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Subthreshold conditions as precursors for full syndrome disorders: A 15-year longitudinal study of multiple diagnostic classes

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Abstract

Background—There has been increasing interest in the distinction between subthreshold and full syndrome disorders and specifically whether subthreshold conditions escalate or predict the onset of full syndrome disorders over time. Most of these studies, however, examined whether a single subthreshold condition escalates into the full syndrome form of that disorder. Equally important, though, is whether subthreshold conditions are likely to develop other full syndrome disorders and whether these associations are maintained after adjusting for comorbidity.

Methods—A 15-year longitudinal study of subthreshold psychiatric conditions was conducted with 1505 community drawn young adults. We examined whether 1) subthreshold major depression, bipolar, anxiety disorders, alcohol use, substance use, conduct disorder and/or ADHD were precursors for the corresponding (homotypic) full syndrome disorder; 2) subthreshold conditions were precursors for other (heterotypic) FS disorders; and 3) these homotypic and heterotypic precursors persisted after adjusting for comorbidity.

Results—Subthreshold major depression, anxiety, alcohol use, substance use, and conduct all escalated into their corresponding full syndrome and nearly all homotypic developments were maintained after adjusting for comorbid subthreshold and FS conditions. Many heterotypic associations were also observed and most remained after controlling for comorbidity, particularly among externalizing disorders (e.g., alcohol, substance, conduct/antisocial personality disorder).

Conclusions—Many subthreshold conditions have predictive validity as they may represent precursors for full syndrome disorders. Alternatively, dimensional conceptualizations of psychopathology which include these more minor conditions may yield greater validity. Subthreshold conditions may represent good targets for preventive interventions.

Keywords

subthreshold; escalation; precursors; internalizing; externalizing

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Since the advent of well-specified psychiatric diagnostic systems, such as the DSM's 1980 3rd revision, reliability of diagnoses has greatly improved as has the precision of prevalence rates. These systems employ specific thresholds for determining 'caseness' but, recently, interest in studying subthreshold conditions (i.e., slightly below the threshold) has increased (Pincus, McQueen, & Elinson, 2003). This work is especially important because subthreshold conditions are common (Lewinsohn, Shankman, Gau & Klein, 2004), and are associated with functional impairment (Kessler, Zhao, Blazer, & Swartz, 1997) Studying subthreshold conditions can help determine whether full syndromes (FS) are qualitatively different from conditions below diagnostic thresholds or whether they are merely more

severe forms on a continuum (Flett, Vredenburg, & Krames, 1997; Lewinsohn, Solomon, Steeley, & Zeiss, 2000a).

Among subthreshold conditions, subthreshold depression has been studied the most extensively. Subthreshold depressive conditions, such as minor depression or Brief Recurrent Depression, have been associated with significant impairment (Gotlib, Lewinsohn, & Seeley, 1995; Kessler et al., 1997), and increased treatment utilization (Judd, Paulus, Wells & Rapaport, 1996). Similar results have been found for subthreshold bipolar (Lewinsohn, Klein & Seeley, 2000b), anxiety (Batelaan, De Graaf, Van Balkom, Vollebergh, & Beekman, 2007), and alcohol and substance use disorders (Pollock & Martin, 1999).

The clinical significance and validity of subthreshold conditions can be addressed with several different methods (Robins & Guze, 1970). Cross-sectional studies can establish the prevalence of subthreshold conditions and whether they are associated with impairment. Family studies can elucidate whether FS and subthreshold conditions are associated with qualitatively distinct familial liabilities. Using data from the Oregon Adolescent Depression Project (OADP), we have begun to examine these questions (Lewinsohn et al., 2004; Shankman, Klein, Lewinsohn, Seeley & Small, 2008). In this paper, we will extend these studies by examining the prospective course of subthreshold conditions. Specifically, we will examine whether subthreshold conditions are likely to develop or escalate into FS disorders.

Subthreshold depression (Fergusson, Horwood, Ridder & Beautrais, 2005; Lewinsohn et al., 2000a) bipolar disorder (Lewinsohn et al, 2000b; Regeer et al., 2006) and anxiety disorder (Merikangas et al., 2003) have been shown to escalate into the FS condition over time. These and similar studies have led many to argue that subthreshold conditions may be precursors of the FS (Eaton, Badawi & Melton, 1995, Pincus et al., 2003).

Most subthreshold studies only examine whether a single subthreshold condition is likely to develop into the FS form of that disorder over time (i.e., homotypic development). Equally important, however, is whether subthreshold conditions predict the development of other FS disorders over time (i.e., heterotypic development), as heterotypic developments can elucidate whether subthreshold conditions are precursors to broad classes of psychopathologies. With the possible exception of MDD and bipolar disorder, heterotypic developments have been largely ignored in the subthreshold literature (Lewinsohn et al., 2000b; Regeer et al., 2006).

We predict that, in addition to homotypic escalation, several subthreshold conditions will develop into heterotypic FS disorders, as there is substantial comorbidity and familial co-aggregation among subthreshold and FS conditions (Angst, Merikangas & Preisig, 1997; Lewinsohn et al., 2004; Shankman et al., 2008). Given the phenotypic and genotypic clustering of psychopathologies into broad classes of internalizing and externalizing disorders (Kendler, Prescott, Myers, & Neale, 2003; Krueger & Markon, 2006), we expect that subthreshold internalizing disorders such as depression and anxiety will escalate into FS forms of each other (Fergusson et al., 2005), and subthreshold externalizing disorders such as alcohol, substance, and conduct /antisocial personality disorder (ASPD) will escalate into FS forms of one another (Hicks et al., 2007). It is also possible that externalizing subthreshold conditions may escalate into internalizing conditions given recent support (Kim-Cohen et al., 2003), though these findings are less likely than within class escalation.

Methods

Participants

The present study uses data from the OADP (Lewinsohn, Hops, Roberts, Seeley & Andrews, 1993; Lewinsohn et al., 2000b; Shankman et al., 2008), a longitudinal community study of young adults who were assessed four times: age (SD; range) 16.6 (1.2; 14–20), 17.7 (1.2; 15–21), 24.6 (0.6; 23–28), and 30.4 (0.7; 29–34). Participants were randomly selected for the initial assessment from nine high-schools representative of urban and rural districts in western Oregon. A total of 1,709 adolescents completed the initial (T_1) assessments between 1987 and 1989. The participation rate at T_1 was 61% (see Lewinsohn et al. (1993) for sampling details). Each participant (and guardian when under 18) gave written informed consent and received a description of the study.

One year later, 1,507 of the adolescents (88%) returned for a second evaluation (T_2). Differences between the sample and the larger population from which it was selected, and between participants and those who dropped out of the study before T_2, were small (Lewinsohn et al., 1993).

All participants with a history of psychopathology by T_2 (*N*=644) and a random sample of participants from OADP with no history of psychopathology (*N*=457) were invited to participate in a third (T_3) evaluation around age 24. All non-white T_2 participants were retained in the T_3 sample to maximize ethnic diversity. Of the 1,101 T_2 participants selected for T_3, 941 (85%) completed the T3 evaluation. At age 30, all T_3 participants were invited for the T_4 assessment. 816 (87%) of the T3 participants completed the T_4 assessment.

Diagnostic Measures

At T_1 and T_2, participants were interviewed with a version of the Kiddie Schedule for Affective Disorders-Schizophrenia (K-SADS-E) (Orvaschel, Puig-Antich, Chambers, Tabrizi, & Johnson, 1982) that included additional items to derive DSM-III-R diagnoses. Follow-up assessments at T_2 to T_3 were jointly administered with the Longitudinal Interval Follow-Up Evaluation (LIFE; Keller, Lavori, Friedman, & Nielsen, 1987). The K-SADS-E/LIFE procedure provided information regarding the onset and course of disorders since the previous interview. The T_4 interview consisted of a joint administration of the LIFE and the Structured Clinical Interview for DSM–IV (Spitzer, Williams, Gibbon, & First, 1990) to probe for new or continuing psychiatric episodes since T_3. Diagnoses were based on DSM-III-R criteria for T_1–T_2 and DSM-IV criteria for T_3–T_4. Even though the criteria for the disorders examined in this study changed (albeit slightly) between DSM-III-R and DSM-IV, Kappas between the two criteria sets were >.98 at T_3, suggesting near perfect concordance. Interviews at T_3 and T_4 were conducted by telephone, which generally yields comparable results to face-to-face interviews (Rohde, Lewinsohn, & Seeley, 1997).

Diagnostic interviewers had advanced degrees in a mental health field and had completed a 70-hour course in diagnostic interviewing. At each of the 4 assessments, a randomly selected sample of interviews indicated good to excellent interrater reliabilities for the FS diagnoses reported in this study (Rohde et al., 1997; Rohde et al., 2007). Data to compute interrater reliabilities for T1 subthreshold conditions were not available.

T1 Subthreshold Groups

Using the definitions from our previous reports (Lewinsohn et al., 2004; Shankman et al., 2008), seven subthreshold groups were formed. We did not examine eating disorders because of the few individuals with subthreshold (N=21) and FS (N=12) eating disorders. A participant was considered subthreshold if at or before T1, he/she met criteria for a particular

subthreshold condition, but had not by T1 had the FS form of that disorder (they were allowed to have other FS conditions). While the definitions of subthreshold conditions are somewhat arbitrary, they are all definitions used in previous family and follow-up studies (e.g., Lewinsohn et al., 2004). Subthreshold MDD was 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 (yielding at least three total symptoms) (Lewinsohn, Klein, Durbin, Seeley, & Rohde, 2003). These criteria are similar to the criteria for RDC (Spitzer, Endicott, & Robins,1978) and DSM-IV minor depression, but with 1 more symptom and a shorter minimum duration (1 week vs. 2). A participant could not have subthreshold MDD if they had dysthymia or bipolar depression. Subthreshold bipolar was defined as having experienced an episode of abnormally and persistently elevated, expansive, or irritable mood, plus one or more manic or hypomanic symptoms (Lewinsohn et al., 2000b). Subthreshold anxiety was defined as the presence of at least three total anxiety symptoms across the following disorders – panic disorder, agoraphobia without panic, social and simple phobia, obsessive-compulsive disorder, separation anxiety, overanxious disorder, acute stress disorder, generalized anxiety disorder, and post-traumatic stress disorder. The rank-order prevalence of subthreshold anxiety disorders mirrors the rank-order prevalence of FS anxiety disorders in this sample (Lewinsohn et al., 2004). Subthreshold alcohol use disorder was defined as one or more symptoms of alcohol dependence and not had abuse (Rohde, Lewinsohn, & Seeley, 1996). This definition was chosen because it defines a group that lies on a continuum between abstainers and FS alcohol abuse or dependence (Rohde et al., 1996; Saunders & Lee, 2000). Similarly, subthreshold substance use disorder was defined as one or two symptoms of any substance dependence (excluding alcohol and tobacco) (Pollock & Martin, 1999). Subthreshold conduct disorder was defined as two or more symptoms of conduct disorder but never meeting FS criteria for oppositional defiant, or ASPD (Lewinsohn et al., 2004). Subthreshold ADHD was defined as five or more symptoms which ensures that all cases had more than half of the symptoms required for the FS diagnosis (Biederman et al., 1996).

FS at Follow-up

We examined six FS classes of disorders at follow-up – depression (MDD or dysthymia), bipolar disorder (bipolar I, II or cyclothymia), any anxiety disorder (see list from above), alcohol use disorder (abuse or dependence), non-alcohol, non-tobacco substance abuse or dependence - hereafter “substance use disorder,” and conduct/ASPD. No participants developed ADHD for the first time at follow-up.

Data Analyses

Participants were included in the study if they were followed up at least once. We excluded two participants with psychosis from all analyses yielding 1505 participants. As we were interested in predicting first onset of a FS condition, for each disorder, we excluded participants who had that FS disorder before or at T1 (FS depression: N=307; bipolar: N=15; anxiety: N=123; alcohol: N=70; substance use disorder: N=88; conduct: N=40; ADHD: N=41). Thus, the N’s for each disorder vary slightly (e.g., those with T1 bipolar were excluded from analyses predicting follow-up bipolar).

As participants with no history of psychopathology were undersampled for the T3 follow-up, participants were weighted by their probability of selection for T3 (standard errors were adjusted in inferential statistics). Rates of development of FS disorders were analyzed using Cox proportional hazard models with the time-to-event variable being age of onset for those who developed the disorder and age at last assessment for those who did not develop the disorder (i.e., censored observations). Cox models provide estimates of hazard ratios with confidence intervals for survival data. Time-to-event analyses such as these are powerful

methods of identifying effects that may be obscured by analytic strategies that only examine the proportion of individuals who experienced an event at a single time point. In addition, time-to-event analyses maximize statistical power as they allow for the inclusion of participants lost to attrition and take the length of follow-up into account. The proportional hazards assumption was tested by including a Time X Predictor interaction term in each Cox model (Singer & Willett, 1991). The proportional hazard assumption was met if the interaction term was nonsignificant, in which case the interaction term was removed from the model. Few significant Time X Predictor interaction terms needed to be retained in order to account for nonproportional hazards. Cox models were conducted in two sets – 1) adjusting for gender (as gender related to the predictor and the outcome) and 2) adjusting for gender and comorbid conditions at T_1.

The primary contrast compared participants with the subthreshold condition by T1 and participants with neither that subthreshold nor FS condition by T1. These groups were compared on the likelihood of developing the FS at any point during follow-up for the first time. In order to examine whether the heterotypic developments (e.g., subthreshold anxiety developing conduct/ASPD) were similar to those observed in FS conditions (e.g., FS anxiety developing conduct/ASPD), we also examined what other FS disorders were developed by participants with each T1 FS condition. We are not reporting comparable analyses for the homotypic associations (e.g., T1 FS anxiety predicting follow-up FS anxiety) as those would be examining the recurrence or continuation of the disorder, not first onset. However, it should be noted that all T1 FS disorders robustly predicted recurrence/continuation.

Results

Table 1 presents the N's and characteristics of each of the subthreshold groups at T1. Women were more likely to have subthreshold MDD and anxiety and men were more likely to have subthreshold conduct disorder and ADHD. Participants in all subthreshold groups were more likely than their respective control groups to have co-occurring subthreshold and FS conditions. Those with subthreshold MDD, alcohol, substance, conduct and ADHD were slightly older at T1 than their respective control groups as well. Because of the small differences in ages, we did not adjust for baseline age in the Cox models below.

Predicting FS conditions at follow-up (T2 thru T4)

We first determined what percentage of the sample developed a disorder for the first time during the follow-up period (i.e., excluding those with each respective baseline diagnosis). First time incidence rates were 24.5% (N=294) for depression, 1.2% (N=18) for bipolar disorder, 9.8% (N=136) for anxiety disorders, 21.2% (N=304) for alcohol, 12.1% (N=171) for substance use disorder, and 1.6% (N=24) for conduct disorder/ASPD (ASPD). Table 2 presents the results of which diagnostic groups at T1 developed which FS conditions at follow-up adjusted for gender. As noted above, no subjects developed FS ADHD during the follow-up, hence this was not included as an outcome.

In Table 2, the middle row of each condition presents the results for the subthreshold conditions. With the exception of subthreshold bipolar disorder, homotypic escalations were observed as subthreshold conditions significantly predicted a first onset of the FS condition over time. We also observed the following heterotypic developments. Those with subthreshold bipolar disorder developed FS depressive and anxiety disorders. Those with subthreshold alcohol developed FS substance use disorder and conduct disorder/ASPD. Those with subthreshold substance developed FS alcohol use disorders and a trend for bipolar and anxiety disorders. Those with subthreshold conduct developed FS bipolar, anxiety, alcohol use, and substance use disorders. Those with subthreshold ADHD developed FS alcohol and substance use disorders, and conduct disorder/ASPD.

We next examined whether the heterotypic results for FS conditions were similar to that of the subthreshold conditions. These results are presented in the top row of each condition in Table 2. The majority of the heterotypic associations observed for subthreshold conditions were also found for FS conditions. However, FS disorders were associated with more conditions at follow-up than subthreshold conditions.

Predicting follow-up FS disorders adjusting for comorbidity

The second set of analyses examined whether the significant homotypic and heterotypic associations reported in the previous section were due to comorbid conditions. Because the focus of this study is on subthreshold psychopathology, these analyses were only conducted for subthreshold conditions. A covariate was included if it was significantly associated with the IV (i.e., subthreshold condition at T1) and the DV (i.e., follow-up FS diagnoses) in Table 2. As an example of how comorbidity was adjusted, subthreshold anxiety, subthreshold conduct, and FS MDD were included as covariates in the model examining whether subthreshold bipolar predicted onset of anxiety. Thus, each analysis, by necessity, included a different set of covariates. Table 3 presents the T1 associations among subthreshold and FS conditions.

The results of the models adjusting for comorbid subthreshold and FS conditions are displayed in Table 4. Only the cells that were significant in the Table 2 analyses are included in Table 4. With the exception of subthreshold anxiety, all of the homotypic escalations from Table 2 remained significant after adjusting for comorbidity. The majority of the heterotypic developments also remained significant after adjusting for comorbidity with three exceptions: subthreshold conduct disorder no longer predicted FS anxiety disorder, subthreshold ADHD no longer predicted FS alcohol use disorder, and subthreshold alcohol no longer predicting FS substance use disorder.

Discussion

To our knowledge, this 15-year longitudinal study is the first to examine many subthreshold conditions as predictors of first onsets of FS conditions. As we included numerous disorders, we were able to examine both homotypic escalation, and heterotypic developments. In addition, unlike most studies of subthreshold conditions, we reported whether these conditions maintained their predictive power after adjusting for comorbidity. In sum, our results suggest that subthreshold conditions have both important homotypic and heterotypic predictive power. Our study therefore adds to the growing literature on the validity of subthreshold psychopathologies. We now discuss the homotypic and heterotypic findings separately.

Homotypic escalation

With the exception of subthreshold bipolar and ADHD, all of subthreshold conditions had an increased probability of escalating over time into their respective FS condition (e.g., subthreshold MDD predicted FS depression). Moreover, these effects remained significant after adjusting for comorbidity (with the exception of subthreshold anxiety) suggesting a direct pathway between subthreshold and FS.

These homotypic findings have several implications. First, subthreshold conditions appear to be precursors of FS conditions (Eaton et al., 1995). Second, it may be that a reduced threshold is more appropriate to define ‘caseness’ (Andrews, Slade, Sunderland & Anderson, 2007). This is consistent with other longitudinal studies in which asymptomatic individuals generally remain asymptomatic over time, but FS and subthreshold individuals fluctuate between threshold and subthreshold (Merikangas et al, 2003; Wittchen, Lieb,

Pfister, & Schuster, 2000). However, our data suggest that there may be meaningful differences between subthreshold and FS individuals, as the latter are associated with a worse course (see top rows in Table 2). Third, our results support the argument for a dimensional diagnostic system, in that they suggest that subthreshold and FS conditions fall on a continuum (Helzer, Kraemer, & Kreuger, 2006; Widiger, & Samuel, 2005). This view is also consistent with the argument that subthreshold conditions are quantitatively (though not qualitatively) different from FS conditions (Flett et al., 1997). Indeed, numerous studies have found that subthreshold psychopathology is associated with significant impairment (Lewinsohn et al., 2000b; Pincus et al., 2003).

Unfortunately, it was very difficult to detect homotypic escalation in the subthreshold ADHD and bipolar groups in our sample. According to the DSM-IV, symptoms of ADHD must be present before age 7, and our sample was approximately 16 at baseline. In addition, only 18 individuals developed a bipolar disorder for the first time during follow-up (15 already had bipolar by T1) giving us low power to detect escalation to FS bipolar. In order to examine whether these two subthreshold disorders demonstrate homotypic escalation, future studies should include an earlier baseline age and/or a sample with higher incidence of bipolar depression.

Heterotypic development

Few subthreshold studies have examined heterotypic developments (subthreshold forms of one disorder predict FS forms of other disorders) and no study has examined the broad range of diagnostic classes explored in this study. It is thus noteworthy that we observed numerous significant heterotypic developments.

Most interesting were the heterotypic developments of ‘externalizing disorders’ (alcohol, substance, conduct disorder, and ADHD). These disorders often predicted the development of the others, were occasionally bidirectional (subthreshold substance predicted FS alcohol and subthreshold alcohol predicted FS substance), and did not predict the development of internalizing disorders (depression and anxiety). These findings are strikingly similar to our previous reports in which subthreshold externalizing disorders co-occurred and were associated with significant familial co-aggregation (Lewinsohn et al., 2004; Shankman et al., 2008). Taken together, these results are consistent with the idea that these conditions share a common underlying liability for externalizing behaviors (Hicks et al., 2007; Krueger & Markon, 2006). However, it must be noted that if externalizing disorders completely shared a common underlying etiology, then adjusting for their comorbidity (as we did for the results in Table 4) should have eliminated any predictive power for a single subthreshold externalizing condition. This was not the case, as most of the heterotypic and homotypic developments for externalizing disorders remained significant in Table 4, suggesting that each subthreshold externalizing condition has unique, as well as shared predictive validity.

Heterotypic developments within externalizing conditions were more robust than heterotypic developments within internalizing conditions. Even before adjusting for comorbidity, subthreshold depression and anxiety did not predict the FS version of the other. This is consistent with other “multimorbidity” studies in which externalizing disorders ‘clustered together’ more tightly than internalizing disorders (Kendler et al., 2003; Krueger & Markon, 2006). Given that subthreshold depression and anxiety evidenced homotypic escalation, it is possible that these two subthreshold conditions may be specific precursors rather than general risk factors for broad psychopathologies.

Subthreshold bipolar disorder predicted full threshold depressive and anxiety disorders - even after adjusting for comorbidity. These findings are nearly identical to the results of other longitudinal studies of subthreshold conditions that examined these heterotypic

developments (MacQueen et al., 2003; Reeger et al., 2006). They also correspond to our OADP family studies of subthreshold conditions (Lewinsohn et al., 2004; Shankman et al., 2008) suggesting that these pairs of disorders share a common liability. Recent hierarchical models of psychopathology have emphasized the distinction between internalizing and externalizing disorder, but have rarely addressed whether bipolar disorder is an internalizing or externalizing disorder (or neither) (Watson, 2005). Our data suggest that bipolar disorder may belong with the internalizing disorders. Unfortunately, due to the small number of individuals who developed FS bipolar disorder for the first time at follow-up, we had limited power to examine whether subthreshold depression and anxiety predict the development of FS bipolar disorder.

The findings that subthreshold conduct disorder predicted FS bipolar and FS anxiety were the only heterotypic developments that 'crossed' between internalizing and externalizing disorders. The few new onsets of bipolar disorder and thus the very wide confidence interval suggests that the former finding be regarded cautiously, though it is noteworthy that this effect was maintained even after adjusting for comorbidity. The finding that subthreshold conduct disorder predicted FS anxiety is intriguing given that anxiety and conduct disorder/ASPD are not generally viewed as closely related conditions and an absence of anxiety has been emphasized in classical conceptualizations of psychopathy (Cleckley, 1941). However, our recent family study of subthreshold psychopathology found that subthreshold conduct disorder was associated with higher familial rates of anxiety disorders and subthreshold anxiety was associated with higher familial rates of conduct disorder/ASPD suggesting a shared familial liability of the two conditions (Shankman et al., 2008). Moreover, recent conceptualizations have argued that anxiety may be associated with the behavioral aspects of psychopathy (which are emphasized in DSM criteria for conduct disorder/ASPD) more than the affective-interpersonal components (Kim-Cohen et al., 2003; Verona, Patrick, & Joiner, 2001).

This study had a number of strengths: a large representative sample of adolescents assessed up to four occasions over 15 years, inclusion of multiple subthreshold and FS conditions, and an examination of the effects of comorbidity. However, it should be noted that the Ns in some groups were small, so we had to aggregate certain disorders into higher order categories (e.g., examining anxiety disorders as a group), and the prevalence rates of some disorders were too small to include (e.g., eating disorders). This may have masked some additional pathways that may be important. Second, given the sampling strategies, the raw prevalence rates are likely inflated but this would not affect the comparisons of the groups. Third, due to the multiple comparisons, some findings (particularly some of the heterotypic associations), may have been due to a Type I error and thus require replication. Fourth, participants were only assessed through age 30 and may not have passed through the full period of risk for some disorders such as MDD. For these disorders, our results may therefore only generalize to those with an early onset. Finally, although our definitions of subthreshold conditions were consistent with the literature, they are admittedly somewhat arbitrary. Future studies are needed to empirically validate different definitions of subthreshold

Conclusion

These findings highlight the importance of broadening studies of subthreshold psychopathology to multiple disorders and for systematic examination of 'multimorbidity.' In addition to demonstrating that subthreshold psychopathologies escalate into FS disorders, we also found evidence for multiple heterotypic developments between subthreshold conditions and other FS disorders. Finally, together with our recent family study of subthreshold psychopathology (Shankman et al., 2008), the present study argues strongly

that those with subthreshold conditions should not be classified as "noncases" and treated as if they have a similar prognosis to those who are asymptomatic (Fergusson et al., 2005; Gotlib et al., 1995). Subthreshold conditions may therefore represent good targets for preventive interventions. Future diagnostic systems should consider lowering the diagnostic "threshold" or adopting dimensional conceptualizations for particular psychopathologies (Widiger & Samuel, 2005).

Key points

- There is a relation between subthreshold (conditions below diagnostic cutoff) and full syndrome (FS) disorders
- Studies have examined whether subthreshold conditions escalate into FS, but rarely adjust for comorbidity
- We found that subthreshold MDD, anxiety, alcohol, substance and conduct escalated into their cooresponding (FS) disorders, even after adjusting for comorbidity
- Some subthreshold conditions were precursors for other (heterotypic) FS disorders, particularly among externalizing conditions
- Young adults with subthreshold conditions can be targeted for preventative treatments as they are at risk for developing FS disorders over time

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Table 1

Characteristics of subthreshold groups at T1.

	% female	% comorbid SUB at T1	% comorbid FS at T1
Subthresh.-MDD (N=394)	59.0%**	43.0%**	12.3%**
Non-subthresh/non-FS MDD (N=804)	44.6%	23.6%	5.7%
Subthresh-Bipolar (N=59)	53.4%	66.2%**	51.4%**
Non-subthresh/non-FS Bipolar (N=1434)	51.8%	45.8%	17.5%
Subthresh-Anxiety (N=247)	58.8%*	61.3%**	23.5%**
Non-subthresh/ non-FS Anxiety (N=1135)	49.3%	36.6%	12.7%
Subthresh-Alcohol (N=198)	50.0%	63.2%**	36.1%**
Non-subthresh/ non-FS Alcohol (N=1237)	52.0%	39..8%	13.8%
Subthresh-Substance (N=87)	49.2%	68.6%**	33.3%**
Non-subthresh/ non-FS Substance (N=1330)	52.1%	43.9%	14.9%
Subthresh-Conduct (N=94)	40.0%*	69.2%**	45.0%**
Non-subthresh/ non-FS Conduct (N=1371)	53.0%	44.3%	16.1%
Subthresh-ADHD (N=86)	36.0%*	71.9%**	36.0%**
Non-subthresh/ non-FS ADHD (N=1378)	53.2%	44.6%	16.6%

T1= Time 1. Percentages are weighted for probability of selection for T3. FS=Full syndrome. Subthresh=subthreshold. MDD=Major Depressive Disorder. ADHD=Attention deficit, hyperactivity disorder.

** different from non-sub, non-FS group at $p < .01$

* different from non-sub, non-FS group at $p < .05$.

Table 2

Predicting first onset of FS conditions during T2–T4 from baseline FS and SUB conditions (not adjusted for comorbidity)

Diagnoses at T1	Met diagnostic criteria for Full syndrome for first time at T2, T3, or T4					
	Depression (N=1198)	**Bipolar (N=1493)**	**Anxiety (N=1382)**	**Alcohol (N=1435)**	**Substance (N=1417)**	**Conduct/ASPD (N=1465)**
FS-depression	**N/A**	**3.6%** **HR =4.7 (1.1–19.9)**	**21.1%** **HR = 2.1 (1.4–3.2)**	**31.1%** **HR = 1.6 (1.3–2.2)**	17.4%	**2.1%** **HR = 2.9 (1.1–7.5)**
SUB-MDD	**35.3%** **HR =1.6 (1.2–2.0)**	0.8%	9.2%	20.8%	10.6%	1.6%
Non-MDD	19.3%	0.5%	6.6%	17.9%	11.0%	1.5%
FS-Bipolar	12.5%	**N/A**	25.0%	18.2%	30.0%	0%
SUB-Bipolar	**51.4%** **HR =2.1 (1.3–3.4)**	3.4%	**25.0%** **HR = 3.0 (1.5–6.0)**	34.5%	13.0%	1.8%
Non-Bipolar	23.8%	1.1%	9.3%	20.7%	11.9%	1.6%
FS-Anxiety	**55.6%** **HR=2.3 (1.6–3.2)**	2.5%	**N/A**	29.5%	16.2%	1.7%
SUB-Anxiety	28.2%	1.2%	**14.6%** **HR=1.5 (1.0–2.3)**	21.4%	14.7%	1.7%
Non-Anxiety	21.9%	1.1%	8.8%	20.3%	11.1%	1.6%
FS-Alcohol	41.7% HR = 1.6 (0.9–2.9)+	4.3% HR = 3.6 (1.0–13.3)+	16.9% HR= 1.8 (0.9–3.5)+	**N/A**	**35.7%** **HR =3.6 (1.8–7.5)**	**10.9%** **HR=12.0 (4.5–32.2)**
SUB-Alcohol	30.2%	1.5%	11.4%	**36.4%** **HR = 2.0 (1.5–2.7)**	**21.8%** **HR = 2.0 (1.4%3.0)**	2.1%
Non-Alcohol	23.3%	1.0%	9.2%	18.8%	10.1%	1.1%
FS-Substance	35.0%	**4.7%** **HR = 4.3 (1.3–14.3)**	**18.4%** **HR = 2.0 (1.1–3.5)**	**45.7%** **HR = 2.2 (1.4–3.4)**	**N/A**	**8.3%** **HR = 7.8(3.0–20.0)**
SUB-Substance	25.9%	3.5% HR = 3.3 (0.9–12.0)+	15.2% HR =1.7 (1.0–3.2)+	**43.6%** **HR = 2.5 (1.7–3.7)**	**37.9%** **HR =4.1 (2.7–6.3)**	3.8%
Non-Substance	24.1%	0.8%	9.0%	19.0%	10.4%	1.1%
FS-Conduct	27.3%	2.5%	8.1%	**68.0%** **HR =4.4 (2.5–7.5)**	**62.5%** **HR =7.9 (4.4–14.1)**	**N/A**
SUB-Conduct	33.3%	**6.5%** **HR = 6.5 (2.1–19.6)**	**17.3%** **HR = 1.9 (1.0–3.3)**	**43.4%** **R = 2.4 (1.7–3.4)**	**28.4%** **HR =2.6 (1.6–4.1)**	**7.4%** **HR = 6.7 (2.6–17.2)**
Non-conduct	24.1%	0.8%	9.4%	18.9%	10.2%	1.2%
FS-ADHD	**40.6%** **HR =2.1 (1.2–3.8)**	2.5%	14.7%	38.9% HR= 1.6 (0.9–2.8)+	**28.6%** **HR = 2.5 (1.3–4.7)**	2.9%

Diagnoses at T1	Met diagnostic criteria for Full syndrome for first time at T2, T3, or T4					
	Depression (N=1198)	**Bipolar (N=1493)**	**Anxiety (N=1382)**	**Alcohol (N=1435)**	**Substance (N=1417)**	**Conduct/ASPD (N=1465)**
SUB-ADHD	33.3%	2.4%	13.7%	**36.3% HR = 1.6 (1.1–2.5)**	**29.6% HR = 3.0 (1.9–4.8)**	**6.5% HR = 4.4(1.5–12.6)**
Non-ADHD	23.7%	1.1%	9.5%	19.8%	10.5%	1.3%

SUB=Subthreshold. FS=full syndrome. Percentages are observed incidence of diagnosis at T2–T4. Comparison group for Hazard ratios (HR) is non-SUB, non-FS. 95% confidence intervals are presented next to HR. HR are adjusted for sex. HR that are bolded are significant at $p<.05$. Plus-sign = $.05< p<.10$

Table 3

Associations among proband subthreshold (SUB) and full syndrome (FS) conditions at T1 (Total N=1505)

	FS-Dep (n=307)	SUB-MDD (N=394)	FS-Bip (N=12)	SUB-Bip (N=59)	FS-Anx (N=123)	SUB-Anx (N=247)	FS-Alc (N=70)	SUB-Alc (N=198)	FS-Subst (N=88)	SUB-Subst (N=87)	FS-Con (N=40)	SUB-Con (N=94)	FS-ADH (N=41)	SUB-ADH (N=86)
FS-Dep	--	--	Not applic.	**2.8 (1.7–4.8)**	**4.4 (3.0–6.4)**	**1.8 (1.3–2.5)**	**4.0 (2.5–6.5)**	**2.6 (1.9–3.6)**	**5.4 (3.5–8.3)**	**2.1 (1.3–3.3)**	**3.3 (1.8–6.3)**	**3.7 (2.4–5.6)**	n.s.	**2.5 (1.6–3.9)**
SUB-MDD	--	--	Not applic.	n.s.	n.s.	**1.9 (1.4–2.6)**	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
FS-Bip	Not applic.	Not applicable	--	--	**5.8 (1.7–19.4)**	**3.7 (1.2–11.7)**	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
SUB-Bip	24 (7.8%)	21 (5.3%)	--	--	**6.1 (3.4–11.0)**	**2.3 (1.3–4.1)**	n.s.	n.s.	n.s.	n.s.	n.s.	2.9 (1.4–6.1)	5.6 (2.4–13.2)	2.3 (1.0–5.3)
FS-Anx	60 (19.5%)	36 (9.1%)	4 (33.3%)	19 (32.2%)	--	--	**2.2 (1.1–4.3)**	n.s.	n.s.	n.s.	n.s.	**1.9 (1.0–3.5)**	**2.4 (1.0–5.5)**	**2.1 (1.1–3.9)**
SUB-Anx	73 (23.8%)	93 (23.6%)	5 (41.7%)	18 (30.5%)	--	--	**1.8 (1.0–3.2)**	n.s.	**1.8 (1.1–2.9)**	n.s.	**2.2 (1.1–4.5)**	**1.7 (1.1–2.8)**	n.s.	**2.5 (1.5–4.0)**
FS-Alc	34 (11.1%)	24 (6.1%)	1 (8.3%)	4 (6.8%)	11 (8.9%)	18 (7.3%)	--	--	**45.3 (25.8–79.4)**	**2.6 (1.2–5.4)**	**15.4 (7.7–30.8)**	**3.0 (1.5–6.0)**	**3.0 (1.1–7.9)**	n.s.
SUB-Alc	72 (23.5%)	53 (13.5%)	1 (8.3%)	9 (15.3%)	23 (18.7%)	42 (17.0%)	--	--	**2.7 (1.6–4.4)**	**4.4 (2.8–7.0)**	**2.6 (1.3–5.3)**	**2.9 (1.8–4.7)**	n.s.	**2.4 (1.5–4.0)**
FS-Subst	48 (15.6%)	17 (4.3%)	2 (16.7%)	5 (8.5%)	12 (9.8%)	22 (8.9%)	42 (60.0%)	24 (12.1%)	--	--	**12.9 (6.6–25.3)**	**5.4 (3.1–9.3)**	**2.9 (1.2–7.1)**	n.s.
SUB-Subst	29 (9.4%)	22 (5.6%)	1 (8.3%)	6 (10.2%)	8 (6.5%)	19 (7.7%)	9 (12.9%)	32 (16.2%)	--	--	**3.7 (1.6–8.6)**	**3.2 (1.7–5.9)**	n.s.	**4.3 (2.4–7.9)**
FS-Con	18 (5.9%)	11 (2.8%)	0 (0.0%)	3 (5.1%)	3 (2.4%)	12 (4.9%)	15 (21.4%)	11 (5.6%)	16 (18.2%)	7 (8.0%)	--	--	**8.9 (3.7–21.6)**	**5.2 (2.4–11.4)**
SUB-Con	43 (14.0%)	22 (5.6%)	1 (8.3%)	9 (15.3%)	13 (10.6%)	23 (9.3%)	11 (15.7%)	27 (13.6%)	20 (22.7%)	14 (16.1%)	--	--	**3.9 (1.7%8.7)**	n.s.
FS-ADH	9 (2.9%)	11 (2.8%)	1 (8.3%)	7 (11.9%)	7 (5.7%)	7 (2.8%)	5 (7.1%)	8 (4.0%)	6 (6.8%)	2 (2.3%)	7 (17.5%)	8 (8.5%)	--	--
SUB-ADH	32 (10.4%)	23 (5.8%)	2 (16.7%)	7 (11.9%)	13 (10.6%)	27 (10.9%)	6 (8.6%)	22 (11.1%)	5 (5.7%)	16 (18.4%)	9 (22.5%)	8 (8.5%)	--	--

Number of cases and percentage of condition in column are given below diagonal. For example, of the 307 cases with FS MDD, 60 (19.5%) also had FS-anxiety. Odds ratios (OR) are given above diagonal and comparison group for OR is non-SUB, non-FS probands. 95% Confidence intervals are presented below odds ratios. Dep=Major Depressive Disorder or dysthymia; Bip=Bipolar disorder; Anx=Anxiety disorder; Alc=Alcohol use disorder; Subst=non-alcohol substance use disorder; Con=Conduct disorder. ADH=Attention deficit hyperactivity disorder. FS=full syndrome. SUB=subthreshold. OR that are bolded are significant at $p<.05$. n.s. = non-significant.

Table 4

Subthreshold conditions predicting first occurrence of full syndrome disorders adjusting for comorbidity

	Met diagnostic criteria for Full syndrome for first time at T2–T4					
	Depression (N=1198)	**Bipolar (N=1493)**	**Anxiety (N=1382)**	**Alcohol Use disorders (N=1435)**	**Substance disorders (N=1417)**	**Cond/ASPD (N=1465)**
T1 subthreshold MDD	**HR = 1.6 (1.2–2.0)**	-	-	-	-	-
T1 subthreshold Bipolar	**HR = 1.7 (1.0–2.7)**	-	**HR = 2.4 (1.2–4.7)**	-	-	-
T1 subthreshold Anxiety	-	-	HR = 1.3 (0.8–2.0)	-		-
T1 subthreshold Alcohol	-	-	-	**HR = 1.5 (1.1–2.1)**	HR = 1.2 (0.8–1.9)	-
T1 subthreshold Substance	-	-	-	**HR = 1.7 (1.1–2.6)**	**HR = 2.9 (1.8–4.6)**	-
T1 subthreshold Conduct	-	**HR = 3.9 (1.6–9.4)**	HR = 1.2 (0.7–2.2)	**HR = 1.7 (1.1–2.6)**	**HR = 1.9 (1.2–3.3)**	**HR = 4.6 (1.5–13.8)**
T1 subthreshold ADHD	-	-	-	HR = 1.3 (0.9–2.0)	**HR = 2.2 (1.3–3.7)**	**HR = 3.9 (1.4–11.2)**

DV is developed FS diagnosis at either T2, T3, or T4 (i.e., by age 30). HR are adjusted for sex and comorbid subthreshold and full syndrome conditions that are associated with IV and DV (see text). Only HR that were significant before adjusting for comorbidity are presented. Comparison is SUB cases who developed the disorder vs. non-subthreshold, non-Full syndrome cases who developed the disorder. HR that are bolded are significant at $p<.05$. Shaded HR are homotypic developments. Nonshaded HR are heterotypic developments.