

Degenhardt L, Hall W, Lynskey M (2003). Exploring the association between cannabis use and depression. *Addiction* **98**, 1493–1504.

Dembo R, Allen N, Farrow D, Schmeidler J, Burgos W (1985). A causal analysis of early drug involvement in three inner-city neighborhood settings. *International Journal of the Addictions* **20**, 1213–1237.

Dube SR, Anda RF, Felitti VJ, Chapman DP, Williamson DF, Giles WH (2001). Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the Adverse Childhood Experiences Study. *Journal of the American Medical Association* **286**, 3089–3096.

Efron B (1988). Logistic regression, survival analysis, and the Kaplan–Meier curve. *Journal of the American Statistical Association* **83**, 414–425.

Falk DE, Yi HY, Hilton ME (2008). Age of onset and temporal sequencing of lifetime DSM-IV alcohol use disorders relative to comorbid mood and anxiety disorders. *Drug and Alcohol Dependence* **94**, 234–245.

First MB, Spitzer RL, Gibbon M, Williams JBW (2002). *Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Non-Patient Edition* (*SCID-I/NP*). Biometrics Research, New York State Psychiatric Institute: New York.

Furr-Holden CD, Ialongo NS, Anthony JC, Petras H, Kellam SG (2004). Developmentally inspired drug prevention: middle school outcomes in a school-based randomized prevention trial. *Drug and Alcohol Dependence* **73**, 149–158.

Gilchrist RH, Arnold EL (2008). Long-term efficacy of ADHD pharmacotherapy in children. *Pediatric Annals* **37**, 46–51.

Glantz MD (2002). Introduction to the special issue on the impact of childhood psychopathology interventions on subsequent substance abuse: pieces of the puzzle. *Journal of Consulting and Clinical Psychology* **70**, 1203–1206.

Glantz MD, Conway KP, Colliver JD (2005). Drug abuse heterogeneity and the search for subtypes. In *Drug Abuse Epidemiology* (ed. Z. Sloboda), pp. 15–27. Springer: New York, NY.

Glantz MD, Leshner AI (2000). Drug abuse and developmental psychopathology. *Development and Psychopathology* **12**, 795–814.

Grant BF, Harford TC (1995). Comorbidity between DSM-IV alcohol use disorders and major depression: results of a national survey. *Drug and Alcohol Dependence* **39**, 197–206.

Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, Pickering RP, Kaplan K (2004*a*). Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of General Psychiatry* **61**, 807–816.

Grant BF, Stinson FS, Dawson DA, Chou SP, Ruan WJ, Pickering RP (2004*b*). Co-occurrence of 12-month alcohol and drug use disorders and personality disorders in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of General Psychiatry* **61**, 361–368.

Halli SS, Rao KV, Halli SS (1992). *Advanced Techniques of Population Analysis*. Plenum: New York, NY.

Haro JM, Arbabzadeh-Bouchez S, Brugha TS, de Girolamo G, Guyer ME, Jin R, Lepine JP, Mazzi F, Reneses B, Vilagut G, Sampson NA, Kessler RC (2006). Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health surveys. *International Journal of Methods in Psychiatric Research* **15**, 167–180.

Helzer JE, Canino GJ, Yeh EK, Bland RC, Lee CK, Hwu HG, Newman S (1990). Alcoholism – North America and Asia. A comparison of population surveys with the Diagnostic Interview Schedule. *Archives of General Psychiatry* **47**, 313–319.

Hicks BM, Krueger RF, Iacono WG, McGue M, Patrick CJ (2004). Family transmission and heritability of externalizing disorders: a twin-family study. *Archives of General Psychiatry* **61**, 922–928.

Jane-Llopis E, Matytsina I (2006). Mental health and alcohol, drugs and tobacco: a review of the comorbidity between

mental disorders and the use of alcohol, tobacco and illicit drugs. *Drug and Alcohol Review* **25**, 515–536.

Jeffery RW (1989). Risk behaviors and health. Contrasting individual and population perspectives. *American Psychologist* **44**, 1194–1202.

Kellam SG, Anthony JC (1998). Targeting early antecedents to prevent tobacco smoking: findings from an epidemiologically based randomized field trial. *American Journal of Public Health* **88**, 1490–1495.

Kendall PC, Kessler RC (2002). The impact of childhood psychopathology interventions on subsequent substance abuse: policy implications, comments, and recommendations. *Journal of Consulting and Clinical Psychology* **70**, 1303–1306.

Kessler RC (1995). Epidemiology of psychiatric comorbidity. In *Textbook in Psychiatric Epidemiology* (ed. M. T. Tsuang, M. Tohen and G. E. P. Zahner), pp. 179–197. Wiley-Liss: New York, NY.

Kessler RC (2004). The epidemiology of dual diagnosis. *Biological Psychiatry* **56**, 730–737.

Kessler RC, Aguilar-Gaxiola S, Andrade L, Bijl R, Borges G, Caraveo-Anduaga JJ, DeWit DJ, Kolody B, Merikangas KR, Molnar BE, Vega WA, Walters EE, Wittchen H-U (2003). Cross-national comparisons of comorbidities between substance use disorders and mental disorders: results from the International Consortium in Psychiatric Epidemiology. In *Handbook for Drug Abuse Prevention Theory, Science, and Practice* (ed. W. J. Bukoski and Z. Sloboda), pp. 447–472. Plenum: New York, NY.

Kessler RC, Aguilar-Gaxiola S, Andrade L, Bijl R, Borges G, Caraveo-Anduaga JJ, DeWit DJ, Kolody B, Merikangas KR, Molnar BE, Vega WA, Walters EE, Wittchen H-U, Üstün TB (2001). Mental–substance comorbidities in the ICPE surveys. *Psychiatria Fennica* **32**, 62–80.

Kessler RC, Berglund P, Chiu WT, Demler O, Heeringa S, Hiripi E, Jin R, Pennell BE, Walters EE, Zaslavsky A, Zheng H (2004). The US National Comorbidity Survey Replication (NCS-R): design and field procedures. *International Journal of Methods in Psychiatric Research* **13**, 69–92.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* **62**, 593–602.

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of General Psychiatry* **51**, 8–19.

Kessler RC, Merikangas KR (2004). The National Comorbidity Survey Replication (NCS-R): background and aims. *International Journal of Methods in Psychiatric Research* **13**, 60–68.

Kessler RC, Nelson CB, McGonagle KA, Edlund MJ, Frank RG, Leaf PJ (1996). The epidemiology of co-occurring addictive and mental disorders: implications for prevention and service utilization. *American Journal of Orthopsychiatry* **66**, 17–31.

Kessler RC, Pecora PJ, Williams J, Hiripi E, O'Brien K, English D, White J, Zerbe R, Downs AC, Plotnick R, Hwang I, Sampson NA (2008). The effects of enhanced foster care on the long-term physical and mental health of foster care alumni. *Archives of General Psychiatry* **65**, 625–633.

Kessler RC, Üstün TB (2004). The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *International Journal of Methods in Psychiatric Research* **13**, 93–121.

King SM, Iacono WG, McGue M (2004). Childhood externalizing and internalizing psychopathology in the prediction of early substance use. *Addiction* **99**, 1548–1559.

Knauper B, Cannell CF, Schwarz N, Bruce ML, Kessler RC (1999). Improving the accuracy of major depression age of onset reports in the US National Comorbidity Survey. *International Journal of Methods in Psychiatric Research* **8**, 39–48.

Kranzler HR, Del Boca FK, Rounsaville BJ (1996). Comorbid psychiatric diagnosis predicts three-year outcomes in alcoholics: a posttreatment natural history study. *Journal of Studies on Alcohol* **57**, 619–626.

Krueger RF, Markon KE, Patrick CJ, Benning SD, Kramer MD (2007). Linking antisocial behavior, substance use, and personality: an integrative quantitative model of the adult externalizing spectrum. *Journal of Abnormal Psychology* **116**, 645–666.

Kushner MG, Sher KJ, Erickson DJ (1999). Prospective analysis of the relation between DSM-III anxiety disorders and alcohol use disorders. *American Journal of Psychiatry* **156**, 723–732.

Lewis CE, Rice J, Helzer JE (1983). Diagnostic interactions: alcoholism and antisocial personality. *Journal of Nervous and Mental Disease* **171**, 105–113.

Lukassen J, Beaudet MP (2005). Alcohol dependence and depression among heavy drinkers in Canada. *Social Science and Medicine* **61**, 1658–1667.

McQuay HJ, Moore RA (1997). Using numerical results from systematic reviews in clinical practice. *Annals of Internal Medicine* **126**, 712–720.

Merikangas KR, Mehta RL, Molnar BE, Walters EE, Swendsen JD, Aguilar-Gaziola S, Bijl R, Borges G, Caraveo-Anduaga JJ, DeWit DJ, Kolody B, Vega WA, Wittchen HU, Kessler RC (1998). Comorbidity of substance use disorders with mood and anxiety disorders: results of the International Consortium in Psychiatric Epidemiology. *Addictive Behaviors* **23**, 893–907.

Nelson JC (2008). Anxious depression and response to treatment. *American Journal of Psychiatry* **165**, 297–299.

Pardini D, White HR, Stouthamer-Loeber M (2007). Early adolescent psychopathology as a predictor of alcohol use disorders by young adulthood. *Drug and Alcohol Dependence* **88** (Suppl. 1), S38–S49.

Patton GC, Coffey C, Carlin JB, Degenhardt L, Lynskey M, Hall W (2002). Cannabis use and mental health in young people: cohort study. *British Medical Journal* **325**, 1195–1198.

Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK (1990). Comorbidity of mental disorders with alcohol and other drug abuse. Results from the

Epidemiologic Catchment Area (ECA) Study. *Journal of the American Medical Association* **264**, 2511–2518.

Roberts RE, Roberts CR, Xing Y (2007). Comorbidity of substance use disorders and other psychiatric disorders among adolescents: evidence from an epidemiologic survey. *Drug and Alcohol Dependence* **88** (Suppl. 1), S4–S13.

Sartorius N, Baghai TC, Baldwin DS, Barrett B, Brand U, Fleischhacker W, Goodwin G, Grunze H, Knapp M, Leonard BE, Lieberman J, Nakane Y, Pinder RM, Schatzberg AF, Svestka J, Baumann P, Ghalib K, Markowitz JC, Padberg F, Fink M, Furukawa T, Fountoulakis KN, Jensen P, Kanba S, Riecher-Rossler A (2007). Antidepressant medications and other treatments of depressive disorders: a CINP Task Force report based on a review of evidence. *International Journal of Neuropsychopharmacology* **10** (Suppl. 1), S1–S207.

SAS Institute (2002). *SAS 9.1.3 Help and Documentation*. SAS Publishing: Cary, NC.

Schuckit MA, Hesselbrock V (1994). Alcohol dependence and anxiety disorders: what is the relationship? *American Journal of Psychiatry* **151**, 1723–1734.

Semple DM, McIntosh AM, Lawrie SM (2005). Cannabis as a risk factor for psychosis: systematic review. *Journal of Psychopharmacology* **19**, 187–194.

Simon GE, Von Korff M (1992). Re-evaluation of secular trends in depression rates. *American Journal of Epidemiology* **135**, 1411–1422.

Simon GE, Von Korff M (1995). Recall of psychiatric history in cross-sectional surveys: implications for epidemiologic research. *Epidemiologic Reviews* **17**, 221–227.

Sung M, Erkanli A, Angold A, Costello EJ (2004). Effects of age at first substance use and psychiatric comorbidity on the development of substance use disorders. *Drug and Alcohol Dependence* **75**, 287–299.

Swendsen JD, Merikangas KR (2000). The comorbidity of depression and substance use disorders. *Clinical Psychology Review* **20**, 173–189.

Verona E, Sachs-Ericsson N (2005). The intergenerational transmission of externalizing behaviors in adult participants: the mediating role of childhood abuse. *Journal of Consulting and Clinical Psychology* **73**, 1135–1145.

Waldman ID, Slutske WS (2000). Antisocial behavior and alcoholism: a behavioral genetic perspective on comorbidity. *Clinical Psychology Review* **20**, 255–287.

Walter SD (1978). Calculation of attributable risks from epidemiological data. *International Journal of Epidemiology* **7**, 175–182.

Weinberg NZ, Glantz MD (1999). Child psychopathology risk factors for drug abuse: overview. *Journal of Clinical Child Psychology* **28**, 290–297.

White HR, Xie M, Thompson W, Loeber R, Stouthamer-Loeber M (2001). Psychopathology as a predictor of adolescent drug use trajectories. *Psychology of Addictive Behaviors* **15**, 210–218.

Wilens TE, Biederman J, Adamson JJ, Henin A, Sgambati S, Gignac M, Sawtelle R, Santry A, Monuteaux MC (2008). Further evidence of an association between adolescent bipolar disorder with smoking and substance use disorders: a controlled study. *Drug and Alcohol Dependence* **95**, 188–198.

Willoughby T, Chalmers H, Busseri MA (2004). Where is the syndrome? Examining co-occurrence among multiple problem behaviors in adolescence. *Journal of Consulting and Clinical Psychology* **72**, 1022–1037.

Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB (2002). Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Archives of Internal Medicine* **162**, 1867–1872.

Wolter KM (1985). *Introduction to Variance Estimation*. Springer-Verlag: New York.

Zilberman ML, Tavares H, Blume SB, el-Guebaly N (2003). Substance use disorders: sex differences and psychiatric comorbidities. *Canadian Journal of Psychiatry* (*Revue Canadienne de Psychiatrie*) **48**, 5–13.