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ORIGINAL ARTICLE

Lifetime co-morbidity of DSM-IV disorders in the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A)

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Background. Research on the structure of co-morbidity among common mental disorders has largely focused on current prevalence rather than on the development of co-morbidity. This report presents preliminary results of the latter type of analysis based on the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A).

Method. A national survey was carried out of adolescent mental disorders. DSM-IV diagnoses were based on the Composite International Diagnostic Interview (CIDI) administered to adolescents and questionnaires self-administered to parents. Factor analysis examined co-morbidity among 15 lifetime DSM-IV disorders. Discrete-time survival analysis was used to predict first onset of each disorder from information about prior history of the other 14 disorders.

Results. Factor analysis found four factors representing fear, distress, behavior and substance disorders. Associations of temporally primary disorders with the subsequent onset of other disorders, dated using retrospective age-of-onset (AOO) reports, were almost entirely positive. Within-class associations (e.g. distress disorders predicting subsequent onset of other distress disorders) were more consistently significant (63.2%) than between-class associations (33.0%). Strength of associations decreased as co-morbidity among disorders increased. The percentage of lifetime disorders explained (in a predictive rather than a causal sense) by temporally prior disorders was in the range 3.7–6.9% for earliest-onset disorders [specific phobia and attention deficit hyperactivity disorder (ADHD)] and much higher (23.1–64.3%) for later-onset disorders. Fear disorders were the strongest predictors of most other subsequent disorders.

Conclusions. Adolescent mental disorders are highly co-morbid. The strong associations of temporally primary fear disorders with many other later-onset disorders suggest that fear disorders might be promising targets for early interventions.

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Introduction

Epidemiological surveys of child–adolescent mental disorders consistently find high co-morbidity (Fergusson *et al*. 1994; Newman *et al*. 1996; Angold *et al*. 1999). Several longitudinal studies have examined temporal progression among these co-morbid disorders (Pine *et al*. 1998; Stein *et al*. 2001; Reinke & Ostrander, 2008). However, these studies have generally (McGee *et al*. 1992; Fergusson *et al*. 1993; Costello *et al*. 1996), although not always (Lieb *et al*. 2000; Shankman *et al*. 2009), focused on point prevalence in each wave or the cumulation of point prevalence estimates across multiple waves (Costello *et al*. 2003; Kim-Cohen *et al*. 2003). For example, the Great Smoky Mountain Study assessed 3-month mental disorders once yearly in three cohorts of children (Costello *et al*. 2003). This approach makes it impossible to distinguish associations of primary disorders with onset

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versus persistence of secondary disorders. Such a distinction, which would require examining temporal sequencing across lifetime rather than recent disorders, could have value in interpreting longitudinal associations and strategizing about intervention possibilities (Angold *et al*. 1999). There are exceptions, however. For example, the Early Developmental Stages of Psychopathology Study (Wittchen *et al*. 1998) is a large-scale longitudinal study that examined temporal sequencing of lifetime disorders in a cohort of adolescents followed into adulthood. Among the important findings this design allowed are that temporally prior generalized anxiety disorder (GAD) predicts the subsequent onset of other anxiety disorders more strongly than the subsequent onset of depression (Beesdo *et al*. 2010) and that social phobia is associated with subsequent onset of temporally secondary depression (Beesdo *et al*. 2007). However, this kind of analysis has never been used to examine temporal sequencing of disorder onsets across the full range of commonly occurring mental disorders.

The current report presents results of a preliminary analysis of the associations between temporally prior lifetime disorders and the subsequent first onset of temporally secondary disorders based on the data collected in the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A), a national survey of adolescent DSM-IV disorders (Merikangas *et al*. 2009). The results are only preliminary because the data are cross-sectional and temporal associations are inferred from retrospective age-of-onset (AOO) reports. Nonetheless, intriguing results emerge that could be useful in generating hypotheses to be examined in subsequent longitudinal studies. Previous studies would lead us to expect stronger inter-temporal associations within than between anxiety-mood and behavioral disorders (Reinke & Ostrander, 2008; Copeland *et al*. 2009) and strong associations of temporally primary behavior disorders with later substance disorders (Tapert *et al*. 2002; Elkins *et al*. 2007; Copeland *et al*. 2009), but we had no initial hypotheses about other specifications.

Method

Sample

Adolescents (ages 13–17 years) were interviewed between February 2001 and January 2004 in dual-frame household and school samples described elsewhere (Kessler *et al*. 2009*a*, *b*). The household sample included 904 adolescents (879 in school, 25 drop-outs) from households in the National Comorbidity Survey Replication (NCS-R; Kessler & Merikangas, 2004). The school sample included 9244 adolescents from a representative sample of schools in the adult sample areas of that survey. The conditional adolescent response rate was 86.8–82.6% (household and school samples respectively). The household sample includes school drop-outs and adolescents residing in areas where schools refused to participate. A high (72.0%) percentage of initially selected schools refused to participate and were replaced with matched replacement schools. Comparison of household sample respondents from non-participating schools with school sample respondents from replacement schools found no evidence of bias in estimates of either disorder prevalence or correlates (Kessler *et al*. 2009*a*).

One parent or surrogate (henceforth referred to as parents) of participating adolescents was asked to complete a self-administered questionnaire about the adolescent's developmental history and mental health. The conditional response rate was 82.5–83.7% (household and school samples respectively). This report focuses on the 6483 adolescent–parent pairs where complete data are available from both adolescents and parents. The fact that parent data were available for only a subset of adolescent respondents was taken into consideration by weighting the data in complete parent–adolescent pairs to adjust for differences with incomplete pairs. These weighting procedures are discussed in detail elsewhere (Kessler *et al*. 2009*a*, *b*).

Written parent informed consent and adolescent assent were obtained before surveying either the parent or adolescent. Each respondent was given US$50 for participation. These recruitment and consent procedures were approved by the Human Subjects Committees of both Harvard Medical School and the University of Michigan. Once the survey was completed, cases were weighted for within-household probability of selection (household sample) and deviation from Census population sociodemographic/geographic distributions, making each sample nationally representative on the sociodemographic/geographic variables. The samples were then merged with sums of weights proportional to relative sample sizes adjusted for design effects in estimating disorder prevalence. These procedures are detailed elsewhere (Kessler *et al*. 2009*a*, *b*).

Diagnostic assessment

Adolescents were administered the fully structured Composite International Diagnostic Interview (CIDI) modified to simplify language and use examples relevant to adolescents (Merikangas *et al*. 2009). The 15 DSM-IV disorders assessed include mood disorders (major depressive disorder/dysthymia, bipolar I–II disorder and subthreshold bipolar disorder), anxiety

disorders [panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia, specific phobia, GAD, post-traumatic stress disorder (PTSD), separation anxiety disorder (SAD)], behavior disorders [attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder, eating disorders (anorexia nervosa, bulimia nervosa, binge-eating behavior)] and substance disorders (alcohol and drug abuse, alcohol and drug dependence with abuse). There were no other exclusionary diagnoses. These disorders include all those assessed in most previous adolescent epidemiological studies.

Adolescent interviews assessed all disorders. Parent questionnaires assessed only disorders for which parent reports have previously been found important in diagnosis: behavior disorders (Johnston & Murray, 2003) and depression/dysthymia (Braaten *et al*. 2001). Parent and adolescent reports were combined at the symptom level using an 'or' rule (except in the case of ADHD, where only parent reports were used based on evidence of invalidity of adolescent reports). All diagnoses were made using DSM-IV distress/impairment criteria and organic exclusion rules, but diagnostic hierarchy rules were not used because we wanted to study co-morbidity among hierarchy-free disorders.

A clinical reappraisal study interviewed adolescent–parent pairs by telephone with the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) Lifetime Version (Kaufman *et al*. 1997). As detailed elsewhere, concordance was good between survey and clinical diagnoses (Kessler *et al*. 2009*c*), with an area under the receiver operating characteristic curve (AUC) of 0.81–0.94 for fear disorders, 0.79–0.86 for distress disorders, 0.78–0.98 for behavior disorders, and 0.92–0.98 for substance disorders. Parent and adolescent reports both contributed to the AUC when both were assessed for depression/dysthymia (0.75, 0.71 and 0.87 for adolescent, parent and combined reports respectively), ODD (0.71, 0.66 and 0.85) and conduct disorder (0.59, 0.96 and 0.98), but only parent reports contributed to the AUC for ADHD (0.57, 0.71 and 0.78). Adolescent disorder AOO reports were obtained retrospectively using probes shown experimentally to maximize recall accuracy among adults (Knauper *et al*. 1999).

Analysis methods

AOO curves were generated using the actuarial method (Halli *et al*. 1992). Tetrachoric factor analysis (principal axis method) with promax rotation was used to examine bivariate co-morbidity. Temporal unfolding was studied by examining predictive associations between temporally primary disorders (based on retrospective AOO reports) and first onset of later disorders with multivariate discrete-time survival models using a person-year dataset (Willett & Singer, 1993). The details of this modeling procedure, which we have used extensively in previous NCS reports, are presented elsewhere (Kessler *et al*. 2005). Each model predicted first onset of one disorder from information about prior lifetime occurrence of the other 14 disorders controlling basic sociodemographic variables [sex, race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Other), region of the country (Northeast, Midwest, South, West), urbanicity (Major Metropolitan Area, other urbanized area, rural area), parent education (less than high school, high school, some college, college graduate, coded for the parent with the higher level of education), number of biological parents with whom the adolescent lives (0–2), birth order (only child, oldest, youngest, other), number of siblings, and age].

Several more complex models allowed non-additive associations to exist among the predictor disorders. One of these added to the additive multivariate model a series of dummy variables for number of prior lifetime disorders beginning with two. These dummy variables represent gross interaction terms that require the coefficient to be the same for all combinations of disorders of a given number (e.g. all pairs of disorders, all sets of three disorders). A somewhat more complex model weighted the disorders in each of these sets to have differential slopes proportional to the main effects of the disorders. Another specification allowed for interactions between a continuous measure of number of prior lifetime disorders and each type of prior lifetime disorders. More detailed information about these models has been presented in a previous report (Alonso *et al*. 2011). The best-fitting model among these alternatives was selected using Akaike's Information Criterion (AIC; Burnham & Anderson, 2002). Survival coefficients and standard errors were exponentiated to produce odds ratios (ORs) and 95% confidence intervals (CIs).

Population attributable risk proportions (PARPs) were calculated to describe the strength of association between predictor disorders and outcome disorders. PARPs are the proportions of outcome disorders that would not have occurred in the absence of predictor disorders under the model if the survival coefficients represent causal effects. The proportions were calculated by generating a conditional predicted probability of first onset of each outcome disorder at each year of life of each respondent from the coefficients in the best-fitting survival model twice: once using all model coefficients and then again omitting coefficients for the predictor disorders. The actuarial method (Halli *et al*.

1992) was used to cumulate conditional predicted probabilities to respondent age at interview. PARP was defined as $1 - R$, where R represents the ratio of the mean cumulative predicted probability in the second specification divided by the mean cumulative predicted probability in the first specification.

As the survey data are both clustered and weighted, the design-based Taylor series linearization method implemented in the SUDAAN software system (SUDAAN, 2002) was used to estimate standard errors of prevalence estimates and 95% CIs of ORs. Significance of predictor sets was evaluated using Wald χ^2 tests based on design-based variance–covariance matrices. Statistical significance was consistently evaluated using 0.05-level two-sided tests.

Results

Lifetime prevalence and co-morbidity

A previous NCS-A report documented high lifetime prevalence of disorders (Merikangas *et al*. 2010). Overall prevalence is even higher in the current data because we included subthreshold bipolar disorder, which was omitted from the earlier report (Table 1). Co-morbidity is also more common because we analyze hierarchy-free diagnoses, with 27.9% of respondents meeting criteria for two or more disorders and a mean of 3.5 disorders among those with co-morbidity. All but two of the 105 tetrachoric correlations among disorder pairs [$(15 \times 14)/2$] are positive (82.5% statistically significant), with a median of 0.29 and interquartile range (IQR, 25th–75th percentiles) of 0.20–0.37. (The tetrachoric correlation matrix is available on request.)

Factor analysis finds four factors with unrotated eigenvalues >1.0. Oblique (promax) rotation shows that the first factor is similar to what previous studies referred to as a fear factor (Krueger, 1999; Watson, 2005), with high loadings for panic and phobias (0.67–0.79) (Table 1). The second factor represents what previous studies referred to as a distress factor, including depression, GAD, PTSD and SAD (0.51–0.87). The third factor represents behavior disorders (0.49–0.94) and the fourth represents alcohol–drug disorders (0.89–0.91), although conduct disorder (0.44) and bipolar disorder (0.40) also have elevated loadings. Disorders in the fear factor are the most common (26.1%), followed by distress (25.4%), behavior (22.7%) and substance (11.4%) disorders. The factors are all significantly correlated with each other, from a high Pearson correlation of 0.44 between fear and distress disorders to a low correlation of 0.16 between fear and substance disorders.

AOO distributions

The retrospectively reported median (IQR) AOO of any disorder is 8 (6–13) years. A clear temporal order exists across disorders within classes (Fig. 1) Specific phobia has the earliest AOO (median) within fear disorders (6), SAD within distress disorders (8), and ADHD within behavior disorders (6). The next earliest AOO distributions are for other fear (11–12) and behavior (12–13) disorders. Bipolar disorder (14), the remaining distress disorders (14), eating disorders (15), and substance disorders (16) have the latest median AOO.

Bivariate associations between earlier and later disorders

We estimated 210 (14×15) bivariate survival models, each with one lifetime disorder as a time-varying predictor of subsequent first onset of one other disorder, controlling for sociodemographics. In total, 89.3% of coefficients were positive and 59.5% significant. (Detailed results are available upon request.) The median (IQR) OR of the significant positive survival coefficients was 3.1 (2.3–3.9). Only two coefficients were negative and significant, both involving associations of substance disorders with later agoraphobia.

The best-fitting model

The best-fitting multivariate model pooled across all outcomes predicted first onset of each disorder from dummy variables for prior disorders plus summary measures of number of prior disorders. (Detailed results of model fitting are available on request.) The number-of-disorders measures include dummy variables for 2 to $\geqslant 7$ disorders.

Coefficients associated with pure disorders

The disorder type coefficients in the best-fitting model represent predictive associations of disorders that occur to people with no prior disorders. As there are a large number of coefficients for these pure disorders, it is useful to focus on summary statistics. (Detailed results are available on request.) A total of 40.0% of pure-disorder coefficients are positive and statistically significant (Table 2). The median (IQR) OR is 3.1 (2.4–3.9). Only one of the 210 coefficients is negative and significant. Approximately two-thirds (63.2%) of within-class coefficients are significant *versus* 33.0% of between-class coefficients. The median (IQR) significant within-class OR [3.9 (3.0–4.8)] is higher than the comparable between-class OR [2.9 (2.4–3.5)].

The same general pattern holds within each class of disorders, with 50.0–100% of within-class ORs

Table 1. *Lifetime prevalence of estimated DSM-IV disorders along with standard errors of prevalence estimates* (S.E.) *and rotated* (*promax*) *factor pattern of co-morbid disorders in the subsample with complete parent data* ($n = 6483$)[a]

	Prevalence[b]		Rotated factor pattern (standardized regression coefficients)			
	%	S.E.	I. Fear disorders	II. Distress disorders	III. Behavior disorders	IV. Substance disorders
I. Fear disorders						
Specific phobia	19.9	1.0	0.70	0.06	0.12	−0.10
Agoraphobia[c]	2.6	0.4	0.79	0.10	−0.13	0.00
Social phobia	8.5	0.6	0.67	0.09	0.03	0.09
Panic disorder[d]	2.4	0.2	0.68	−0.07	−0.10	0.15
Any fear disorder	26.1	1.0				
II. Distress disorders						
Separation anxiety disorder	7.6	0.5	0.37	0.51	0.11	−0.27
Post-traumatic stress disorder	4.7	0.4	0.02	0.79	−0.03	0.13
Major depressive episode/dysthymia	18.6	1.1	0.04	0.53	0.38	0.17
Generalized anxiety disorder	2.2	0.4	0.07	0.87	−0.08	0.01
Any distress disorder	25.4	0.9				
III. Behavior disorders						
ADHD	8.1	0.6	−0.15	−0.13	0.94	−0.07
Oppositional defiant disorder	12.6	0.9	0.04	0.01	0.70	0.25
Conduct disorder	6.8	0.9	−0.02	0.09	0.49	0.44
Eating disorders[e]	5.1	0.4	0.20	0.11	0.54	−0.14
Any behavior disorder	22.7	1.3				
IV. Substance disorders						
Alcohol abuse[f]	6.1	0.5	−0.18	0.23	−0.11	0.89
Drug abuse[f]	8.9	0.8	0.10	−0.05	0.02	0.91
Any substance disorder	11.4	0.9				
V. Other disorders						
Bipolar disorder[g]	6.2	0.4	0.38	−0.23	0.10	0.40
VI. Total number of disorders						
Any disorder	51.3	1.3				
Exactly one disorder	23.4	0.9				
Exactly two disorders	12.0	0.6				
Three or more disorders	15.9	1.0				

ADHD, Attention deficit hyperactivity disorder; S.E., standard error.

[a] Eigenvalues of unrotated factors: 5.2, 2.2, 1.1, 1.0, 0.9. Correlations among factors in promax rotated four-factor solution: I–II 0.44; I–III 0.25, I–IV 0.16, II–III 0.31, II–IV 0.29, III–IV 0.43.

[b] The prevalence estimates reported here are higher than those in an earlier NCS-A report (Merikangas *et al*. 2010) because disorders were defined here without diagnostic hierarchy rules and included subthreshold bipolar disorder. Estimated co-morbidity is higher than in the earlier report because hierarchy rules were not used.

[c] Agoraphobia is assessed with or without panic disorder.

[d] Panic disorder is assessed with or without agoraphobia.

[e] Includes anorexia nervosa, bulimia nervosa and binge-eating disorder.

[f] With or without dependence.

[g] Includes bipolar I, bipolar II and subthreshold bipolar disorder.

being significant *versus* 15.9–64.3% of between-class coefficients. The percentage of significant between-class coefficients is much lower in predicting fear (15.9%) than other (29.6–64.3%) disorders. One or two disorders are the most powerful within-class predictors in each class: specific phobia and social phobia among the fear disorders; major depression for distress disorders; and ADHD and conduct disorders for behavior disorders. Fear disorders have the highest proportion of significant between-class coefficients predicting other disorders (52.3%), followed by distress (36.4%), behavior (29.6%) and substance (15.4%) disorders. Two of the three most consistent predictors are fear disorders [social phobia (81.8%)

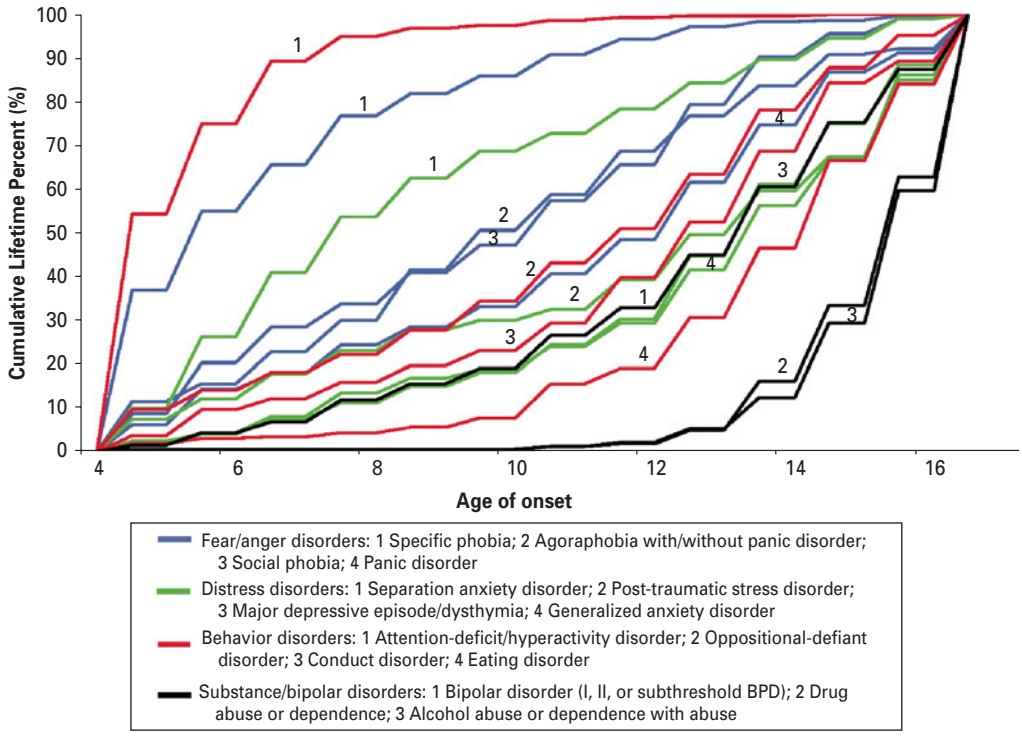

Fig. 1. Age-of-onset (AOO) distributions based on retrospective AOO reports among respondents with lifetime DSM-IV/Composite International Diagnostic Interview (CIDI) disorders.

and specific phobia (72.7%)], the other being major depression (72.7%).

Coefficients associated with co-morbidity

The coefficients associated with number of predictor disorders in the best-fitting model represent predictive associations of co-morbidity expressed as deviations from the pure-disorder coefficients. For example, absent effects of co-morbidity, respondents with three predictor disorders having pure-disorder ORs of, say, 1.3, 1.5 and 1.7 would have an expected OR of 3.3 (i.e. $1.3 \times 1.5 \times 1.7$). If the actual OR for these respondents is 4.0, then the number-of-disorders OR would be 1.2 (i.e. 4.0/3.3), indicating that the predictive effect of co-morbidity is 20% higher than expected from the pure-disorder coefficients. The best-fitting model assumes that these number-of-disorders coefficients are a function of each respondent's weighted number of predictor disorders, with weights defined by the pure-disorder coefficients.

With this interpretation in mind, 87.2% of the number-of-disorder coefficients in the best-fitting model are less than 1.0 across equations, indicating a general pattern of subadditive interaction in the logistic specification; that is, a pattern in which the joint effects of the interacting predictors are significantly less than those estimated in a model that assumes that no interactions exist (Table 3). One-third of these subadditive coefficients are statistically significant whereas none of the ORs greater than 1.0 are significant. This pattern of the predictive associations of co-morbidity generally being less than the product of their parts becomes stronger as the number of disorders in the co-morbid profile increases from a median OR of 0.8 for two disorders to 0.1 for seven or more disorders.

PARPs

PARPs vary widely across outcomes (IQR 35.6–54.5%) (Table 4). The lowest PARPs in terms of the outcomes are associated with specific phobia (3.7%) and ADHD (6.9%), the two earliest-onset disorders. This reflects the low prevalence and generally insignificant association of prior disorders predicting these two disorders. A similar interpretation applies to SAD, the outcome disorder with the next lowest risk proportion (23.1%). SAD has a comparatively early AOO distribution and is predicted by a lower than average proportion of prior disorders. The other 12 disorders, when considered as outcomes, all have risk proportions of 35.0% or higher. Those with the highest risk proportions have comparatively late AOO distributions and are either significantly predicted by the majority of other disorders (alcohol abuse, bipolar

Table 2. *Predictive associations (percent significant and range of significant odds ratios) of temporally primary pure lifetime estimated DSM-IV disorder types with the subsequent first onset of other estimated DSM-IV disorders based on the best-fitting multivariate survival model (n = 6483)*[a]

	Predictor disorders											
	Fear disorders		Distress disorders		Behavior disorders		Substance disorders		Bipolar disorder		All disorders	
Outcome disorders	%[g]	OR[h]	%[g]	OR[h]	%[g]	OR[h]	%[g]	OR[h]	%[g]	OR[h]	%[g]	OR[h]
I. Fear disorders												
Specific phobia	33.3	3.9	50.0	1.8–3.2	0	–	0	–	0	–	21.4	1.8–3.9
Agoraphobia[b]	66.7	4.8–9.2	50.0	2.8–3.3	0	–	0	–	0	–	28.6	2.8–9.2
Social phobia	66.7	3.6–4.2	50.0	1.8–2.1	0	–	0	–	0	–	30.8	1.8–4.2
Panic disorder[c]	33.3	3.3	25.0	3.1	0	–	0	–	0	–	14.3	3.1–3.3
II. Distress disorders												
Separation anxiety disorder	50.0	2.4–2.7	66.7	2.4–4.7	0	–	0	–	0	–	28.6	2.4–4.7
Post-traumatic stress disorder	50.0	3.0–3.9	66.7	3.7–4.7	0	–	50.0	4.7	100.0	3.2	42.9	3.0–4.7
Major depressive episode/dysthymia	100.0	1.7–3.3	33.3	3.4	100.0	2.3–3.4	50.0	4.4	0	–	71.4	1.7–4.4
Generalized anxiety disorder	50.0	2.8–3.1	100.0	2.5–5.1	0	–	50.0	4.3	0	–	42.9	2.5–5.1
III. Behavior disorders												
ADHD	0	–	0	–	66.7	3.7–5.6	0	–	0	–	20.0	3.7–5.6
Oppositional defiant disorder	75.0	1.9–2.9	50.0	2.0–3.6	66.7	2.3–4.9	0	–	0	–	50.0	1.9–4.9
Conduct disorder	50.0	1.8–3.4	25.0	4.4	66.7	2.3–3.0	50.0	10.3	0	–	42.9	1.8–10.3
Eating disorders[d]	50.0	2.4–3.7	50.0	2.5–3.8	66.7	2.2–4.1	0	–	0	–	42.9	2.2–4.1
IV. Substance disorders												
Alcohol abuse[e]	25.0	2.6	25.0	3.1	50.0	2.8–3.5	100.0	8.3	0	–	35.7	2.6–8.3
Drug abuse[e]	50.0	2.4	25.0	2.1	75.0	2.8–6.1	100.0	8.4	100.0	3.2	57.1	2.1–8.4
V. Other disorders												
Bipolar disorder[f]	75.0	2.8–4.3	50.0	1.8–5.7	100.0	2.3–4.4	0	–	0	–	64.3	1.8–5.7

OR, Odds ratio; ADHD, attention deficit hyperactivity disorder.

[a] Based on a discrete-time (person-year) survival model in which first lifetime onset of each of the 15 estimated DSM-IV disorders is predicted by 14 dummy variables for prior lifetime history of the other disorders, dummy variables for number of prior lifetime disorders (2 to ⩾7), and sociodemographic controls (sex, race/ethnicity, region of the country, urbanicity, parent education, number of biological parents with whom the adolescent lives, birth order, number of siblings, and age).

[b] Agoraphobia is assessed with or without panic disorder.

[c] Panic disorder is assessed with or without agoraphobia.

[d] Includes anorexia nervosa, bulimia nervosa and binge-eating disorder.

[e] With or without dependence.

[f] Includes bipolar I, bipolar II and subthreshold bipolar disorder.

[g] Percentage of coefficients that are significant at the 0.05 level using two-sides design-based significance tests.

[h] Range of significant ORs.

Table 3. *Predictive associations (odds ratios) along with 95% confidence intervals (CIs) of number of lifetime estimated DSM-IV disorders with the subsequent first onset of other estimated DSM-IV disorders based on the best-fitting multivariate survival model (n = 6483)*[a]

	Number of predictor disorders											
	2		3		4		5		6		⩾7	
Outcome disorders	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
I. Fear disorders												
Specific phobia	1.0	0.5–2.0	0.3	0.1–1.1	0.9	0.2–4.9	0.7	0.1–7.0	1.2	0.1–11.4	3.6	0.3–45.5
Agoraphobia[b]	0.6	0.2–1.7	0.4	0.0–2.4	0.4	0.0–3.8	0.1	0.0–2.0	0.0*	0.0–0.8	0.0	0.0–6.4
Social phobia	0.8	0.4–1.9	0.6	0.2–2.0	0.4	0.1–2.7	0.1	0.0–1.5	0.1*	0.0–0.7	1.0	0.0–65.5
Panic disorder[c]	0.9	0.4–2.2	1.1	0.2–6.7	0.4	0.0–7.6	0.3	0.0–6.4	0.4	0.0–14.1	0.0	0.0–5.1
II. Distress disorders												
Separation anxiety disorder	0.7	0.3–1.6	1.0	0.3–3.2	0.9	0.2–4.7	0.7	0.1–5.4	0.0*	0.0–0.2	1.8	0.1–51.6
Post-traumatic stress disorder	0.7	0.3–1.6	0.6	0.1–2.3	0.1*	0.0–0.3	0.1*	0.0–0.7	0.1	0.0–1.7	0.0*	0.0–0.4
Major depressive disorder/ dysthymia	0.8	0.4–1.3	0.4*	0.2–0.8	0.2*	0.1–0.6	0.1*	0.0–0.2	0.1*	0.0–0.4	–	–
Generalized anxiety disorder	1.0	0.0–3.6	0.9	0.1–5.5	0.7	0.1–9.0	0.2	0.0–3.5	0.2	0.0–8.8	0.0	0.0–28.6
III. Behavior disorders												
ADHD	1.2	0.3–5.1	3.0	0.3–30.2	0.6	0.0–15.3						
Oppositional defiant disorder	0.8	0.4–1.6	0.6	0.3–1.2	0.2*	0.0–0.9	0.1*	0.0–0.8	0.0*	0.0–0.4	0.0*	0.0–0.5
Conduct disorder	1.0	0.5–2.4	0.4	0.1–1.2	0.4	0.6–2.0	0.2	0.0–1.3	0.1	0.0–1.0	0.2	0.0–9.6
Eating disorders[d]	0.8	0.3–2.1	0.3*	0.1–0.8	0.2	0.0–1.2	0.2	0.0–1.4	0.1	0.0–1.3	0.0*	0.0–0.04
IV. Substance disorders												
Alcohol abuse[e]	0.6	0.2–1.8	0.6	0.1–2.8	0.3	0.0–2.2	0.1*	0.0–0.9	0.0*	0.0–0.4	0.0	0.0–1.6
Drug abuse[e]	0.9	0.4–1.9	0.4	0.2–1.3	0.2*	0.0–1.0	0.1*	0.0–1.0	0.3	0.0–4.6	0.0*	0.0–0.4
V. Other disorders												
Bipolar disorder[f]	0.4*	0.2–0.8	0.2*	0.1–0.6	0.2	0.0–0.7	0.0*	0.0–0.3	0.0*	0.0–0.02	0.0*	0.0–0.02

OR, Odds ratio; ADHD, attention deficit hyperactivity disorder.

[a] Based on a discrete-time (person-year) survival model in which first lifetime onset of each of the 15 estimated DSM-IV disorders is predicted by 14 dummy variables for prior lifetime history of the other disorders, dummy variables for number of prior lifetime disorders (2 to ⩾7), and sociodemographic controls (sex, race/ethnicity, region of the country, urbanicity, parent education, number of biological parents with whom the adolescent lives, birth order, number of siblings, and age).

[b] Agoraphobia is assessed with or without panic disorder.

[c] Panic disorder is assessed with or without agoraphobia.

[d] Includes anorexia nervosa, bulimia nervosa and binge-eating disorder.

[e] With or without dependence.

[f] Includes bipolar I, bipolar II and subthreshold bipolar disorder.

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

disorder), very strongly predicted by a smaller number of other disorders (panic disorder, agoraphobia), or less strongly predicted by highly prevalent disorders (GAD).

Focusing on predictor disorders, the fear disorders have the highest PARPs in predicting nearly three-quarters of all outcome disorders, including other fear disorders, all four distress disorders, eating disorder, and bipolar disorder. There are only five exceptions: ADHD, where, as noted earlier, the risk proportion is very low overall; ODD and conduct disorders, where the highest risk proportions are associated with other behavior disorders; and substance disorders, where the highest risk proportions are associated with behavior disorders. As predictors, substance disorders consistently have the lowest risk proportions. Distress disorders generally have higher proportions than behavior disorders in predicting fear and distress disorders, but lower in predicting behavior and substance disorders.

Discussion

It is important to recognize that the analyses reported here focused on predictors of first onset of co-morbid conditions. The investigation of persistence is a

Table 4. *Population attributable risk proportions (PARPs) of temporally primary lifetime estimated DSM-IV disorder types predicting subsequent first onset of other estimated DSM-IV disorders based on the best-fitting multivariate survival model (n = 6483)*[a]

Outcome disorders	Types of predictor disorders					
	Fear disorders	Distress disorders	Behavior disorders	Substance disorders	Bipolar disorder	All disorders
I. Fear disorders						
Specific phobia	1.7	1.3	1.2	0.5	0.5	3.7
Agoraphobia[b]	63.3	23.2	−18.8	−0.0	1.0	62.2
Social phobia	29.0	5.9	0.4	−0.2	0.2	35.6
Panic disorder[c]	28.2	15.5	1.5	0.0	2.1	41.5
II. Distress disorders						
Separation anxiety disorder	19.4	7.0	0.9	0.6	0.7	23.1
Post-traumatic stress disorder	38.2	27.0	11.4	3.8	8.1	54.5
Major depression/dysthymia	20.5	4.6	18.7	0.2	−0.0	37.9
Generalized anxiety disorder	43.0	40.6	7.4	2.8	−4.8	64.3
III. Behavior disorders						
ADHD	3.0	1.1	3.6	0.0	0.8	6.9
Oppositional defiant disorder	12.0	13.3	19.0	−0.2	2.3	36.4
Conduct disorder	16.0	12.3	17.4	3.7	0.7	40.4
Eating disorders[d]	28.4	14.8	16.2	0.5	2.1	43.6
IV. Substance disorders						
Alcohol abuse[e]	11.4	11.2	27.4	11.1	3.8	48.8
Drug abuse[e]	15.7	9.6	29.5	7.1	7.0	42.7
V. Other						
Bipolar disorder[f]	32.2	25.1	19.0	0.0	–	57.2

ADHD, Attention deficit hyperactivity disorder.

[a] Based on a discrete-time (person-year) survival model in which first lifetime onset of each of the 15 DSM-IV/CIDI disorders is predicted by 14 dummy variables for prior lifetime history of the other disorders, dummy variables for number of prior lifetime disorders (2 to ⩾7), and sociodemographic controls (sex, race/ethnicity, region of the country, urbanicity, parent education, number of biological parents with whom the adolescent lives, birth order, number of siblings, and age).

[b] Agoraphobia is assessed with or without panic disorder

[c] Panic disorder is assessed with or without agoraphobia

[d] Includes anorexia nervosa, bulimia nervosa, and binge-eating disorder

[e] With or without dependence

[f] Includes bipolar I, bipolar II and subthreshold bipolar disorder.

separate matter that requires additional analysis not undertaken here. Furthermore, with regard to onset, the analysis examined only aggregate associations and did not consider the possibility of variation in the structure or predictors of co-morbidity in childhood *versus* adolescence, among boys *versus* girls, or by other potentially important subgrouping distinctions.

Three sample limitations are noteworthy: that the school-level response rate was fairly low, the individual-level response rate relatively low, and the sample excluded adolescents not enrolled in school. Methodological analysis reported elsewhere reduces concern about the first limitation, as no evidence of bias was found due to school replacement (Kessler *et al*. 2009*a*). The finding in previous methodological studies that non-respondents have higher rates of mental illness than respondents implies that the second limitation probably led prevalence estimates to be conservative, although estimates of predictive associations might be biased either upward or downward and differentially across predictor disorders (Kessler *et al*. 1995). The third limitation reduces the external validity of findings.

Two limitations concerning measurement are also noteworthy: that diagnoses were based on lay interviews and questionnaires rather than clinical assessments and that lifetime diagnoses and AOO reports were based on retrospective recall rather than prospective data. Concern about the first limitations is somewhat reduced by the good concordance with clinical diagnoses (Kessler *et al*. 2009*c*). The second

limitation presumably reduced lifetime prevalence estimates (Patten, 2009; Moffitt *et al*. 2010), distorted AOO reports (Simon & von Korff, 1995), and could have biased estimates of predictive associations differentially across disorders depending on between-disorder differences in failure to recall lifetime occurrence and/or AOO. It would be very valuable to correct these limitations by replicating the complex analyses carried out here with long-term longitudinal data.

As several prospective studies of child–adolescent mental disorders exist (Newman *et al*. 1996; Pine *et al*. 1998; Costello *et al*. 2003; Reinke & Ostrander, 2008), a question can be raised why retrospective analysis of the sort reported here has value. The answer is that most existing prospective studies, with a few notable exceptions (Wittchen *et al*. 1998; Olino *et al*. 2010), did not obtain data on lifetime prevalence of mental disorders, making it impossible to carry out analyses of the associations between prior lifetime disorders and subsequent first lifetime onset of secondary disorders in the majority of such studies. Replication of the kinds of analyses reported here should be encouraged in the prospective studies that would support them. The results of the current analyses should be useful in providing preliminary hypotheses to be investigated in these prospective studies. This has traditionally been a major value of retrospective studies (Mantel & Haenszel, 1988).

In the context of these limitations, the differential AOO patterns found here are consistent with considerable previous evidence that ADHD, specific phobia and SAD have the earliest age of onset and that generalized anxiety, depressive and substance disorders have the latest age of onset of the adolescent disorders considered here (Kessler *et al*. 2007). Very similar patterns were found in parallel analyses carried out previously in a cross-national sample of adults (Kessler *et al*. 2011). The high co-morbidity found among disorders is also consistent with previous evidence (Angold *et al*. 1999).

The four-factor structure found in the NCS-A is also generally similar to findings from previous studies (Krueger, 1999; Vollebergh *et al*. 2001; Watson, 2005; Kessler *et al*. 2009*b*). Although several different specifications of the factor analysis model (e.g. at the person-level *versus* person-year level, with and without subthreshold bipolar disorder, with and without corrections for differential validity of diagnoses) yielded very similar results, replication in independent datasets is needed before considering this pattern stable.

One exception to the consistency of the NCS-A results with previous factor analyses is that SAD loaded with distress disorders in the NCS-A but with fear disorders in some previous studies (Lahey *et al*. 2004). It is unclear why this occurred, but it is noteworthy that the loading of SAD on the distress factor was the weakest among all distress disorders and that SAD had the largest cross-loading with the fear factor of any distress disorder.

Another discrepancy with previous factor analysis studies is that substance disorders loaded separately from behavior disorders in the NCS-A. Substance and behavior disorders have generally loaded together in previous studies. However, this might reflect the fact that most previous factor analysis studies did not include as many behavior disorders as the NCS-A. The fact that substance and behavior disorders loaded separately in the NCS-A suggests that they have unique underlying psychopathological processes in adolescence (Krueger, 1999), a possibility that is indirectly consistent with the finding in behavior genetic studies that substance disorders have unique genetic loadings not shared with behavior disorders (Kendler *et al*. 2003) that vary in importance across the life course (Kendler *et al*. 2008).

A final factor analysis result that warrants comment is that the summary measure of eating disorders in the NCS-A loaded with behavior disorders rather than with distress disorders. Previous research has generally found that anorexia nervosa is more strongly related than bulimia nervosa or binge-eating disorder to internalizing disorders (e.g. Godart *et al*. 2006), whereas bulimia nervosa and binge-eating disorder are strongly related to behavioral disorders (e.g. Marmorstein *et al*. 2007). It is relevant in this regard that the vast majority of NCS-A respondents with eating disorders had bulimia nervosa or binge-eating disorder rather than anorexia nervosa.

The finding of stronger within-class than between-class predictive associations is consistent with previous longitudinal studies of prevalent disorders among youth (Newman *et al*. 1996; Costello *et al*. 2003; Reinke & Ostrander, 2008), although we are unaware of previous comparable studies of first onset of lifetime disorders. Comparable results were also found in our previous cross-national study of the development of co-morbidity among adults (Kessler *et al*. 2011). The finding that fear disorders are the most important between-class predictors is consistent with, but goes beyond, previous research showing that early-onset anxiety disorders predict later distress disorders (Lewinsohn *et al*. 1995; Pine *et al*. 1998; Stein *et al*. 2001; Costello *et al*. 2003). Substance use disorders, at the other extreme, generally do not predict later disorders but are predicted strongly by earlier disorders. Although associations of behavior disorders with later substance disorders are well documented (Costello *et al*. 1999; Fergusson *et al*. 2007), the

predictive associations of primary fear and distress disorders have been less consistently examined (Costello *et al*. 2003).

The asymmetric associations across time-lagged disorder pairs could be due either to unmeasured common causes (e.g. genetic influences) or to causal influences of the predictor disorders on outcome disorders. There is no definitive way to distinguish these two possibilities with either retrospective or prospective non-experimental data. To the extent that the primary disorders are causes, however, successful early intervention might help to prevent the onset of subsequent co-morbid disorders. To the extent that predictive associations are due to underlying common causes, temporally primary disorders might be useful risk markers (Kraemer *et al*. 1997) in targeting indicated interventions. Fear disorders stand out as especially important in the latter regard because they are such consistently strong predictors of later disorders. It is noteworthy in this regard that childhood-onset specific phobias can often be treated very effectively with inexpensive exposure-based therapies (Gros & Anthony, 2006; Hamm, 2009).

We are aware of no previous broad-based analysis of lifetime co-morbidity predicting the subsequent first onset of a range of secondary disorders other than our own prior cross-national cross-section study of adults (Kessler *et al*. 2011). Our finding of largely subadditive predictive associations of co-morbid disorders, which we also found in our adult study, is consequently unique. It is important to note that this subadditivity is based on a logistic model, which means that an additive specification with a linear or other link function might fit the data. However, our efforts to find an alternative link function that provided a better fit of the data with an additive specification was unsuccessful. This subadditive pattern has potentially important implications for intervention because it suggests that intervening with a single co-morbid disorder might not be effective in preventing subsequent disorder onset, as incremental predictive effects of individual disorders decrease with the number of other disorders. To the extent that primary disorders are causes, treatment of the entire cluster of co-morbid disorders is likely to be more effective than treatment of individual primary disorders in secondary prevention among patients with co-morbidity (Moses & Barlow, 2006). Perhaps even more important, however, we have shown that the innovative methodology used here yields substantively plausible results. Although many of these results do little more than replicate previous findings, the methodology has the potential to yield much more nuanced results when applied, as we hope it will be in the future, to prospective datasets.

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Declaration of Interest

R. C. Kessler has been a consultant for AstraZeneca, Analysis Group, Bristol-Myers Squibb, Cerner-Galt Associates, Eli Lilly & Company, GlaxoSmithKline Inc., HealthCore Inc., Health Dialog, Integrated Benefits Institute, John Snow Inc., Kaiser Permanente, Matria Inc., Mensante, Merck & Co., Inc., Ortho-McNeil Janssen Scientific Affairs, Pfizer Inc., Primary Care Network, Research Triangle Institute,

Sanofi-Aventis Groupe, Shire US Inc., SRA International, Inc., Takeda Global Research & Development, Transcept Pharmaceuticals Inc., and Wyeth-Ayerst; has served on advisory boards for Appliance Computing II, Eli Lilly & Company, Mindsite, Ortho-McNeil Janssen Scientific Affairs, and Wyeth-Ayerst; and has had research support for his epidemiological studies from Analysis Group Inc., Bristol-Myers Squibb, Eli Lilly & Company, EPI-Q, GlaxoSmithKline, Johnson & Johnson Pharmaceuticals, Ortho-McNeil Janssen Scientific Affairs., Pfizer Inc., Sanofi-Aventis Groupe, and Shire US, Inc.

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