

# The prevalence and co-morbidity of subthreshold psychiatric conditions

PETER M. LEWINSOHN\*, STEWART A. SHANKMAN, JEFFREY M. GAU  
AND DANIEL N. KLEIN

*Oregon Research Institute, 1715 Franklin Blvd, Eugene, Oregon, USA*

## ABSTRACT

**Background.** In previous studies of subthreshold conditions, co-morbidity has been largely ignored. The purpose was to examine rates of co-morbidity among subthreshold disorders and between subthreshold and full-syndrome disorders for the major non-psychotic classes of disorders from DSM-IV.

**Method.** Participants came from the Oregon Adolescent Depression Project (mean age = 16.6 years; females = 52.1%). On the basis of a diagnostic interview (K-SADS), participants were assigned to eight subthreshold disorders (MDD, bipolar, eating, anxiety, alcohol use, substance use, conduct, ADHD).

**Results.** Of the 1704 adolescents in the analyses, 52.5% had at least one subthreshold disorder. Of those, 40.0% had also experienced a co-morbid subthreshold condition, and 29.9% of those had a second co-morbid subthreshold condition. Of those with a subthreshold, 36.4% also had a full syndrome. The subthreshold forms of externalizing disorders were co-morbid with each other. As expected, subthreshold anxiety was co-morbid with subthreshold MDD but subthreshold anxiety was also co-morbid with subthreshold alcohol, conduct, and ADHD. The pattern of co-morbidities was nearly identical for males and females.

**Conclusions.** The hypotheses that externalizing disorders would be co-morbid with other externalizing disorders and that internalizing disorders would be co-morbid with other internalizing disorders was partially supported. Co-morbidities between subthreshold disorders and between subthreshold disorders and full syndrome should impact future research and clinical practice. The assessment of subthreshold disorders needs to include the assessment of other subthreshold and full-syndrome conditions.

## INTRODUCTION

Before the classic work of Feighner and colleagues (Feighner *et al.* 1972) which provided a framework for diagnosing psychiatric disorders, the reliability and validity for psychiatric disorders was rather weak. Since that time, the development and increased use of psychiatric diagnostic systems such as the ICD-10 (WHO, 1994) and DSM-IV (APA, 1994) has greatly

improved the reliability of diagnoses and enhanced the accuracy of prevalence rates of specific psychiatric conditions. In these systems, an individual is determined to be a case of a particular disorder when they exceed a cut-off of a diagnostic algorithm.

The goal of these systems is to carve nature at its joints (Plato's *Phaedrus*; Plato, 1998) and thus parse the domain of mental disorders into specific categories. Most researchers, though, including the creators of these systems, believe that this objective has not yet been achieved (Spitzer & Wakefield, 1999). While one hopes that the criteria and cut-off are based on sound

\* Address for correspondence: Dr Peter M. Lewinsohn, Senior Research Scientist, Oregon Research Institute, 1715 Franklin Blvd., Eugene, OR 97403-1983, USA.  
(Email: pete@ori.org)

empirical and clinical considerations, the fact that these systems are continuously revised and that few are entirely satisfied with them suggests that the determination of caseness of a disorder is ultimately somewhat arbitrary (Helzer & Hudziak, 2002).

Recently, there has been an increased interest in studying individuals with psychiatric conditions that are subthreshold (SUB), i.e. below the cut-off for the full syndrome (FS) (Pincus *et al.* 1999; Helmchen & Linden, 2000).<sup>†</sup> These studies are significant for several reasons. From a diagnostic standpoint, studying SUB conditions can address the validity of systems such as the DSM-IV and ICD-10. These systems imply that SUB conditions do not reflect the same construct as the full disorder (Fechner-Bates *et al.* 1994). However, if SUB conditions are associated with similar correlates and impairment as FS (though to a lesser extent), then perhaps they are merely milder forms of the FS and not categorically different constructs (Flett *et al.* 1997; Lewinsohn *et al.* 2000*b*).

The bulk of the studies that have examined SUB psychopathology have focused on unipolar depression. Some have used elevated scores (in the absence of meeting criteria for DSM diagnosis) in symptom scales such as the Center for Epidemiologic Studies Depression Scale (Radloff, 1977; Gotlib *et al.* 1995) and the Hamilton Depression Rating Scale (Hamilton, 1960; Lewinsohn *et al.* 2000*b*). Others have described SUB conditions such as minor depression (Kessler *et al.* 1997) and Brief Recurrent Depression (Angst & Hochstrasser, 1994). In all of these studies SUB depression has been found to be associated with significant impairment and treatment utilization (Sadek & Bona, 2000). Prospective studies have also reported that individuals with SUB cases have an increased risk for future major depressive episodes (Broadhead *et al.* 1990; Maier *et al.* 1997; Lewinsohn *et al.* 2000*b*). Finally, patients with SUB depression have demonstrated a significant response rate to antidepressant treatment (Paykel *et al.* 1988; Szegedi *et al.* 1997). Findings such as these have led some to argue in favor of replacing the present categorical diagnostic

systems with dimensional ones (Wakefield, 1992; Widiger, 1993).

The validity of other SUB conditions has also been examined as well as their relationship with the FS disorder. SUB bipolar disorder has been shown to be associated with significant impairment and health-care utilization (Lewinsohn *et al.* 1995*a*; Angst *et al.* 2002) and elevated familial rates of FS bipolar disorder (Lewinsohn *et al.* 2000*c*). Similar findings have also been reported for SUB panic disorder (Katerndahl & Realini, 1998), eating disorders (Lewinsohn *et al.* 2000*d*) and alcohol and drug use disorders (Martin *et al.* 1995; Rohde *et al.* 1996; Neumark *et al.* 2000).

The majority of the studies that have examined the validity of SUB conditions and their relationship with the full disorder have only looked at one disorder in isolation. Consequently, co-morbidity has been largely ignored in the SUB literature, with the possible exception of co-morbid SUB depression and anxiety (Roy-Byrne *et al.* 1994; Angst *et al.* 1997). When co-morbidity is addressed, it is typically treated as a nuisance variable that adds noise to a study (Judd *et al.* 1996). On the other hand, others contend that co-morbidity should be examined for its own sake in order to determine the proper etiological and nosological boundaries of psychiatric conditions (Lewinsohn *et al.* 1995*b*; Krueger *et al.* 1998; Krueger, 1999; see Maser & Cloninger, 1990, for the impact of co-morbidity on prognosis and treatment response).

In accordance with this latter view, we intend to investigate the role of co-morbidity in SUB disorders in a series of papers using data from the Oregon Adolescent Depression Project (OADP). The OADP is a large-scale study of the epidemiology of depression and other psychiatric conditions in a community sample of adolescents (Lewinsohn *et al.* 1993, 1994). The use of an adolescent age sample is particularly interesting because psychiatric conditions with an early-onset tend to be associated with greater impairment (Kovacs *et al.* 1994). In this paper, we focus on SUB forms of eight classes of non-psychotic disorders from DSM-IV: major depression, bipolar depression, eating disorders, alcohol disorders, substance disorders, anxiety disorders, conduct disorder, and attention-deficit hyperactivity disorder (ADHD).

<sup>†</sup> Subthreshold cases are often called 'subsyndromal' although subthreshold is the more precise term as these conditions can be defined as syndromes in their own right (Helmchen & Linden, 2000).

In the present paper, we will examine the rates of co-morbidity among SUB disorders and the relationships between SUB disorders and FS diagnoses. There is very little research on both of these issues. Few studies of SUB disorders have addressed the second point and those that have only reported the co-morbidity rates for a particular SUB disorder, e.g. for SUB eating disorders (Lewinsohn *et al.* 1993) and SUB alcohol use disorders (Rohde *et al.* 1996). To our knowledge, no study has reported the co-morbidity rates between SUB conditions. Besides shedding light on the boundaries of these conditions, it may also be a crucial first step in assessing the clinical and psychosocial characteristics of the various SUB disorders. It is possible that some of the aforementioned findings regarding impairment and course of SUB conditions may be quite different once co-morbidity is taken into account.

On the assumption that the presence of one condition albeit a SUB condition increases the probability for the presence of a second SUB condition we expected that there should be a significant degree of co-morbidity among SUB conditions and between SUB and FS disorders. We also expected that internalizing disorders such as major depression and anxiety disorders would be more likely to be associated with each other than with externalizing conditions such as alcohol or substance use disorders, and conversely, that externalizing conditions would be more likely to be associated with each other than with internalizing disorders. These two broad factors have previously been found in assessments of child psychopathology (Achenbach & Dumenci, 2001) and in adult psychopathology (Krueger, 1999; Vollebergh *et al.* 2001), and we expected that SUB disorders might show a similar pattern. Thus, while particular patterns were expected, there is little theoretical basis on which to make predictions about specific co-morbidities.

## METHOD

### Subjects and procedure

OADP participants were randomly selected in three cohorts from nine senior high schools representative of urban and rural districts in western Oregon (approximately 10 200 students). Sampling fractions of 10, 18.5, and 20% were

used for each cohort; sampling within each school was proportional to the size of the school, size of the grade within the school, and proportion of males and females within the grade (grades 9–12). A total of 1709 adolescents completed an initial ( $T_1$ ) assessment (interview and questionnaire) between 1987 and 1989 with an overall participation rate of 61% among those who were originally contacted. Several checks for representativeness of the sample were made (greater sampling details are provided by Lewinsohn *et al.* (1997a)). An *a priori* decision was made to exclude participants with a history of non-affective psychosis leaving 1704 participants available for analysis.

### Demographic characteristics

Slightly more than half of the 1704 adolescents in the sample were female (52.1%), with an average age of 16.6 years (s.d. = 1.2 years). A total of 8.9% were non-white; 53.2% were living with two biological parents; and 12.1% had repeated a grade in school. Parental education level (maximum value for mother or father) was as follows: 2.3% had not completed high school, 14.8% had completed high school, 32.2% had a partial college education, and 41.1% had an academic or professional degree.

### Diagnostic interview

Adolescents were interviewed with a version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) that combined features of the Epidemiological version (K-SADS-E; Orvaschel *et al.* 1982) and the Present Episode version (K-SADS-P), which included additional items to derive diagnoses of most disorders as per DSM-II-R criteria (APA, 1987).

All but one of the 27 diagnostic interviewers had advanced degrees in clinical or counseling psychology or social work and all had completed a 70-hour didactic and experiential course in diagnostic interviewing. Before conducting interviews, all interviewers were required to demonstrate a minimum  $\kappa$  of 0.80 across all symptoms for at least two consecutive training interviews and on one videotaped interview of an adolescent with evidence of psychopathology.

Based on a randomly selected sample ( $n = 233$ ), inter-rater reliability for lifetime diagnoses was moderate-to-excellent: MDD ( $\kappa = 0.86$ ),

bipolar ( $\kappa=0.49$ ), eating disorders ( $\kappa=0.66$ ), alcohol abuse/dependence ( $\kappa=0.84$ ), drug abuse/dependence ( $\kappa=0.84$ ), anxiety disorders ( $\kappa=0.76$ ), conduct disorder ( $\kappa=0.93$ ), and ADHD ( $\kappa=0.89$ ). Inter-rater reliability for lifetime diagnoses of SUB disorders (definitions of SUB disorders are given below) was also moderate-to-excellent with the exception of SUB bipolar disorder: MDD ( $\kappa=0.79$ ), bipolar ( $\kappa=0.29$ ), eating disorders ( $\kappa=0.66$ ), alcohol use disorder ( $\kappa=1.00$ ), substance use disorder ( $\kappa=0.73$ ), anxiety disorder ( $\kappa=0.63$ ), conduct disorder ( $\kappa=0.68$ ), and ADHD ( $\kappa=0.82$ ).

### SUB groups

Eight SUB groups were formed for the purpose of this study: MDD ( $n=441$ ), bipolar disorder ( $n=75$ ), eating disorder ( $n=23$ ), anxiety disorders ( $n=282$ ), alcohol use disorder ( $n=241$ ), substance use disorder ( $n=104$ ), conduct disorder ( $n=111$ ), and ADHD ( $n=102$ ). A stipulation for all SUB categories is that FS for that particular disorder (or class of disorders, as measured per DSM-III-R) was never diagnosed. All other symptom data refers to symptoms as defined per DSM-III-R. While the definitions of SUB conditions are somewhat arbitrary, most of them are based on definitions used in previous studies. Only one SUB category, conduct disorder, was defined by the authors as part of the current study. SUB conduct disorder is defined as exhibiting at least two symptoms of the disorder and was chosen to ensure that, within this community sample, only the top 10% of participants with the presence of conduct disorder symptoms, but without a FS diagnosis, would be included. In addition to never having met criteria for FS conduct disorder a lifetime history of oppositional defiant disorder could not be present. The remaining seven SUB categories used definitions from previous studies. SUB MDD is defined as an episode of depressed mood or loss of interest or pleasure lasting at least 1 week, plus at least two of the seven associated symptoms (Lewinsohn *et al.* in press). These criteria are similar to the criteria for minor depressive disorder set forth by the Research Diagnostic Criteria (Spitzer *et al.* 1978) and DSM-IV (APA, 1994), differing in that our definition required more symptoms (three instead of two) but a shorter minimum duration (1 week instead of 2). An adolescent could not

have SUB MDD if they had a diagnosis of dysthymic disorder. SUB bipolar is defined as having experienced a distinct period of abnormally and persistently elevated, expansive, or irritable mood, in addition to having one or more manic or hypomanic symptoms (Lewinsohn *et al.* 2000a). SUB eating is defined as having either SUB anorexia or SUB bulimia (Lewinsohn *et al.* 2000b). SUB anorexia is defined as refusal to maintain body weight at or above minimally normal weight for age and height plus at least one additional diagnostic symptom. SUB bulimia is defined as having recurrent episodes of binge eating plus one additional symptom. SUB anxiety is defined as the presence of at least three anxiety symptoms across the following DSM-III-R anxiety disorders – panic disorder, agoraphobia without a history of panic, social phobia, simple phobia, OCD, separation anxiety, and overanxious disorder. The rank-order prevalence of SUB anxiety disorders in this study mirrors the rank-order prevalence of FS anxiety disorders reported in a previous adolescent co-morbidity study with the same population (Lewinsohn *et al.* 1997b). SUB alcohol use disorder is defined as those who met criteria for one or more diagnostic symptoms of alcohol abuse or dependence (Rohde *et al.* 1996), but having never met criteria for a FS diagnosis. This definition differs from other subthreshold definitions such as hazardous alcohol use (Saunders & Lee, 2000) in that it is not directly tied to adverse health effects. Our one or more symptoms cut-off definition was chosen because it defines an alcohol use group that lies on a continuum between abstainers and those with FS alcohol use or dependence (Rohde *et al.* 1996). SUB substance use disorder is defined as never having met criteria for any substance (excluding alcohol and cigarettes) abuse or dependence, but having one or two symptoms (Pollock & Martin, 1999). SUB ADHD is defined as having five or more symptoms which ensures that all SUB cases have one more than half the symptoms required for the FS diagnosis (Biederman *et al.* 1996).

### Statistical analysis

The dichotomous measures were analyzed using contingency-table analysis and the reporting of odds ratios (ORs) to contrast different SUB and FS comparisons.

Table 1. Prevalence rates of subthreshold (SUB) conditions and demographic information (full sample = 1704 adolescents)

	MDD	Bipolar	Eating	Anxiety	Alcohol	Substance	Conduct	ADHD
<b>Subthreshold</b>								
Prevalence – % ( <i>n</i> )	25.9 (441)	4.4 (75)	1.3 (23)	16.5 (282)	14.1 (241)	6.1 (104)	6.5 (111)	6.4 (102)
% of those with SUB condition with 2 SUBs	33.6	26.7	39.1	38.3	39.0	34.6	40.5	34.3
% of those with SUB condition with > 2 SUBs	14.3	41.3	21.7	25.2	25.7	40.4	31.5	38.2
% Female	57.8 <sup>a,b</sup>	54.7	91.3 <sup>a</sup>	60.3 <sup>a</sup>	50.2	49.0	41.4 <sup>a</sup>	41.2 <sup>a</sup>
Age (years), Mean (s.d.)	16.1 (1.2)	16.3 (1.2)	16.2 (1.3)	16.1 (1.2)	16.5 (1.2) <sup>a</sup>	16.4 (1.1) <sup>a</sup>	16.4 (1.3) <sup>a</sup>	16.1 (1.3)
Parent with a bachelor's degree	42.6	40.0	30.4	41.1	34.9	42.3	30.6 <sup>a</sup>	38.2
Living with <2 biological parents	46.7	50.7	43.5	50.4	53.1 <sup>a</sup>	57.7 <sup>a</sup>	64.9 <sup>a</sup>	52.0
<b>Threshold</b>								
Prevalence – % ( <i>n</i> )	18.4 (313)	0.9 (15)	0.8 (13)	8.3 (142)	4.9 (84)	6.3 (107)	3.3 (56)	3.4 (51)
% of those with FS disorder with 2 FS disorders	24.4	46.7	30.8	38.5	25.0	29.9	30.4	25.5
% of those with FS disorder with > 2 FS disorders	17.1	20.0	46.2	17.5	51.2	45.8	46.4	27.5
% Female	70.2 <sup>a,b</sup>	60.0	92.3 <sup>a</sup>	68.5 <sup>a</sup>	53.6	48.6	26.8 <sup>a</sup>	27.5 <sup>a</sup>
Age (years), Mean (s.d.)	16.3 (1.2) <sup>a</sup>	15.7 (1.1)	16.5 (0.9)	16.2 (1.2)	16.6 (1.2) <sup>a</sup>	16.3 (1.3) <sup>a</sup>	16.1 (1.2)	16.2 (1.3)
Parent with a bachelor's degree	33.3 <sup>a,b</sup>	46.7	30.8	36.4	36.9	29.9	16.1 <sup>a</sup>	33.3
Living with 2 biological parents	58.1 <sup>a,b</sup>	53.3	38.5	53.8	67.9 <sup>a</sup>	70.1 <sup>a</sup>	60.7	51.0

<sup>a</sup> Differed from those without SUB or FS disorder (i.e. controls) at  $p \leq 0.01$ .

<sup>b</sup> FS disorder differs from SUB condition at  $p \leq 0.01$ .

## RESULTS

Table 1 represents the prevalences and demographic information for subjects with SUB and FS disorders. Of the 1704 adolescents in the analyses, 52.5% ( $n = 895$ ) had at least one SUB disorder. As with FS disorders, co-morbidity of SUB conditions was the rule rather than the exception. Of the 895 adolescents with a SUB disorder, 40.0% ( $n = 358$ ) had a co-morbid SUB condition. In addition, 36.4% ( $n = 326$ ) of those with a SUB condition had a lifetime diagnosis of a co-morbid FS disorder.

The pattern of prevalence rates between the SUB and FS disorders were quite similar. A rank-order correlation between the prevalences of the eight different SUB conditions with those of the eight FS conditions was significant (Spearman's  $\rho = 0.833$ ,  $p < 0.01$ ). MDD and anxiety were the two most prevalent conditions while bipolar and eating conditions were the least prevalent. There were also differences on a few demographic variables. In Table 1, we compared those with a SUB condition, a FS disorder, and neither SUB or FS on several key demographic variables (age, gender ratio, parental education and per cent living with fewer than two biological parents). Because

of the exploratory nature and large number of comparisons, we used a significance level of  $\leq 0.01$  instead of the traditional 0.05 in order to protect against making a Type I error. Gender distributions for SUB disorders were consistent with those of FS disorders. Those with SUB eating disorders were overwhelmingly more likely to be female than male (91.3% of those with SUB; and 92.3% of those with FS). A similar gender difference was also found for participants with anxiety and MDD conditions. An analogous male preponderance was found for those with conduct disorder and ADHD.

We next explored whether having a SUB condition of one disorder increased the risk for another SUB condition. As above, we used a significance level of  $\leq 0.01$  instead of the traditional 0.05. The results of these analyses are displayed in Table 2. In the upper triangle, the number of co-morbid cases is followed by the percentage of those with the disorder listed in the column within parentheses. The OR followed by the 99% confidence interval (CI) within parentheses are reported in lower triangle. For example, 37 of the 111 adolescents with SUB conduct disorder (33.3%) also had a co-morbid SUB alcohol use disorder (OR 3.4, 99% CI 2.0–5.9). In general, there was a

Table 2. *Co-morbidity of subthreshold (SUB) disorders with other subthreshold disorders at T<sub>1</sub><sup>a</sup>*

	SUB MDD (n=441)	SUB bipolar (n=75)	SUB eating (n=23)	SUB anxiety (n=282)	SUB alcohol (n=241)	SUB substance (n=104)	SUB conduct (n=111)	SUB ADHD (n=102)
SUB MDD	—	23 (30.7%)	5 (21.7%)	108 (38.3%)	97 (27.8%)	28 (26.9%)	24 (21.6%)	29 (28.4%)
SUB bipolar	n.s.	—	4 (17.4%)	25 (8.9%)	14 (5.8%)	9 (8.7%)	10 (9.0%)	11 (10.8%)
SUB eating	n.s.	4.8 (1.1–20.4)	—	4 (1.4%)	4 (1.7%)	1 (1.0%)	1 (0.9%)	3 (2.9%)
SUB anxiety	2.0 (1.4–2.9)	2.7 (1.4–5.1)	n.s.	—	53 (22.0%)	21 (20.2%)	29 (26.1%)	33 (32.4%)
SUB alcohol	n.s.	n.s.	n.s.	1.5 (1.0–2.4)	—	40 (38.5%)	37 (33.3%)	27 (26.5%)
SUB substance	n.s.	n.s.	n.s.	n.s.	4.4 (2.5–7.6)	—	17 (15.3%)	18 (17.6%)
SUB conduct	n.s.	n.s.	n.s.	1.9 (1.0–3.4)	3.4 (2.0–5.9)	3.1 (1.5–6.5)	—	10 (9.8%)
SUB ADHD	n.s.	2.9 (1.2–7.0)	n.s.	2.6 (1.5–4.6)	2.3 (1.3–4.3)	3.8 (1.8–7.8)	n.s.	—

<sup>a</sup> Co-morbidity rates are reported in the upper triangle with number of cases followed by percentage of disorder in column within parentheses. Odds ratio followed by the 99% confidence interval within parentheses are reported in the lower triangle.

MDD, major depressive disorder; ADHD, attention-deficit hyperactivity disorder. n.s., Not significant at  $p \leq 0.01$ .

Of the 895 adolescents with a SUB disorder, 40.0% ( $n=358$ ) had a co-morbid SUB condition.

Table 3. *Co-morbidity of subthreshold (SUB) disorders with full syndrome (FS) disorders*

	SUB MDD (n=441)	SUB bipolar (n=75)	SUB eating (n=23)	SUB anxiety (n=282)	SUB alcohol (n=241)	SUB substance (n=104)	SUB conduct (n=111)	SUB ADHD (n=102)
FS MDD (n=313)	—	<b>27 (36.0%)</b> <b>2.6 (1.4–5.0)</b>	<b>10 (43.5%)</b> <b>3.5 (1.2–10.5)</b>	<b>73 (25.9%)</b> <b>1.7 (1.2–2.6)</b>	<b>82 (34.0%)</b> <b>2.8 (1.9–4.1)</b>	<b>33 (31.7%)</b> <b>2.2 (1.2–3.9)</b>	<b>47 (42.3%)</b> <b>3.7 (2.2–6.2)</b>	<b>38 (37.3%)</b> <b>2.9 (1.6–5.0)</b>
FS bipolar (n=15)	n.a.	—	0 (0%) n.s.	5 (1.8%) n.s.	2 (0.8%) n.s.	1 (1.0%) n.s.	1 (0.9%) n.s.	2 (2.0%) n.s.
FS eating (n=13)	1 (0.2%) n.s.	<b>3 (4.0%)</b> <b>6.7 (1.2–37.8)</b>	—	4 (1.4%) n.s.	2 (0.8%) n.s.	4 (3.8%) <b>7.1 (1.5–34.0)</b>	0 (0%) n.s.	1 (1.0%) n.s.
FS anxiety (n=142)	38 (8.6%) n.s.	<b>22 (29.3%)</b> <b>5.2 (2.6–10.5)</b>	4 (17.4%) n.s.	—	29 (12.0%) n.s.	13 (12.5%) n.s.	14 (12.6%) n.s.	14 (13.7%) n.s.
FS alcohol (n=84)	28 (6.3%) n.s.	5 (6.7%) n.s.	<b>4 (17.4%)</b> <b>4.2 (1.0–17.9)</b>	<b>22 (7.8%)</b> <b>1.9 (1.0–3.6)</b>	—	9 (8.7%) n.s.	<b>12 (10.8%)</b> <b>2.6 (1.1–6.0)</b>	<b>11 (10.8%)</b> <b>2.5 (1.1–6.1)</b>
FS substance (n=107)	23 (5.2%) n.s.	7 (9.3%) n.s.	3 (13.0%) n.s.	25 (8.9%) n.s.	<b>32 (13.3%)</b> <b>2.8 (1.6–5.0)</b>	—	<b>25 (22.5%)</b> <b>5.4 (2.8–10.3)</b>	8 (7.8%) n.s.
FS conduct (n=56)	15 (3.4%) n.s.	5 (6.7%) n.s.	2 (8.7%) n.s.	14 (5.0%) n.s.	<b>17 (7.1%)</b> <b>2.8 (1.3–6.0)</b>	<b>8 (7.7%)</b> <b>2.7 (1.0–7.5)</b>	—	<b>12 (11.8%)</b> <b>4.7 (2.0–11.4)</b>
FS ADHD (n=51)	15 (3.4%) n.s.	<b>10 (13.3%)</b> <b>6.0 (2.3–15.6)</b>	1 (4.3%) n.s.	9 (3.2%) n.s.	10 (4.1%) n.s.	2 (1.9%) n.s.	<b>9 (8.1%)</b> <b>3.3 (1.2–8.7)</b>	—

The SUB conditions are listed by columns. The FS disorders are listed by rows. Number of cases and % of SUB condition cases are given in the top of each cell. For example, of the 282 cases with subthreshold anxiety disorder, 73 (25.9%) also had a FS diagnosis of MDD. Odds ratios and 99% confidence intervals are reported in the lower half. Bold comparisons are significant at  $p \leq 0.01$ . n.a., Not applicable.

MDD, major depressive disorder; ADHD, attention-deficit hyperactivity disorder. n.s., Not significant at  $p \leq 0.01$ .

A total of 36.4% ( $n=326$ ) of the 895 adolescents who had a SUB disorder had a co-morbid FS disorder; 63.4% ( $n=326$ ) of the 514 adolescents who had a FS disorder had a co-morbid SUB disorder.

great deal of co-morbidity among the SUB conditions. Interestingly, SUB major depression was only significantly co-morbid with SUB anxiety and marginally associated with SUB bipolar disorder.

In general, the SUB forms of the externalizing disorders appeared to be co-morbid with each other. SUB substance use, alcohol use, and conduct disorder were all co-morbid with each other. ADHD (which is often considered an externalizing disorder) was also co-morbid with substance and alcohol use although not with SUB conduct disorder. Interestingly, SUB anxiety, which is often considered an

internalizing disorder, co-occurred with SUB alcohol, conduct, and ADHD as well.

Table 3 examines whether SUB conditions were associated with FS of other disorders. As with Table 2, there was a great deal of co-morbidity between SUB conditions and other FS disorders. Several patterns emerge from Table 3. For one, none of the six possible FS disorders were co-morbid with SUB major depression but all of the seven SUB disorders were associated a FS diagnosis of major depression. (Because of the DSM hierarchy, it is not possible for an individual to have SUB MDD and a FS bipolar disorder.) This

asymmetry of association was not found for any other condition.

It is also interesting to examine whether the SUB and FS form of two disorders were significantly co-morbid with each other (i.e. SUB A significantly associated with FS B and SUB B significantly associated with FS A). This was only true for three of the 28 possible combinations (conduct–alcohol, conduct–substance, and conduct–ADHD). As mentioned above, with the exception of conduct–ADHD, all of the SUB forms of these disorders significantly co-occurred as well and are considered externalizing disorders.

Given the high rate of co-morbidity between SUB conditions and between SUB and FS disorders, we wanted to examine the extent to which individuals with co-morbid SUB conditions were the same as those with co-morbid FS conditions. Fig. 1 addresses this by dividing the sample into those with only one condition (i.e. either one FS, 8.3%; or one SUB, 19.0%) or two or more conditions (i.e. two or more SUBs with no FS, 11.2%; at least one SUB and at least one FS, 18.6%; or two or more FS with no SUB, 3.3%). As can be seen, if individuals had a SUB condition, they were more likely to have a co-morbid condition than they were to only have one SUB condition (29.8% *v.* 19.0% respectively). Moreover, if an individual had a FS condition, they were also more likely to have a co-morbid condition than to only have one FS disorder (21.9% *v.* 8.3% respectively).

Finally, because of the gender differences found for SUB and FS disorders, we re-ran all of the analyses for Tables 2 and 3 controlling for gender. The pattern of results was nearly identical.

## DISCUSSION

This paper provides the first analysis of the co-morbidity of SUB conditions in a large epidemiological sample of adolescents. Previous research on SUB conditions have focused on one SUB condition at a time and therefore could not take into account co-morbidity among SUB conditions and between SUB and FS conditions. Our goal was therefore to describe the relations between eight classes of SUB and FS psychiatric conditions.

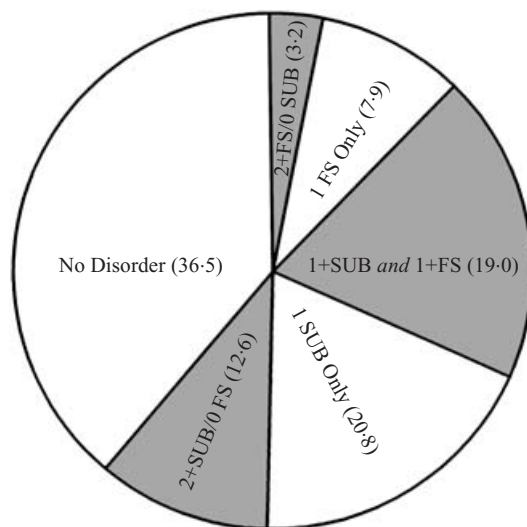


FIG. 1. Full Syndrome (FS) and subthreshold (SUB) co-morbidity rates in an adolescent community sample.

We found that over half (52.5%) of the adolescents and young adults in this sample had experienced a SUB condition at some point in their lifetime and 40% of those with at least one SUB condition had at least a second SUB condition. Moreover, 36.4% of the participants with a SUB condition had a co-morbid FS diagnosis as well. Though these rates may seem high, it is important to note that studies have found co-morbidity rates as high as 48% for lifetime diagnoses of FS disorders (Kessler *et al.* 1994). The actual prevalence rates of SUB disorders of course differed from epidemiological studies of FS disorders (Lewinsohn *et al.* 1993; Kessler *et al.* 1994) but the rank distribution was very similar (e.g. MDD and anxiety disorders most prevalent, eating and bipolar disorders least prevalent).

This study also reported the extent to which SUB and FS disorders were co-morbid. As expected, many of the conditions that are often considered externalizing disorders (substance use, alcohol use, conduct disorder, and ADHD) were co-morbid with each other and with their respective FS conditions. The major internalizing disorders (MDD and anxiety disorders) demonstrated a similar pattern though not as strongly. SUB anxiety disorders were co-morbid with both SUB MDD and FS MDD, although SUB MDD was not significantly co-morbid

with FS anxiety disorders. Clark & Watson (1991) have proposed that MDD and anxiety co-occur frequently because they are both characterized by negative affectivity.

The present study found that SUB depression was not associated with any FS diagnosis and only significantly associated with one SUB condition (anxiety). As discussed earlier, SUB depression has been found to be associated with significant impairment (Gotlib *et al.* 1995; Kessler *et al.* 1997; Judd *et al.* 2000; Rappaport *et al.* 2002). It appears likely that the impairment is not attributable to co-morbid conditions (either SUB or FS) but rather to the SUB depression itself. A related and unexpected finding was that FS depression was associated with all of the other SUB conditions. It will be interesting to examine the clinical correlates of FS MDD when these co-morbid SUB conditions are taken into account. We are currently examining these hypotheses within this sample.

Despite the small number for bipolar conditions (FS, 15; SUB, 75), several interesting patterns of co-morbidity emerged. SUB bipolar conditions were co-morbid with SUB eating, anxiety, and ADHD as well as FS MDD, eating, anxiety, and ADHD. This is consistent with the important differential diagnoses proposed by Geller and Biederman for childhood and adolescent bipolar conditions (Biederman *et al.* 1996; Geller & Luby, 1997).

This is the first in a series of papers where we hope to address the clinical significance (validity) of the specific SUB conditions in this paper. Specifically, we will examine (a) whether SUB conditions are associated with impairment, (b) whether there is specific familial transmission of SUB conditions (i.e. are SUB conditions associated with elevated familial rates of SUB and FS conditions), and (c) whether individuals with SUB conditions are at risk for future FS forms of that disorder (specific escalation) and/or other disorders (general escalation).

There are several limitations to the present study. Firstly, because this is the first attempt to examine the co-morbidity of SUB conditions and because of the large number of comparisons, cross-validation of the findings is necessary. Secondly, given the small numbers for eating disorders (both SUB and FS), any negative results for this condition may have been due to a lack of power. Thirdly, our findings

are based on an adolescent community sample and the results may differ in an adult sample or a clinical sample as individuals seeking treatment may be more likely to exhibit multiple psychiatric conditions (i.e. Berkson's Bias; Berkson, 1946). Fourthly, while we examined co-morbidity among eight of the major classes of non-psychotic psychiatric disorders, there are several disorders that were not included in this analysis (e.g. somatoform disorders, oppositional defiant disorder, PTSD, dissociative disorders, adjustment disorders, psychiatric disorders due to general medical conditions).

Our results have two important implications for future research and clinical practice. Firstly, for research, given that there is such a high rate of co-morbidity among SUB conditions and between SUB and FS conditions, it is clear that findings about prognosis, including escalation, psychosocial impairment, and familial transmission need to control for co-morbidity. Secondly, clinical assessment needs to involve assessment of other FS conditions as well as SUB disorders. This places quite a burden on researchers and clinicians, but it may be necessary to determine the extent to which associated characteristics are uniquely associated with SUB and to anticipate course and plan treatment.

## REFERENCES

- Achenbach, T. M. & Dumenci, L. (2001). Advances in empirically based assessment: revised cross-informant syndromes and new DSM-oriented scales for the CBCL, YSR, and TRF: comment on Lengua, Sadowski, Friedrich, and Fisher (2001). *Journal of Consulting and Clinical Psychology* **69**, 699–702.
- Angst, J., Gamma, A. & Lewinsohn, P. M. (2002). The evolving epidemiology of bipolar disorder. *World Psychiatry* **1**, 146–148.
- Angst, J. & Hochstrasser, B. (1994). Recurrent brief depression: the Zurich study. *Journal of Clinical Psychiatry* **55** (Suppl.), 3–9.
- Angst, J., Merikangas, K. R. & Preisig, M. (1997). Subthreshold syndromes of depression and anxiety in the community. *Journal of Clinical Psychiatry* **58**, 6–10.
- APA (1987). *Diagnostic and Statistical Manual of Mental Disorders, III-R*. American Psychiatric Association: Washington, DC.
- APA (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th edn). American Psychiatric Association: Washington, DC.
- Berkson, J. (1946). Limitations of the application of four-fold table analysis to hospital data. *Biometrics* **2**, 47–53.
- Biederman, J., Faraone, S., Mick, E., Wozniak, J., Chen, L., Ouellette, C., Marris, A., Moore, P., Garcia, J., Mennin, D. & LeRon, E. (1996). Predictors of persistence and remission of ADHD into adolescence: results from a four-year prospective follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry* **35**, 343–351.
- Broadhead, W. E., Blazer, D. G., George, L. K. & Tse, C. K. (1990). Depression, disability days, and days lost from work in a prospective epidemiologic survey. *Journal of the American Medical Association* **264**, 2524–2528.



- Clark, L. A. & Watson, D. (1991). Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology* **100**, 316–336.
- Fechner-Bates, S., Coyne, J. C. & Schwenk, T. L. (1994). The relationship of self-reported distress to depressive disorders and other psychopathology. *Journal of Consulting and Clinical Psychology* **62**, 550–559.
- Feighner, J. P., Robins, E., Guze, S. B., Woodruff, R. A., Winokur, G. & Muñoz, R. F. (1972). Diagnostic criteria for use in psychiatric research. *Archives of General Psychiatry* **26**, 57–63.
- Flett, G. L., Vredenburg, K. & Krames, L. (1997). The continuity of depression in clinical and nonclinical samples. *Psychological Bulletin* **121**, 395–416.
- Geller, B. & Luby, J. (1997). Child and adolescent bipolar disorder: a review of the past 10 years. *Journal of the American Academy of Child and Adolescent Psychiatry* **36**, 1168–1176.
- Gotlib, I. H., Lewinsohn, P. M. & Seeley, J. R. (1995). Symptoms versus a diagnosis of depression: differences in psychosocial functioning. *Journal of Consulting and Clinical Psychology* **63**, 90–100.
- Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology and Neurosurgery* **23**, 56–61.
- Helmchen, H. & Linden, M. (2000). Subthreshold disorders in psychiatry: clinical reality, methodological artifact, and the double-threshold problem. *Comprehensive Psychiatry* **41**, 1–7.
- Helzer, J. E. & Hudziak, J. J. (eds.) (2002). *Defining Psychopathology in the 21st Century: DSM-V and Beyond*. American Psychiatric Publishing, Inc., Washington, DC.
- Judd, L. L., Paulus, M. J., Schettler, P. J., Akiskal, H. S., Endicott, J., Leon, A. C., Maser, J. D., Mueller, T., Solomon, D. A. & Keller, M. B. (2000). Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? *American Journal of Psychiatry* **157**, 1501–1504.
- Judd, L. L., Paulus, M. P., Wells, K. B. & Rapaport, M. H. (1996). Socioeconomic burden of subsyndromal depressive symptoms and major depression in a sample of the general population. *American Journal of Psychiatry* **153**, 1411–1417.
- Katerndahl, D. A. & Realini, J. P. (1998). Associations with subsyndromal panic and the validity of DSM-IV criteria. *Depression and Anxiety* **8**, 33–38.
- Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., Wittchen, H. U. & Kendler, K. S. (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, R. C., Zhao, S., Blazer, D. G. & Swartz, M. (1997). Prevalence, correlates, and course of minor depression and major depression in the National Comorbidity Survey. *Journal of Affective Disorders* **45**, 19–30.
- Kovacs, M., Krol, R. S. M. & Voti, L. (1994). Early onset psychopathology and the risk for teenage pregnancy among clinically referred girls. *Journal of the American Academy of Child and Adolescent Psychiatry* **33**, 106–113.
- Krueger, R. F. (1999). The structure of common mental disorders. *Archives of General Psychiatry* **56**, 921–926.
- Krueger, R. F., Caspi, A., Moffitt, T. E. & Silva, P. A. (1998). The structure and stability of common mental disorders (DSM-III-R): a longitudinal-epidemiological study. *Journal of Abnormal Psychology* **107**, 216–227.
- Lewinsohn, P. M., Gotlib, I. H. & Seeley, J. R. (1997a). Depression-related psychosocial variables in adolescence: are they specific to depression? *Journal of Abnormal Psychology* **106**, 365–375.
- Lewinsohn, P. M., Hops, H., Roberts, R. E., Seeley, J. R. & Andrews, J. A. (1993). Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III-R disorders in high school students. *Journal of Abnormal Psychology* **102**, 133–144.
- Lewinsohn, P. M., Klein, D. N., Durbin, C. E., Seeley, J. R. & Rohde, P. (in press). Family study of subthreshold depressive symptoms: risk factor for MDD? *Journal of Affective Disorders*.
- Lewinsohn, P. M., Klein, D. N. & Seeley, J. R. (1995a). Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *Journal of the American Academy of Child and Adolescent Psychiatry* **34**, 454–463.
- Lewinsohn, P. M., Klein, D. N. & Seeley, J. R. (2000c). Bipolar disorder during adolescence and young adulthood in a community sample. *Bipolar Disorders* **2**, 281–293.
- Lewinsohn, P. M., Roberts, R. E., Seeley, J. R., Rohde, P., Gotlib, I. H. & Hops, H. (1994). Adolescent psychopathology: II. Psychosocial risk factors for depression. *Journal of Abnormal Psychology* **103**, 302–315.
- Lewinsohn, P. M., Rohde, P. & Seeley, J. R. (1995b). Adolescent psychopathology: III. The clinical consequences of comorbidity. *Journal of the American Academy of Child and Adolescent Psychiatry* **34**, 510–519.
- Lewinsohn, P. M., Rohde, P., Seeley, J. R., Klein, D. N. & Gotlib, I. H. (2000a). Natural course of adolescent major depressive disorder in a community sample: predictors of recurrence in young adults. *American Journal of Psychiatry* **157**, 1584–1591.
- Lewinsohn, P. M., Solomon, A., Seeley, J. R. & Zeiss, A. (2000b). Clinical implications of subthreshold depressive symptoms. *Journal of Abnormal Psychology* **109**, 345–351.
- Lewinsohn, P. M., Striegel-Moore, R. & Seeley, J. R. (2000d). The epidemiology and natural course of eating disorders in young women from adolescence to young adulthood. *Journal of the American Academy of Child and Adolescent Psychiatry* **39**, 1284–1292.
- Lewinsohn, P. M., Zinbarg, R., Seeley, J. R., Lewinsohn, M. A. & Sack, W. H. (1997b). Lifetime comorbidity among anxiety disorders and between anxiety disorders and other mental disorders in adolescents. *Journal of Anxiety Disorders* **11**, 377–394.
- Maier, W., Gansicke, M. & Weiffenbach, O. (1997). The relationship between major and subthreshold variants of unipolar depression. *Journal of Affective Disorders* **45**, 41–51.
- Martin, C. S., Kaczynski, N. A., Maisto, S. A., Bukstein, O. M. & Moss, H. B. (1995). Patterns of DSM-IV alcohol abuse and dependence symptoms in adolescent drinkers. *Journal of Studies on Alcohol* **56**, 672–680.
- Maser, J. D. & Cloninger, C. R. (1990). *Comorbidity of Mood and Anxiety Disorders*. American Psychiatric Press, Washington, DC.
- Neumark, Y. D., Van Etten, M. L. & Anthony, J. C. (2000). Alcohol dependence and death: survival analysis of the Baltimore ECA sample from 1981 to 1995. *Substance Use and Misuse* **35**, 533–549.
- Orvaschel, H., Puig-Antich, J., Chambers, W. J., Tabrizi, M. A. & Johnson, R. (1982). Retrospective assessment of prepubertal major depression with the Kiddie-SADS-E. *Journal of the American Academy of Child Psychiatry* **21**, 392–397.
- Paykel, E. S., Hollyman, J. A., Freeling, P. & Sedgwick, P. (1988). Predictors of therapeutic benefit from amitriptyline in mild depression: a general practice placebo-controlled trial. *Journal of Affective Disorders* **14**, 83–95.
- Pincus, H. A., Davis, W. W. & McQueen, L. E. (1999). 'Subthreshold' mental disorders: a review and synthesis of studies on minor depression and other 'brand names'. *British Journal of Psychiatry* **174**, 288–298.
- Plato (1998). *Phaedrus*. Cornell University Press: Ithaca.
- Pollock, N. K. & Martin, C. S. (1999). Diagnostic orphans: adolescents with alcohol symptomatology who do not qualify for DSM-IV abuse or dependence diagnoses. *American Journal of Psychiatry* **156**, 897–901.
- Radloff, L. S. (1977). The CES-D Scale: a self-report depression scale for research in the general population. *Applied Psychological Measurement* **1**, 385–401.
- Rappaport, M. H., Judd, L. L., Schettler, P. J., Yonkers, K. A., Thase, M. E., Kupfer, D. J., Frank, E., Plewes, J. M., Tollefson, G. D. & Rush, A. J. (2002). A descriptive analysis of minor depression. *American Journal of Psychiatry* **159**, 637–643.

- Rohde, P., Lewinsohn, P. M. & Seeley, J. R. (1996). Psychiatric comorbidity with problematic alcohol use in high school adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry* **35**, 101–109.
- Roy-Byrne, P., Katon, W., Broadhead, W. E., Lepine, J. P., Richards, J., Brantley, P. J., Russo, J., Zinbarg, R., Barlow, D. & Liebowitz, M. (1994). Subsyndromal (mixed) anxiety and depression in primary care. *Journal of General Internal Medicine* **9**, 507–512.
- Sadek, N. & Bona, J. (2000). Subsyndromal symptomatic depression: a new concept. *Depression and Anxiety* **12**, 30–39.
- Saunders, J. B. & Lee, N. K. (2000). Hazardous alcohol use: its delineation as a subthreshold disorder, and approaches to its diagnosis and management. *Comprehensive Psychiatry* **41** (2 Suppl. 1), 95–103.
- Spitzer, R. L., Endicott, J. & Robins, E. (1978). Research diagnostic criteria: rationale and reliability. *Archives of General Psychiatry* **35**, 773–782.
- Spitzer, R. L. & Wakefield, J. C. (1999). DSM-IV diagnostic criterion for clinical significance: does it help solve the false positives problem? *American Journal of Psychiatry* **156**, 1856–1864.
- Szegedi, A., Wetzel, H., Angersbach, D., Philipp, M. & Benkert, O. (1997). Response to treatment in minor and major depression: results of a double-blind comparative study with paroxetine and maprotiline. *Journal of Affective Disorders* **45**, 167–178.
- Vollebergh, W. A. M., Iedema, J., Bijl, R. V., de Graaf, R., Smit, F. & Ormel, J. (2001). The structure and stability of common mental disorders: the NEMESIS study. *Archives of General Psychiatry* **59**, 603.
- Wakefield, J. C. (1992). Disorder as harmful dysfunction: a conceptual critique of DSM-III-R's definition of mental disorder. *Psychological Review* **99**, 232–247.
- Widiger, T. A. (1993). The DSM-III-R categorical personality disorder diagnoses: a critique and an alternative. *Psychological Inquiry* **4**, 75–90.
- WHO (1994). *The International Statistical Classification of Diseases and Related Health Problems*, 10th edn. World Health Organisation: Geneva.