Addiction
RESEARCH REPORT
doi:10.1111/j.1360-0443.2010.02902.x

Mental disorders as risk factors for substance use, abuse and dependence: results from the 10-year follow-up of the National Comorbidity Survey

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ABSTRACT

Aims The comorbidity of mental disorders and substance dependence is well documented, but prospective investigations in community samples are rare. This investigation examines the role of primary mental disorders as risk factors for the later onset of nicotine, alcohol and illicit drug use, abuse and dependence with abuse. **Design** The National Comorbidity Survey (NCS) was a nationally representative survey of mental and substance disorders in the United States carried out in 1990–92. The NCS-2 re-interviewed a probability subsample of NCS respondents in 2001–03, a decade after the baseline survey. **Participants** A total of 5001 NCS respondents were re-interviewed in the NCS-2 (87.6% of baseline sample). **Results** Aggregate analyses demonstrated significant prospective risks posed by baseline mental disorders for the onset of nicotine, alcohol and illicit drug dependence with abuse over the follow-up period. Particularly strong and consistent associations were observed for behavioral disorders and previous substance use conditions, as well as for certain mood and anxiety disorders. Conditional analyses demonstrated that many observed associations were limited to specific categories of use, abuse or dependence, including several mental disorders that were non-significant predictors in the aggregate analyses. **Conclusions** Many mental disorders are associated with an increased risk of later substance use conditions, but important differences in these associations are observed across the categories of use, abuse and dependence with abuse. These prospective findings have implications for the precision of prevention and treatment strategies targeting substance use disorders.

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Submitted 20 June 2009; initial review completed 24 August 2009; final version accepted 20 November 2009

INTRODUCTION

A considerable literature has amassed documenting strong associations of substance use, abuse and dependence with a range of mental disorders in community samples [1–18]. These forms of comorbidity have been observed for diverse substances and have negative consequences for both the persistence and severity of these disorders [13,19,20]. The reasons for these associations have been debated widely [21–24], including the possibility that they may result in part from causal effects of primary mental disorders. If such effects could be documented rigorously, they would have important implications for refining substance use prevention and treatment strategies. However, the majority of existing epidemiological research has been based upon analyses of syndrome severity changes attributable to comorbidity [18] or, more commonly, upon retrospective estimates concerning the order of disorder onset [6,8,13,15,18]. Such estimates are susceptible to forward telescoping [25] or other memory biases, and therefore do not offer definitive evidence that specific mental disorders are risk factors for the development of substance use, abuse or dependence.

Longitudinal investigations capable of confirming the order of onset of these conditions are limited in number, but several have found that certain mental disorders

predict the later onset of smoking or nicotine dependence [26–28], alcohol abuse or dependence [29–31] and drug abuse or dependence [29,30]. Associations have also been found in the opposite direction [12,26,32,33], but retrospective and prospective studies both indicate that mental disorders have a temporally primary age of onset in the majority of these forms of comorbidity [13,15,21,34]. Although the full impact of primary mental disorders is unknown, simulation studies have estimated that their early treatment or prevention might reduce 15–40% of cases of secondary substance dependence [8,34,35]. These simulations provide upper bound estimates due to the fact that mental-substance disorder comorbidity might be attributable, at least in part, to shared etiological factors rather than solely to the causal effects of mental disorders. To date, these estimates have not been based upon prospective community surveys and it is therefore unclear to what extent they may be distorted by retrospective dating of disorder onset or to biases associated with longitudinal assessments in clinical samples.

An additional concern for comorbidity research is the lack of information regarding the specific stages of substance use trajectories that are associated most strongly with pre-existing mental disorders. The common approach has been to examine mental disorders as predictors of substance dependence among all individuals in a given sample, ignoring the possibility that mental disorders may predict substance use, or the transition from use to abuse, more strongly rather than the onset of dependence alone. An alternative approach would be to examine predictors of these different transitions, thereby gaining information about the precise stage at which mental disorders have their greatest predictive effects. This strategy has been applied recently to investigate the influence of socio-demographic predictors of the transitions between categories substance use, abuse and dependence [36–41] and has provided novel information that is inaccessible to classic analytical approaches. Application of the same approach to mental-substance comorbidity would refine our understanding of the prospective associations between primary mental disorders and the subsequent onset of substance use, abuse and dependence.

Using data from a nationally representative two-wave panel survey of the US population spanning a 10-year period, the current investigation examines the risk of pre-existing mental disorders for the initial onset of use, abuse and dependence relative to three classes of substances: nicotine, alcohol and illicit drugs. Baseline predictors include life-time history of mood disorders, anxiety disorders, behavior disorders and additional substance use conditions. In order to provide comparability with the previous literature [1–3,10,14,15,17,18], unconditional analyses examine mental disorders as risk factors for the first onset of nicotine, alcohol and drug dependence, while conditional analyses then decompose these aggregate associations by examining the predictive effects of mental disorders on transitions from non-use to use, from use to abuse and from abuse to dependence for each substance class.

METHOD

Sample

A total of 5001 respondents participated in the 1990–92 National Comorbidity Survey (NCS) and the 2001–03 NCS follow-up survey (NCS-2). The baseline NCS [42] was a nationally representative US survey of the prevalence and correlates of DSM-III-R mental and substance disorders that was administered to 8098 respondents aged 15–54 years in the non-institutionalized civilian population from the 48 coterminous states. The response rate was 82.4%. Interviews were conducted by professional interviewers and administered in two parts. Part I, which included the core diagnostic interview, was administered to all respondents. Part II, which included assessments of additional disorders and risk factors, was administered to a probability subsample of 5877 respondents including all those in the age range 15–24 years, all others with any life-time DSM-III-R disorder assessed in part I and a random subsample of remaining part I respondents. The part II sample was weighted to adjust for differential probabilities of selection and for non-response bias. Further details about the NCS design and weighting are reported elsewhere [42].

The NCS-2 sought to trace and re-interview the Part II NCS respondents a decade after the NCS. Of the original 5877 part II respondents, 5463 were traced successfully, of whom 166 were deceased and 5001 re-interviewed, for a conditional response rate of 87.6%. The unconditional response rate is 72.2% (0.876×0.824). NCS-2 respondents were administered an expanded version of the baseline interview that assessed onset and course of disorders between the two surveys. Relative to other baseline NCS respondents, NCS-2 respondents were significantly more likely to be female, well educated and residents of rural areas. A propensity score adjustment weight [43] corrected for these discrepancies.

Diagnostic assessment

The baseline NCS assessed life-time DSM-III-R disorders using a modification of the World Health Organization Composite International Diagnostic Interview (CIDI) version 1.1 [44], a fully structured, lay-administered diagnostic interview. Life-time DSM-IV disorders that had first onsets in the decade between the two interviews were assessed in the NCS-2 using CIDI version 3.0 [45].

Alcohol and drug dependence were assessed only among individuals meeting criteria for DSM-IV abuse. DSM organic exclusion rules were used in making diagnoses in both surveys. DSM-IV disorders reported for the first time at the NCS-2 assessment but estimated by respondents to have had their onset prior to baseline were coded as having occurred prior to baseline. Blinded clinical reappraisal interviews administered to a probability subsample of respondents using the Structured Clinical Interview for DSM-III-R [46] in the NCS and the Structured Clinical Interview for DSM-IV (SCID; [47]) in the NCS-2 documented generally good concordance between diagnoses based on the CIDI and independent diagnoses based on blinded clinical reappraisal interviews [48,49].

Baseline predictors of substance use, abuse and dependence at follow-up

The baseline mental disorders used as predictors of substance use, DSM-IV abuse and DSM-IV dependence with abuse at follow-up included specific mood disorders, anxiety disorders, disruptive behavior disorders and additional substance use disorders. Variables were also included to assess the aggregate effects of broad categories of disorder, the number of life-time disorders and any disorder. The baseline socio-demographic variables used as controls in these analyses were the same for all models and were identified previously as having significant associations with substance use, abuse or dependence with abuse [40].

Statistical analyses

Cross-tabulations were used to estimate conditional lifetime prevalence of first onset of DSM-IV nicotine dependence as well as alcohol and illicit drug dependence with abuse at the NCS-2 assessment. Multivariate logistic regression analysis [50] with controls for baseline socio-demographic characteristics was used to estimate associations of baseline mental disorders individually with the first onset of use for each substance at follow-up (T2) among baseline (T1) non-users, the first onset of T2 abuse among T1 non-abusive users and the first onset T2 dependence among T1 non-dependent abusers. For the prediction of nicotine dependence, daily users were T1 non-daily users who became daily users by T2 or T1 non-dependent daily users. For the prediction of alcohol (or drug) abuse, non-abusers were T1 non-regular users of alcohol (or non-users of drugs) who became regular alcohol users (or drug users) at T2 or T1 non-abusive regular alcohol users (or non-abusive drug users). For the prediction of alcohol (or drug) dependence with abuse, non-dependent individuals were T1 non-regular users of alcohol (or non-users of drugs) who became alcohol or drug abusers at T2, T1 non-abusive regular alcohol users (or non-abusive drug users) who became abusers at T2 or T1 non-dependent abusers. Logistic regression coefficients and their standard errors were exponentiated to create odds ratios (ORs) and their 95% confidence intervals. Continuous predictors were divided into categories to minimize the effects of extreme values, while some categories of predictors were combined to stabilize associations when the ORs did not differ meaningfully across contiguous categories. Standard errors and significance tests were estimated using the Taylor series method [51] implemented using the SUDAAN software system [52] to adjust for the geographic clustering of the sample and the use of weights. Multivariate significance was evaluated using Wald χ^2 tests based on design-corrected coefficient variance–covariance matrices. The population-attributable risk proportion (PARP) of the outcomes was computed for the best-fitting model. The PARP can be interpreted as the proportion of observed outcome disorders that would not have occurred if the ORs in the best-fitting model were due to causal effects of baseline mental disorders and if these baseline mental disorders had been prevented. PARP was calculated using simulation methods to generate individual-level predicted probabilities of the outcome disorders twice from the coefficients in the best-fitting model: the first time using all the coefficients in the model and the second time assuming that the coefficients associated with the mental disorders were all zero. The ratio of the predicted prevalence estimates in the two specifications was then used to calculate PARP. The jack-knife repeated replications simulation method [51] implemented using a SAS macro was used to generate standard errors of the PARPs. Statistical significance was evaluated using two-tailed 0.05-level tests.

RESULTS

Onset of nicotine, alcohol and drug dependence (unconditional models)

During the 10-year period between assessments, 10.4% [standard error (SE) = 0.6%, $n = 538$] of the sample had a first onset of DSM-IV nicotine dependence, 1.1% (SE = 0.2%, $n = 57$) had a first onset of DSM-IV alcohol dependence with abuse and 0.9% (SE = 0.2%, $n = 49$) had a first onset of DSM-IV drug dependence with abuse. The global effect for all mental disorders was associated significantly with the onset of nicotine dependence $\chi^2_{(19)} = 142.7$, $P < 0.001$, alcohol dependence with abuse $\chi^2_{(19)} = 187.3$, $P < 0.001$ and illicit drug dependence with abuse $\chi^2_{(19)} = 352.3$, $P < 0.001$. Table 1 presents the unconditional bivariate models for the association of baseline mood disorders with each category of dependence (ORs 1.8–2.1), with the strongest associations observed for bipolar disorder (see Table 1). Anxiety

Table 1 Bivariate models of associations of baseline mental disorders with subsequent onset of nicotine, alcohol and drug dependence.

	T2 onset of nicotine dependence among T1 non-nicotine-dependent (unconditional)[b]			*T2 onset of alcohol dependence with abuse among T1 non-alcohol-dependent (unconditional)*[b]			*T2 onset of illicit drug dependence with abuse among T1 non-illicit drug-dependent (unconditional)*[b]		
Time 1 disorders[a]	*OR*	*(95% CI)*	χ^2	*OR*	*(95% CI)*	χ^2	*OR*	*(95% CI)*	χ^2
Mood disorders									
Dysthymia	1.3	(0.8–2.2)	1.0	4.1	(1.0–17.0)	3.9*	2.7	(0.5–15.6)	1.4
Major depression	1.4*	(1.0–1.9)	5.2*	1.6	(0.7–3.8)	1.1	1.6	(0.7–3.6)	1.3
Bipolar	3.1*	(1.9–5.1)	23.4*	3.6*	(1.1–11.4)	5.1*	5.1*	(1.8–14.7)	9.6*
Any mood disorder	1.8*	(1.3–2.4)	17.0*	1.8	(0.9–3.8)	2.8	2.1	(0.9–4.7)	3.1
PARP (SE)	6.3 (0.5)			3.8 (0.8)			1.3 (1.5)		
Anxiety disorders									
Panic disorder	1.2	(0.7–1.9)	0.6	3.2*	(1.2–8.5)	6.0*	1.1	(0.3–4.0)	0.0
Social phobia	1.4*	(1.0–1.9)	4.1*	3.3*	(1.9–5.8)	17.9*	2.8*	(1.1–7.0)	5.2*
Specific phobia	1.5*	(1.1–1.9)	7.9*	2.7*	(1.2–5.9)	6.7*	2.2	(0.9–5.5)	3.1
GAD	1.0	(0.6–1.6)	0.0	1.6	(0.7–3.9)	1.2	1.2	(0.3–5.9)	0.1
PTSD	1.6*	(1.1–2.4)	5.5*	3.2*	(1.2–8.9)	5.4*	3.9*	(1.5–10.0)	8.5*
Agoraphobia	1.5	(0.9–2.3)	3.1	2.3	(0.7–6.9)	2.2	1.9	(0.4–8.5)	0.8
Separation anxiety	1.4	(0.9–2.0)	2.5	2.7*	(1.1–6.4)	5.4*	3.0*	(1.1–8.6)	4.5*
Any anxiety disorder	1.5*	(1.1–2.0)	7.6*	3.2*	(1.7–5.8)	15.0*	3.5*	(1.2–10.5)	5.3*
PARP (SE)	1.6 (0.5)			32.4 (1.5)			12.7 (3.5)		
Disruptive behavior disorders									
IED	1.5*	(1.0–2.0)	5.1*	6.0*	(2.9–12.6)	24.1*	6.3*	(3.2–12.3)	30.8*
ODD	2.2*	(1.4–3.4)	11.4*	3.9*	(2.0–7.8)	16.3*	3.9*	(1.5–10.0)	8.3*
CD	2.1*	(1.5–3.0)	21.7*	2.0	(0.8–4.9)	2.4	3.5*	(1.6–7.8)	9.8*
ADHD	1.8*	(1.2–2.8)	7.2*	1.8	(0.7–4.9)	1.5	5.2*	(1.9–14.0)	11.2*
ASPD	2.0*	(1.2–3.2)	8.1*	2.4	(0.7–8.2)	2.0	3.8	(0.7–22.2)	2.3
Any disruptive behavior disorder	1.9*	(1.5–2.5)	28.2*	2.8*	(1.3–5.7)	7.9*	4.6*	(1.9–10.8)	12.8*
PARP (SE)	7.5 (0.4)			26.4 (2.1)			37.1 (3.3)		
Substance use disorders									
Alcohol abuse with/without dependence	2.5*	(1.8–3.5)	32.9*	1.4	(0.7–2.9)	1.0	7.6*	(3.2–18.4)	21.7*
Alcohol dependence	2.5*	(1.7–3.6)	25.9*	–	–	–	9.0*	(3.5–23.0)	22.0*
Illicit drug abuse with/without dependence	3.0*	(2.2–4.0)	55.6*	1.3	(0.6–3.2)	0.4	6.4*	(3.0–13.5)	24.5*
Illicit drug dependence	2.4*	(1.8–3.3)	32.5*	1.5	(0.5–4.6)	0.5	–	–	–
Nicotine dependence	–	–	–	1.9*	(1.0–3.4)	4.3*	2.1	(0.8–5.3)	2.5
Any substance use disorder	3.5*	(2.6–4.8)	63.1*	1.7	(0.9–2.9)	3.2	8.2*	(3.9–17.5)	31.7*
PARP (SE)	18.9 (0.8)			8.2 (1.1)			48.9 (3.2)		
Number of life-time disorders									
1	1.2	(0.7–2.2)	57.5*	2.0	(0.6–7.0)	11.9*	4.9	(0.5–45.0)	39.8*
2	2.5*	(1.7–3.7)	–	2.7	(0.8–9.7)	–	38.6*	(3.9–380.1)	–
3	2.7*	(1.6–4.6)	–	2.7	(0.4–18.2)	–	48.2*	(10.0–232.5)	–
4 or more	3.6*	(2.4–5.3)	–	5.6*	(1.7–18.7)	–	64.7*	(7.9–529.0)	–
Any disorder	2.3*	(1.6–3.4)	19.1*	3.1	(1.0–9.5)	3.9*	29.9*	(4.3–208.8)	12.5*
Any disorder—PARP (SE)	37.4 (0.9)			53.5 (1.6)			89.3 (0.8)		
n, # positive	(3659)	(538)		(3936)	(57)		(4444)	(49)	

*Significant at the 0.05 level, two-sided test. [a]Mental disorder abbreviations: 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); ASPD (antisocial personality disorder). [b]Controls for age, sex, race, education, marital status, number of children, region, urbanicity and employment status. CI: confidence interval; OR: odds ratio; PARP: population-attributable risk proportion; SE: standard error.

disorders were associated with the onset of nicotine dependence (OR = 1.5), alcohol dependence with abuse (OR = 3.2) and drug dependence with abuse (OR = 3.5), although differences were observed by disorder type. Panic disorder, social phobia, specific phobia, post-traumatic stress disorder (PTSD) and separation anxiety were linked to the onset of at least one form of dependence, but no association was observed for agoraphobia or generalized anxiety disorder (GAD). All baseline disruptive behavior disorders and substance use disorders (other than the predicted outcome) considered in the NCS were associated with increased risk of nicotine dependence, and most of these disorders were also associated with illicit drug dependence with abuse. The risk of alcohol dependence with abuse was increased only among baseline respondents with intermittent explosive disorder (IED), oppositional defiant disorder (ODD) or nicotine dependence. Considerable variance was observed in the association between the aggregate category of any mental disorder and substance dependence (ORs 2.4–29.9), but the risk of substance disorder onset generally increased as function of the number of pre-existing disorders. With reference to the aggregate category of any disorder, the PARP estimates indicate that their successful treatment would reduce cases of secondary nicotine dependence by 37.4%, alcohol dependence with abuse by 53.5% and illicit drug dependence with abuse by 89.3%.

Onset of daily nicotine use and dependence (conditional models)

The global association of all mental disorders was significant in conditional models predicting the onset of daily nicotine use $\chi^2_{(19)} = 90.0$, $P < 0.001$ and nicotine dependence $\chi^2_{(19)} = 81.2$, $P < 0.001$. Table 2 presents the results of bivariate conditional analyses examining specific baseline mental disorders as predictors of these two categories at follow-up. Mood disorders were associated somewhat more strongly with the development of nicotine dependence than with the onset of non-dependent use, while the predictive role of anxiety disorders was somewhat stronger for non-dependent tobacco use. Despite their lack of association with nicotine dependence in the unconditional model, GAD was associated with daily nicotine use and agoraphobia with nicotine dependence. The strong associations observed previously for behavioral disorders were attenuated in the conditional analyses, with the general category being associated only with the onset of nicotine dependence. All additional substance use disorders remained associated significantly with both categories in the conditional analyses, but the magnitude of risk was greater for the onset of daily tobacco use as opposed to dependence. Consistent with the magnitude of risk observed by category of use or disorder, the treatment of index mood disorders would have their greatest impact on reducing nicotine dependence, while the treatment of anxiety and other substance use disorders would have a greater effect on non-dependent use. The treatment of disruptive disorders would have a small and approximately equal effect on each category. The presence of any mental disorder as well as their number was associated generally with increased risk of onset of each category of substance use, and it is estimated that the treatment of any mental disorder would prevent the onset of 28.5% of daily tobacco use and 22.2% of nicotine dependence cases.

Onset of regular alcohol use, abuse and dependence with abuse (conditional models)

The global association of all mental disorders was significant in conditional models predicting the onset of regular alcohol use $\chi^2_{(18)} = 138.6$, $P < 0.001$, alcohol abuse $\chi^2_{(18)} = 62.7$, $P < 0.001$ and alcohol dependence with abuse $\chi^2_{(18)} = 89.1$, $P < 0.001$. Table 3 demonstrates that few mental disorders were associated with the onset of regular alcohol use over the follow-up. The transition from regular alcohol use to abuse was associated with disruptive behavior disorders as well as additional substance use disorders, and the risk of this transition was significantly greater among individuals with three or more pre-existing mental disorders. The PARP analyses indicate that treatment of most categories of disorder would have a negligible to moderate effect on the risk of regular alcohol use or alcohol abuse. Concerning predictors of alcohol dependence onset among baseline abusers, dysthymia emerged as a significant risk factor, as did several categories of anxiety disorder. Among all disruptive behavior disorders, only IED and ODD predicted the transition from abuse to dependence, and no effect was observed for additional substance use disorders. Despite attenuated associations, however, 43.4% of transitions to secondary alcohol dependence from abuse could, potentially, be prevented with the treatment of any mental disorder.

Onset of drug use, abuse and dependence with abuse (conditional models)

The global association of all mental disorders was significant in conditional models predicting the onset of drug use $\chi^2_{(18)} = 80.6$, $P < 0.001$, drug abuse $\chi^2_{(18)} = 181.7$, $P < 0.001$ and drug dependence with abuse $\chi^2_{(18)} = 67.6$, $P < 0.001$. Table 4 demonstrates that specific mental disorders were frequent predictors of the onset of initial illicit drug use among baseline non-users. Individuals were at greater risk to start using illicit drugs over the follow-up period if they had experienced major depres-

Table 2 Bivariate models of associations of baseline mental disorders with subsequent onset of nicotine regular use/dependence.

	T2 onset of daily tobacco use among T1 non-daily users[b]			*T2 onset of nicotine dependence cases among daily users*[b]		
Time 1 disorders[a]	*OR*	*(95% CI)*	χ^2	*OR*	*(95% CI)*	χ^2
Mood disorders						
Dysthymia	1.5	(0.4–5.8)	0.3	1.8	(0.8–3.9)	2.1
Major depression	1.4	(0.9–2.3)	2.6	1.4	(1.0–2.0)	4.1*
Bipolar	1.8	(0.9–3.7)	2.7	3.9*	(1.7–9.0)	11.3*
Any mood disorder	1.6*	(1.0–2.4)	4.7*	1.9*	(1.3–2.5)	15.3*
PARP (SE)	0.9 (0.4)			5.9 (0.5)		
Anxiety disorders						
Panic disorder	2.0*	(1.1–3.8)	4.8*	0.8	(0.4–1.6)	0.4
Social phobia	1.6*	(1.0–2.5)	4.9*	1.4	(1.0–1.9)	3.8
Specific phobia	1.9*	(1.2–2.9)	9.1*	1.3	(0.9–1.7)	2.6
GAD	3.0*	(1.2–7.6)	5.8*	0.8	(0.5–1.5)	0.4
PTSD	1.8	(0.8–4.1)	2.1	1.7*	(1.1–2.7)	5.2*
Agoraphobia	1.4	(0.9–2.2)	1.8	2.3*	(1.3–4.0)	8.9*
Separation anxiety	0.8	(0.4–1.5)	0.6	1.9*	(1.2–3.1)	6.8*
Any anxiety disorder	1.9*	(1.3–2.8)	11.7*	1.3	(0.9–1.7)	2.7
PARP (SE)	13.5 (1.0)			0.7 (0.5)		
Disruptive behavior disorders						
IED	1.3	(0.7–2.3)	0.7	1.6*	(1.0–2.4)	4.7*
ODD	1.5	(0.8–3.0)	1.5	1.7	(0.9–3.4)	2.6
CD	1.5	(0.9–2.5)	3.0	1.6*	(1.1–2.3)	6.5*
ADHD	1.8*	(1.1–2.9)	6.7*	1.4	(0.8–2.3)	1.6
ASPD	0.7	(0.1–4.6)	0.1	1.6	(0.7–3.5)	1.2
Any disruptive behavior disorder	1.5	(1.0–2.2)	3.8	1.5*	(1.1–2.1)	7.6*
PARP (SE)	2.0 (0.7)			3.5 (0.2)		
Substance use disorders						
Alcohol abuse with/without dependence	2.6*	(1.6–4.4)	14.7*	1.7*	(1.2–2.3)	10.3*
Alcohol dependence	3.0*	(1.7–5.5)	14.1*	1.8*	(1.3–2.6)	13.0*
Illicit drug abuse with/without dependence	4.2*	(1.8–9.4)	12.2*	1.9*	(1.4–2.5)	19.9*
Illicit drug dependence	4.0*	(1.5–10.8)	7.9*	1.7*	(1.2–2.4)	10.7*
Any substance use disorder	3.3*	(1.9–5.5)	21.2*	1.8*	(1.3–2.4)	13.7*
PARP (SE)	15.1 (1.4)			9.1 (0.5)		
Number of life-time disorders						
1	1.0	(0.6–1.8)	52.6*	1.1	(0.6–1.9)	26.9*
2	2.2*	(1.3–3.7)	–	2.0*	(1.2–3.2)	–
3	1.7	(0.9–3.2)	–	1.6	(0.9–2.7)	–
4 or more	4.1*	(2.6–6.5)	–	2.4*	(1.5–3.7)	–
Any disorder	2.0*	(1.4–2.9)	13.8*	1.7*	(1.1–2.6)	6.9*
Any disorder—PARP (SE)	28.5 (1.3)			22.2 (0.8)		
n, # positive	(2510)	(255)		(1426)	(543)	

*Significant at the 0.05 level, two-sided test. [a]Mental disorder abbreviations: 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); ASPD (antisocial personality disorder). [b]Controls for age, sex, race, education, marital status, number of children, region, urbanicity and employment status. CI: confidence interval; OR: odds ratio; PARP: population-attributable risk proportion; SE: standard error.

Table 3 Bivariate models of associations of baseline mental disorder with subsequent onset of alcohol regular use/abuse/dependence.

	T2 onset of regular alcohol use among T1 non-users or non-regular users[b]			*T2 onset of alcohol abuse among regular users*[b]			*T2 onset of alcohol dependence among abusers*[b]		
Time 1 disorders[a]	*OR*	*(95% CI)*	χ^2	*OR*	*(95% CI)*	χ^2	*OR*	*(95% CI)*	χ^2
Mood disorders									
Dysthymia	1.3	(0.4–3.9)	0.2	1.4	(0.4–4.7)	0.3	5.2*	(1.2–22.7)	5.0*
Major depression	1.6	(0.9–3.0)	2.3	1.4	(0.9–2.2)	1.9	1.5	(0.6–4.3)	0.7
Bipolar	0.8	(0.2–2.6)	0.2	2.5	(0.7–8.7)	2.1	2.6	(0.7–8.9)	2.4
Any mood disorder	1.6	(0.9–2.9)	2.3	1.4	(0.9–2.2)	2.3	1.7	(0.7–3.8)	1.5
PARP (SE)	1.2 (0.3)			3.5 (0.6)			4.4 (0.9)		
Anxiety disorders									
Panic disorder	1.5	(0.5–4.5)	0.5	0.8	(0.3–2.2)	0.1	3.8*	(1.5–10.2)	7.8*
Social phobia	1.0	(0.7–1.6)	0.0	1.4	(0.9–2.1)	2.5	2.9*	(1.6–5.1)	14.1*
Specific phobia	1.8*	(1.1–3.2)	4.8*	1.4	(0.9–2.4)	2.2	1.6	(0.7–3.9)	1.4
GAD	1.1	(0.5–2.7)	0.1	1.5	(0.6–3.9)	0.7	1.6	(0.5–5.7)	0.6
PTSD	1.1	(0.4–3.3)	0.1	1.6	(0.7–3.6)	1.5	4.5*	(1.5–13.1)	8.1*
Agoraphobia	1.2	(0.7–2.4)	0.5	1.3	(0.7–2.5)	0.6	2.2	(0.7–6.7)	1.9
Separation anxiety	1.6	(0.8–3.4)	1.6	1.5	(0.8–2.6)	1.9	2.1*	(0.8–5.6)	2.3*
Any anxiety disorder	1.7*	(1.2–2.5)	10.3*	1.2	(0.9–1.7)	1.3	2.7*	(1.5–5.0)	11.6*
PARP (SE)	3.7 (0.4)			4.1 (0.5)			27.6 (3.2)		
Disruptive behavior disorders									
IED	1.6	(0.3–7.8)	0.4	1.8*	(1.1–3.2)	4.8*	3.6*	(1.4–9.0)	7.7*
ODD	1.4	(0.5–3.8)	0.5	2.2	(0.9–5.4)	3.0	3.2*	(1.5–6.7)	10.3*
CD	0.5	(0.2–1.1)	2.9	1.6	(0.9–2.7)	2.5	1.1	(0.4–3.4)	0.1
ADHD	2.0	(1.0–4.1)	4.0*	1.6	(1.0–2.7)	3.6	0.8	(0.2–3.3)	0.1
ASPD	0.4	(0.0–50.6)	0.1	2.4*	(1.2–5.0)	6.0*	1.5	(0.5–5.1)	0.5
Any disruptive behavior disorder	1.2	(0.5–2.9)	0.3	1.8*	(1.1–2.9)	6.9*	1.4	(0.5–3.6)	0.5
PARP (SE)	–0.6 (0.7)			6.7 (0.6)			18.9 (3.9)		
Substance use disorders									
Illicit drug abuse with/without dependence	2.2	(0.8–6.4)	2.3	2.8*	(1.4–5.6)	9.4*	0.5	(0.2–1.2)	2.5
Illicit drug dependence	2.5	(0.8–7.4)	2.8	1.5	(0.5–4.6)	0.5	0.6	(0.2–1.7)	1.1
Nicotine dependence	0.5	(0.2–1.7)	1.2	1.8	(1.0–3.5)	3.5	1.1	(0.6–2.2)	0.1
Any substance use disorder	0.9	(0.4–2.3)	0.0	2.3*	(1.3–4.2)	7.8*	0.7	(0.4–1.3)	1.4
PARP (SE)	0.2 (0.5)			8.5 (0.8)			–6.0 (1.4)		
Number of life-time disorders									
1	2.1	(0.9–4.7)	5.4	1.0	(0.6–1.5)	9.6*	1.4	(0.5–4.0)	11.9*
2	1.5	(0.7–3.1)	–	1.5	(0.8–2.8)	–	2.3	(0.7–7.3)	–
3	1.6	(0.7–3.7)	–	2.4*	(1.1–5.0)	–	0.4	(0.1–3.0)	–
4 or more	2.2	(0.9–5.3)	–	2.3*	(1.2–4.1)	–	2.3	(0.7–7.1)	–
Any disorder	1.8*	(1.0–3.2)	4.5*	1.5*	(1.0–2.1)	5.2*	1.7	(0.6–4.4)	1.2
Any disorder—PARP (SE)	4.6 (0.7)			21.8 (1.1)			43.4 (3.0)		
n, # positive	(766)	(269)		(2337)	(246)		(1122)	(54)	

*Significant at the 0.05 level, two-sided test. [a]Mental disorder abbreviations: 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); ASPD (antisocial personality disorder). [b]Controls for age, sex, race, education, marital status, number of children, region, urbanicity and employment status. CI: confidence interval; OR: odds ratio; PARP: population-attributable risk proportion; SE: standard error.

Table 4 Bivariate models of associations of baseline mental disorder with subsequent onset of illicit drug regular use/abuse/dependence.

	T2 onset of illicit drug use among T1 non-users[b]			*T2 onset of illicit drug abuse among users*[b]			*T2 onset of illicit drug dependence among abusers*[b]		
Time 1 disorders[a]	*OR*	*(95% CI)*	χ^2	*OR*	*(95% CI)*	χ^2	*OR*	*(95% CI)*	χ^2
Mood disorders									
Dysthymia	2.1	(0.5–8.9)	1.2	1.6	(0.4–6.9)	0.4	3.4	(0.3–35.1)	1.1
Major depression	1.9*	(1.2–3.1)	6.9*	0.8	(0.4–1.6)	0.4	0.9	(0.4–1.9)	0.2
Bipolar	2.1	(0.6–6.5)	1.6	2.8*	(1.1–7.2)	5.1*	3.2*	(1.3–7.7)	7.1*
Any mood disorder	1.7*	(1.0–2.8)	4.3*	1.1	(0.6–2.1)	0.1	1.1	(0.6–2.0)	0.0
PARP (SE)	–0.2 (0.4)			–11.1 (1.3)			11.2 (3.0)		
Anxiety disorders									
Panic disorder	3.1*	(1.3–7.5)	6.8*	3.4*	(1.6–7.3)	10.6*	0.4	(0.1–1.8)	1.6
Social phobia	1.9*	(1.2–3.2)	6.9*	2.1*	(1.2–3.6)	7.3*	1.8	(0.8–4.3)	2.1
Specific phobia	2.3*	(1.5–3.6)	14.2*	1.9*	(1.1–3.1)	6.4*	2.1	(0.8–5.6)	2.3
GAD	1.9	(0.9–4.3)	2.8	0.6	(0.2–2.4)	0.5	0.9	(0.2–4.9)	0.0
PTSD	2.1	(0.9–4.8)	3.2	1.5	(0.6–3.8)	1.0	2.3	(0.8–6.9)	2.3
Agoraphobia	1.5	(0.7–3.5)	1.0	2.3	(0.9–5.6)	3.3	1.2	(0.3–5.4)	0.1
Separation anxiety	3.8*	(1.5–9.5)	8.9*	2.8*	(1.2–6.5)	6.3*	2.1	(0.5–8.8)	1.0
Any anxiety disorder	2.3*	(1.5–3.4)	17.0*	1.7*	(1.0–3.0)	4.3*	1.9	(0.9–4.1)	2.9
PARP (SE)	14.2 (0.8)			15.5 (1.8)			23.9 (5.6)		
Disruptive behavior disorders									
IED	3.0*	(1.5–5.7)	11.2*	3.8*	(2.1–6.9)	19.9*	3.4	(1.5–7.7)	8.8
ODD	2.9*	(1.3–6.4)	7.0*	3.7*	(1.9–7.2)	16.6*	1.8	(0.6–5.2)	1.1
CD	2.5*	(1.4–4.2)	11.4*	3.6*	(2.0–6.5)	19.5*	1.4	(0.5–3.5)	0.5
ADHD	4.3*	(2.1–8.5)	17.9*	2.8*	(1.3–5.9)	8.1*	2.9*	(1.1–7.7)	4.9*
ASPD	2.2	(0.1–48.1)	0.3	2.7	(0.9–8.4)	3.1	1.0	(0.2–6.2)	0.0
Any disruptive behavior disorder	2.7*	(1.8–4.1)	26.2*	3.5*	(1.9–6.3)	18.5*	1.9	(0.8–4.5)	2.4
PARP (SE)	12.3 (1.2)			36.1 (2.0)			13.6 (4.0)		
Substance use disorders									
Alcohol abuse with/without dependence	3.0*	(1.4–6.3)	8.3*	2.7*	(1.3–5.9)	7.1*	1.3	(0.6–3.2)	0.5
Alcohol dependence	2.1	(1.0–4.6)	3.6	2.8*	(1.1–6.7)	5.3*	1.7	(0.7–4.1)	1.6
Nicotine dependence	3.9*	(1.6–9.9)	9.0*	1.8	(0.9–3.9)	2.7	0.9	(0.4–2.1)	0.0
Any substance use disorder	2.6*	(1.4–4.6)	10.8*	2.7*	(1.5–5.1)	10.4*	1.7	(0.6–4.5)	1.1
PARP (SE)	10.7 (1.2)			24.5 (1.9)			27.2 (7.0)		
Number of life-time disorders									
1	2.1*	(1.3–3.4)	30.7*	1.5	(0.5–4.3)	35.2*	2.4	(0.2–24.6)	8.8*
2	2.3*	(1.1–4.7)	–	3.8*	(1.3–11.5)	–	8.1	(0.8–80.5)	–
3	3.0*	(1.7–5.3)	–	4.8*	(1.9–12.1)	–	8.3*	(1.2–58.0)	–
4 or more	6.1*	(2.8–13.4)	–	5.1*	(2.0–13.1)	–	7.1	(0.8–63.3)	–
Any disorder	2.7*	(1.8–4.1)	23.3*	3.3*	(1.5–7.7)	8.6*	6.2	(0.8–46.5)	3.3
Any disorder—PARP (SE)	34.2 (1.7)			61.5 (1.6)			71.9 (2.8)		
n, # positive	(1919)	(205)		(2340)	(105)		(495)	(48)	

*Significant at the 0.05 level, two-sided test. [a]Mental disorder abbreviations: 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); ASPD (antisocial personality disorder). [b]Controls for age, sex, race, education, marital status, number of children, region, urbanicity, and employment status. CI: confidence interval; OR: odds ratio; PARP: population-attributable risk proportion; SE: standard error.

sion by the baseline assessment as well as any anxiety disorder with the exception of GAD, PTSD and agoraphobia. Significant prospective associations were also observed for most forms of disruptive behavior disorders, additional substance use disorders, number of disorders or the presence of any disorder. The transition from illicit drug use to abuse was predicted by many of these same disorders, with an additional significant association observed for bipolar disorder (although not major depression). Again, the number of disorders and the aggregate category of any disorder were associated generally with increased risk of transition to abuse. Concerning the transition from abuse to dependence, significant associations were observed only for bipolar disorder and attention deficit hyperactivity disorder. The treatment of any disorder would result in the prevention of 34.2% of cases of initial drug use, 61.5% of cases of abuse among drug users and 71.9% of dependence among drug abusers.

DISCUSSION

Using data from a nationally representative sample, the present investigation examined the prospective associations of mental disorders with transitions to substance use, DSM-IV abuse and DSM-IV dependence with abuse over a 10-year period. Behavioral disorders and pre-existing substance use conditions emerged as the strongest and most consistent predictors of these transitions. The broad categories of any mood or anxiety disorder were also associated frequently with the onset of substance dependence over the subsequent decade, although the magnitudes of these associations varied by disorder type. Specifically, stronger associations were observed for bipolar disorder than other mood disorders, while five of seven anxiety disorders (panic, specific and social phobia, PTSD, separation anxiety) were predictive of at least one form of substance dependence. These findings are consistent with previous results based primarily on cross-sectional surveys demonstrating significant associations of mental disorders with substance dependence [1–5,9,10,12,15,18,29,30,53] and confirm that mental disorders can be conceptualized legitimately as risk factors due to the fact that they precede substance use disorders, are associated with increased probability of their initial onset and permit the population to be divided into high- and low-risk groups [54,55].

Using a conditional approach, aggregate associations were also decomposed in order to identify the category of use, abuse or dependence that is most influenced by pre-existing disorders. Concerning nicotine or illicit drugs, these analyses suggest that certain conditions such as anxiety or additional substance use disorders play a somewhat stronger role in the initial onset of daily smoking or drug use than in the onset of dependence. For alcohol, by contrast, many forms of disorder were associated more strongly with transitions to dependence than with the onset of use or abuse. It is also notable that several baseline mental disorders were unassociated with nicotine, alcohol or drug dependence in the aggregate analyses but emerged as significant risk factors for specific categories of use. Similar discrepancies between classic and conditional analyses have been reported recently concerning the associations of some socio-demographic risk factors with substance use categories [37,39–41].

It is possible that these forms of comorbidity may be attributable to shared vulnerabilities that increase simultaneously the risk of both psychiatric disorders and substance use conditions. However, the diversity of associations observed decreases the likelihood that these forms of comorbidity may be attributable to a small number of shared etiological factors, and such factors by themselves may not explain these prospective patterns of association easily. By contrast, the observation that primary mental disorders are associated with increased risk of later substance use, abuse or dependence provides prerequisite support for causal models of association which may reflect self-medication as well as a number of other causal mechanisms. Should these prospective associations indeed be attributable to the causal influence of primary disorders, population-attributable risk estimates indicate that their early treatment or prevention may potentially reduce a large percentage of secondary substance use conditions. World-wide, it is estimated that 4.1% of lost healthy life years (DALYs) are due to tobacco, 4.0% to alcohol and 0.8% to illicit drugs [56]. For each substance, information concerning stage-specific predictors may contribute to prevention strategies designed to reduce harm among individuals who are already using or abusing substances [57–60].

The strengths of this investigation include its use of prospective data from a nationally representative sample, and the examination of risk posed by primary mental disorders in transitions across several categories of alcohol, tobacco and illicit drug use. Methodological limitations include the fact that alcohol and drug dependence were assessed at follow-up only among respondents who met criteria for abuse. The use of such a gated approach has been found to have little impact on estimates of risk posed by socio-demographic or other individual characteristics [61–63], and may help to identify cases that are more clinically significant [64]. However, a gating strategy reduces prevalence estimates, especially in women [65]. The validity and utility of distinctions between abuse and dependence categories are also debated actively, and it is currently uncertain how this issue may be treated by DSM-V. The present findings, therefore, should be interpreted only within the context

DSM-IV definitions of abuse, or dependence with abuse. The reader should also be reminded that the baseline interview used DSM-III-R criteria. Although the strong concordance in questions administered in both interviews indicates that changes in nosology should not affect substance abuse and dependence rates greatly, these differences were not quantified. Concerning statistical approaches, the findings based on bivariate models may be explained partly by comorbid disorders and therefore may differ from multivariate models that examine the specificity of comorbid associations. The PARP statistics should also be interpreted with caution, as they reflect maximal estimates based on the assumption of exclusively causal associations. Future research is now needed to provide direct comparisons among comorbidity mechanisms in the goal of reducing new cases of substance use disorders that have a considerable impact on morbidity and mortality in the general population [56,66,67].

Declarations of interest

Dr Kessler has been a consultant for GlaxoSmith-Kline Inc., Kaiser Permanente, Pfizer Inc., Sanofi-Aventis, Shire Pharmaceuticals and Wyeth-Ayest; has served on advisory boards for Eli Lilly & Company and Wyeth-Ayerst; and has had research support for his epidemiological studies from Bristol-Myers Squibb, Eli Lilly & Company, GlaxoSmithKline, Johnson & Johnson Pharmaceuticals, Ortho-McNeal Pharaceuticals Inc., Pfizer Inc., and Sanofi-Aventis. Professor Dr Angst has served on the advisory board for Eli Lilly & Company, Janssen Cilag and Sanofi Aventis, and has served on the speakers' bureau for Eli Lilly & Company and AstraZeneca.

Acknowledgements

The NCS data collection was supported by the National Institute of Mental Health (NIMH; R01MH46376). The NCS-2 data collection was supported by the National Institute on Drug Abuse (NIDA; R01DA012058). Data analysis for this paper was supported additionally by NIMH grants R01MH070884, R01MH077883 and U01MH060220, with supplemental support from the Substance Abuse and Mental Health Services Administration (SAMHSA), the Robert Wood Johnson Foundation (RWJF; grant 044780) and the John W. Alden Trust. 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 US Government. A complete list of NCS and NCS-2 publications can be found at http://www.hcp.med.harvard.edu/ncs/. Send correspondence to ncs@hcp.med.harvard.edu. The NCS-2 is carried out in conjunction with the World Health Organization 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 National Institute of Mental Health (R01MH070884), the John D. and Catherine T. MacArthur Foundation, the Pfizer Foundation, the US Public Health Service (R13MH066849, R01MH069864 and R01DA016558), the Fogarty International Center (FIRCA R03TW006481), 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 http://www.hcp.med.harvard.edu/wmh/

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