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ORIGINAL ARTICLE

Family study of subthreshold psychopathology in a community sample

S. A. Shankman[1]*, D. N. Klein[2], P. M. Lewinsohn[3], J. R. Seeley[3] and J. W. Small[3]

[1] *Department of Psychology, University of Illinois at Chicago, Chicago, IL, USA*
[2] *Department of Psychology, Stony Brook University, Stony Brook, NY, USA*
[3] *Oregon Research Institute, Eugene, OR, USA*

Background. There has been increasing interest in the validity and familial transmission of subthreshold psychiatric conditions and the relationship between subthreshold conditions and full syndrome (FS) disorders. However, most of these studies examined a single subthreshold condition and thus fail to take into account the high co-morbidity among subthreshold conditions and between subthreshold conditions and FS disorders.

Method. A family study of subthreshold psychiatric conditions was conducted with 739 community-drawn young adults and their 1744 relatives. We examined (1) whether relatives of probands with subthreshold major depression, bipolar disorder, anxiety disorders, alcohol use, substance use, and/or conduct disorder exhibited an increased rate of the corresponding (homotypic) FS disorder; (2) whether subthreshold disorders were associated with increased familial rates of other (heterotypic) FS disorders; (3) whether subthreshold and FS conditions are associated with similar familial liabilities; and (4) whether these homotypic and heterotypic associations persisted after controlling for co-morbidity.

Results. Significant homotypic associations were observed for subthreshold anxiety, alcohol, conduct, and a trend was observed for major depression. Only the homotypic association for alcohol and conduct remained after controlling for co-morbid subthreshold and FS conditions. Many heterotypic associations were observed and most remained after controlling for co-morbidity.

Conclusions. It is important to broaden the study of subthreshold psychopathology to multiple disorders. In particular cases, controlling for co-morbidity with other subthreshold and FS conditions altered the patterns of familial aggregation. Etiological processes that are common to particular disorders and subthreshold conditions are discussed.

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Introduction

Over the past decade, there has been increasing interest in subthreshold psychiatric disorders, or cases that exhibit significant symptomatology that falls beneath the threshold for the diagnosis (Helmchen & Linden, 2000; Pincus *et al*. 2003). This work has several important implications. First, subthreshold disorders have been reported to be common, and are associated with significant psychosocial impairment and an increased risk for developing the corresponding (or homotypic) full syndrome disorder (Solomon *et al*. 2001; Rucci *et al*. 2003). Thus, subthreshold disorders are clinically significant in their own right, and provide important opportunities for early intervention/prevention.

Second, subthreshold and full syndrome (FS) disorders often appear to have overlapping etiologies. Subthreshold and FS disorders often co-aggregate in families, and as noted above, subthreshold conditions often progress to FS disorders over time (Pincus *et al*. 2003). This suggests that subthreshold and FS disorders can be considered as falling along a spectrum (Angst *et al*. 2000), with subthreshold disorders being viewed as quantitatively milder than, but qualitatively similar to, FS disorders. This is consistent with dimensional or continuum views of psychopathology (Flett *et al*. 1997; Widiger & Samuel, 2005), although the demonstration of an association between subthreshold and FS disorders does not necessarily exclude the possibility of discrete, or qualitative, breaks elsewhere in the distribution (e.g. between subthreshold and non-cases, or subgroups within the larger group of subthreshold and FS cases).

* Address for correspondence: S. A. Shankman, Ph.D., Assistant Professor, Department of Psychology, and Clinical Assistant Professor, Department of Psychiatry, University of Illinois at Chicago, 1007 W. Harrison, Room 1062D; M/C 285, Chicago, IL 60607, USA.
(Email: stewarts@uic.edu)

The majority of work in this area has focused on subthreshold major depressive disorder (MDD) (Flett *et al*. 1997; Solomon *et al*. 2001; Pincus *et al*. 2003). A number of studies have demonstrated that subthreshold MDD is associated with significant psychosocial impairment (e.g. Gotlib *et al*. 1995), exhibits familial co-aggregation with FS MDD (e.g. Kendler & Gardner, 1998; Lewinsohn *et al*. 2003), and predicts the later development of FS MDD (e.g. Horwath *et al*. 1992; Lewinsohn *et al*. 2000*a*; Fergusson *et al*. 2005). Similar findings have been reported for subthreshold bipolar disorder (Angst *et al*. 2003; Lewinsohn *et al*. 2000*b*) and schizophrenia (Cornblatt *et al*. 2003; Olsen & Rosenbaum, 2006). Moreover, there are growing literatures on subthreshold anxiety disorders (Angst *et al*. 1997; Katerndahl & Realini, 1998; Zlotnick *et al*. 2002), substance use disorders (Saunders & Lee, 2000; Chung *et al*. 2002), conduct disorder, antisocial personality disorder and psychopathy (van Honk *et al*. 2002; LeBreton *et al*. 2006; Messer *et al*. 2006), and eating disorders (Lewinsohn *et al*. 2000*c*; LeGrange *et al*. 2006).

However, the large and growing literature on subthreshold mental disorders suffers from an important limitation. Most studies have focused on a single subthreshold disorder and its corresponding FS form. Unfortunately, this fails to consider the possibility that a subthreshold disorder may be associated with multiple FS disorders, and vice versa. Unfortunately, there are few data on the specificity of the associations between subthreshold and FS conditions. Moreover, just as there is high co-morbidity between FS disorders (Kessler *et al*. 2005), there is also high co-morbidity between subthreshold conditions (Lewinsohn *et al*. 2004). Hence, it is possible that the research on the relationships between single pairs of subthreshold and FS disorders is confounded by associations with other co-morbid subthreshold and FS disorders.

In this paper, we report a family study of a variety of subthreshold disorders (MDD, bipolar disorder, anxiety disorders, alcohol use disorders, drug use disorders, and conduct disorder/antisocial personality disorder) in a large community sample of young adults. By examining the relationships between multiple subthreshold disorders in probands and multiple full-threshold disorders in their first-degree relatives, we can determine the specificity of patterns of familial co-aggregation and control for the effects of co-morbidity between subthreshold and FS conditions. We addressed four specific questions: (1) are subthreshold and FS conditions associated with similar familial liabilities?; (2) do the relatives of probands with subthreshold disorders exhibit an increased rate of the corresponding (or homotypic) FS disorder?; (3) do relatives of probands with subthreshold disorders exhibit an increased rate of other (or heterotypic) FS disorders; and (4) do these homotypic and heterotypic associations persist after controlling for co-morbid subthreshold and FS disorders in probands and relatives?

Method

Participants

Probands

The present study uses data from the Oregon Adolescent Depression Project (OADP) (Lewinsohn *et al*. 1993, 1994), a longitudinal community study of high-school students who were assessed twice during adolescence, a third time at approximately age 24, and a fourth time at approximately age 30. Participants were randomly selected for the initial assessment from nine senior high schools representative of urban and rural districts in western Oregon. A total of 1709 adolescents (mean age 16.6, S.D. = 1.2) completed the initial (T_1) assessments between 1987 and 1989. The participation rate at T_1 was 61% (greater sampling details are provided in Lewinsohn *et al*. 1993).

Approximately 1 year later, 1507 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 declined to participate or dropped out of the study before T_2, were small (Lewinsohn *et al*. 1993).

All adolescents with a history of psychopathology by T_2 ($n = 644$) and a random sample of adolescents from the OADP with no history of psychopathology by T_2 ($n = 457$) were invited to participate in a third (T_3) evaluation. All non-white T_2 participants were retained in the T_3 sample to maximize ethnic diversity. Of the 1101 T_2 participants selected for a T_3 interview, 941 (85%) completed the age 24 evaluation. The T_2 diagnostic groups did not differ on the rate of participation at T_3. At age 30, all T_3 participants were asked to complete the T_4 interview assessment. Of the 941 who participated in the T_3 assessment, 816 (87%) completed the T_4 assessment.

Family members

We assessed directly lifetime psychopathology in 1744 biological first-degree family members of the OADP probands during the T_3 evaluation (1008 parents; 736 full siblings). This represented 63.4% of all possible first-degree relatives. Family diagnostic data were available for 739 (90.1%) of the 816 probands with T_3 and T_4 data [2.4 per proband (S.D. = 1.2)].

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Diagnostic measures

At T_1 and T_2, probands were interviewed with a version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS; Orvaschel *et al*. 1982), which combined features of the Epidemiologic and Present Episode versions, and included additional items to derive DSM-III-R diagnoses (APA, 1987). At T_3 and T_4 probands were interviewed using the Longitudinal Interval Follow-up Evaluation (LIFE; Keller *et al*. 1987), which elicited detailed information about the onset and course of psychiatric disorders since the previous evaluation. Diagnoses were based on DSM-III-R criteria (APA, 1987) for T_1 through T_3 and DSM-IVcriteria (APA, 1994) for T_4. Interviews at T_3 and T_4 were conducted by telephone, which generally yields comparable results to face-to-face interviews (Rohde *et al*. 1997; Sobin *et al*. 1993).

Diagnostic interviewers had advanced degrees in a mental health field and had completed a 70-hour didactic and experiential course in diagnostic interviewing. At each of the four assessment waves, a randomly selected sample of proband interviews indicated good to excellent inter-rater reliabilities for the lifetime full threshold diagnoses reported in this study (Lewinsohn *et al*. 1995; Rohde *et al*. 1997, 2007). Data to compute inter-rater reliabilities for subthreshold conditions was not available.

Parents and siblings age 18 years or older were directly interviewed with the non-patient edition of the Structured Clinical Interview for DSM-IV (First *et al*. 1996) during the T_3 assessment wave. Siblings between age 14 and 18 years were interviewed with the K-SADS. All interviewers of family members were unaware of probands' diagnoses. Inter-rater reliabilities for the FS diagnoses in this study were good to excellent, MDD ($\kappa = 0.94$); anxiety ($\kappa = 0.91$); alcohol abuse/dependence ($\kappa = 0.90$); substance abuse/dependence ($\kappa = 0.91$); conduct or antisocial personality disorder (ASPD) ($\kappa = 0.65$).

Definition of subthreshold groups

Six subthreshold proband groups were formed via computer algorithms for the purpose of this study. A proband was considered subthreshold if he/she met criteria for a particular subthreshold condition at any of the four assessments and never met criteria for that full threshold condition (or class of disorders). While the definitions of subthreshold conditions are somewhat arbitrary, they are all based on definitions used in previous family and follow-up studies, including our initial report on co-morbidity of subthreshold conditions (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 a total of at least three symptoms; Lewinsohn *et al*. 2003). 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). A proband could not have subthreshold MDD if they ever met criteria for dysthymic disorder or a bipolar depressive disorder. Subthreshold bipolar was 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*. 2000*b*). Subthreshold anxiety was defined as the presence of at least three anxiety symptoms across the following anxiety disorders – panic disorder, agoraphobia without a history of panic, social phobia, simple phobia, obsessive–compulsive disorder (OCD), separation anxiety, overanxious disorder, generalized anxiety disorder and post-traumatic stress disorder. The rank order prevalence of subthreshold anxiety disorders in this sample mirrors the rank-order prevalence of FS anxiety disorders reported in a previous adolescent co-morbidity study with the same sample (Lewinsohn *et al*. 1997). Subthreshold alcohol use disorder was defined as those who met criteria for one or more symptoms of alcohol abuse or dependence (Rohde *et al*. 1996). 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. A cut-off definition of one or more symptoms was chosen because it defines an alcohol use group that lies on a continuum between abstainers and those with FS alcohol abuse or dependence (Rohde *et al*. 1996). Subthreshold substance use disorder was 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). Subthreshold conduct disorder was defined as having two or more symptoms of conduct disorder but never meeting FS criteria for conduct disorder, oppositional defiant disorder, or antisocial personality disorder (Lewinsohn *et al*. 2004).

Data analyses

As probands with no history of psychopathology were undersampled in the T_3 follow-up, probands and relatives were weighted as a function of the probability of the probands' selection at T_3. Descriptive features were compared between subthreshold proband groups using χ^2 tests for categorical variables. Rates of familial disorders were analyzed using logistic

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Table 1. *Characteristics of proband groups*

	Female (%)	Caucasian (%)	Percentage with different subthreshold condition	Percentage with FS condition	Assessment at which proband first met criteria for subthreshold (%)			
					T_1	T_2	T_3	T_4
Subthreshold MDD ($n=161$)	47.8*	87.6	45.3%	45.3	60.2	11.8	20.5	7.5
Non-subthreshold/FS MDD ($n=161$)	36.6	91.3	37.3%	41.0				
Subthreshold Bipolar ($n=48$)	56.3	93.8	60.4%	83.3	72.9	10.4	10.4	6.3
Non-subthreshold/FS Bipolar ($n=659$)	57.5	89.3	58.4%	73.4				
Subthreshold Anxiety ($n=184$)	63.6**	89.7	51.1%	81.0**	57.6	3.8	23.9	14.7
Non-subthreshold/FS Anxiety ($n=366$)	45.6	90.8	47.5%	59.6				
Subthreshold Alcohol ($n=137$)	61.3	91.2	54.0%	70.1**	40.1	7.3	42.3	10.2
Non-subthreshold/FS Alcohol ($n=325$)	64.6	89.7	48.9%	56.3				
Subthreshold Substance ($n=53$)	54.7	98.1	77.4%**	83.0**	45.3	17.0	22.6	15.1
Non-subthreshold/FS Substance ($n=497$)	60.4	89.7	57.7%	65.0				
Subthreshold Conduct ($n=61$)	52.5	96.7	55.7%	90.2**	78.7	9.8	11.5	0
Non-subthreshold/FS Conduct ($n=629$)	60.7	84.4	57.9%	71.9				

MDD, Major depressive disorder; FS, full syndrome; Bipolar, bipolar spectrum disorder; Anxiety, anxiety disorder; Alcohol, alcohol dependence; Substance, substance dependence; Conduct, conduct disorder or ASPD.

* Different from non-subthreshold, non-FS group at $p<0.05$; ** different from non-subthreshold, non-FS group at $p<0.01$.

regression models. Because age of relatives was bimodally distributed, we adjusted for age of relatives by including relative generation (parent versus sibling) in all models. We also adjusted for relative sex, and, in some analyses, co-morbidity in the probands. Relatives were clustered within families rather than comprising independent observations, hence the use of standard statistical tests would underestimate the standard errors, increasing the chance of Type I errors. Therefore, all statistical comparisons were conducted using Taylor series linearization (or Generalized Estimating Equations), which takes the clustered structure of the data into account (King *et al*. 1996).

The primary contrast focused on the differences between the relatives of disordered probands and non-subthreshold/non-FS probands. Therefore, *n* for each logistic regression model varied as different probands (and their families) were excluded from each model. For example, families of FS MDD probands were excluded for the subthreshold MDD analyses (but not the other analyses), families of subthreshold MDD probands were excluded for the FS MDD analyses (but not the other analyses), etc. In addition, to separate disordered and control relatives from each other (and thus increase the association between proband subthreshold and familial FS conditions), we also excluded relatives who had the subthreshold form of the disorder. Thus, the dichotomous dependent variable used in the logistic regressions was FS condition *versus* non-FS/non-subthreshold condition in relatives.

Results

Descriptive characteristics of probands and relatives

Of the 739 families for whom we had family data, we excluded the families of four probands with non-affective psychosis from all analyses yielding a maximum of 735 probands (1731 relatives).

Table 1 presents the numbers and characteristics of the each of the subthreshold proband groups[1]†. The only gender or racial difference between the groups was that women had elevated rates of subthreshold MDD and subthreshold anxiety. While subthreshold conditions often co-occurred with other subthreshold conditions, only probands with subthreshold substance disorders had a higher rate of other subthreshold conditions than non-subthreshold/non-FS probands. Many subthreshold conditions did,

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however, significantly co-occur with other FS conditions. Probands with subthreshold anxiety, alcohol, substance, and conduct disorder were each more likely to have other co-occurring FS conditions than their respective non-subthreshold/non-FS complements. Table 1 also illustrates when the proband first met criteria for the subthreshold condition. With the exception of subthreshold alcohol, the vast majority of the probands who developed the subthreshold condition did so by early adolescence [i.e. T_1 (age ~16) or T_2 (age ~17)].

Associations with FS conditions in relatives

In the 1731 relatives, 472 (27.3%) had diagnoses of MDD, 282 (16.3%) had diagnoses of anxiety, 495 (28.6%) had diagnoses of alcohol use, 302 (17.4%) had diagnoses of substance use, 62 (3.6%) had diagnoses of conduct/ASPD, and 940 (54.3%) had any Axis I diagnoses. Because there were so few family members with an FS bipolar condition ($n=19$), these analyses were excluded from the study. Table 2 thus presents the results of the family study analyses for FS MDD, anxiety disorders, alcohol use disorders, non-alcohol substance use disorders, conduct/ASPD, and any Axis I disorder.

The first set of analyses examined the associations between proband subthreshold conditions and family FS conditions without adjusting for other co-morbid conditions. These analyses include as covariates relative gender and whether the relative was a parent or sibling[2]. The results of these analyses are presented in Table 2, in the left column for each condition (e.g. proband subthreshold MDD predicting relative FS anxiety: [odds ratio (OR) 2.0, 95% confidence interval (CI) 1.3–3.3]. Subthreshold MDD was associated with familial anxiety, alcohol, any Axis I disorder, and trends for MDD and conduct/ASPD. Subthreshold bipolar disorder was only associated with familial anxiety. Subthreshold anxiety was associated with familial MDD, anxiety, conduct/ASPD, and any Axis I disorder. Subthreshold alcohol was associated with familial MDD, alcohol, conduct/ASPD, and any Axis I disorder. Subthreshold substance use was associated with familial alcohol and any Axis I disorder. Subthreshold conduct was associated with anxiety, alcohol, conduct/ASPD, and a trend for substance use.

To examine whether the subthreshold results reflect a similar pattern to that of FS disorders, we analyzed the association between FS proband diagnoses and FS conditions in relatives. These results are presented in Table 2, in the left column for each condition (e.g. proband FS MDD predicting relative FS anxiety: OR 2.5, 95% CI 1.7–3.8). With one exception (proband subthreshold conduct/ASPD with relative conduct/ASPD), if a subthreshold form of a condition was associated with a particular disorder in relatives, the FS form of that condition was also associated with that particular disorder in relatives. However, FS disorders were associated with more familial disorders than subthreshold conditions.

The second set of family study analyses examined whether the significant associations reported in the previous section were due to co-morbid proband conditions. Rather than including the presence of any co-occurring subthreshold condition, we only included subthreshold and FS conditions as covariates if they were significantly associated with the dependent variable (DV) (i.e. relative condition) and the independent variable (IV) (i.e. proband condition) in the first set of family study analyses. Table 3 presents the lifetime associations among proband subthreshold and FS conditions. As an example, subthreshold bipolar and FS MDD were included as covariates in the model examining the association between proband subthreshold anxiety and relative anxiety as both covariates were associated with the subthreshold anxiety in probands (i.e. the IV) and anxiety in relatives (i.e. the DV). Thus, each analysis included a different set of covariates.

The results of the models adjusting for co-morbid subthreshold and FS conditions are displayed in Table 2, in the right column for each condition (i.e. in columns labeled 'adjusted for co-morbidity'). For subthreshold MDD and subthreshold bipolar disorder, the significant associations and trends from the first set of analyses remained significant after adjusting for co-morbidity, with the exception of FS-MDD. For subthreshold anxiety, the association with relative MDD remained significant, but the other associations became non significant once we adjusted for co-morbidity. For subthreshold alcohol, the associations with relative MDD, alcohol, and any disorder remained significant, but the association with relative conduct/ASPD became non-significant. For subthreshold substance, the significant associations from the first set of analyses became non-significant after we adjusted for co-morbidity. For subthreshold conduct, the associations with relative anxiety and conduct/ASPD remained significant once we adjusted for co-morbidity, but the association with alcohol use and substance use disorder did not.

Discussion

This study extends the growing literature on subthreshold psychiatric disorders by reporting a family study that examined the associations between multiple subthreshold disorders in probands and multiple FS disorders in their first-degree relatives. In addition,

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Table 2 (*a*). *Familial associations between full syndrome (FS) conditions in relatives and proband FS and subthreshold conditions*

	Full threshold diagnosis in relative					
Lifetime proband diagnoses (T1–T4)	MDD ($n=1537$)		Anxiety ($n=1316$)		Alcohol ($n=1626$)	
	Not adjusted for co-morbidity[a]	Adjusted for co-morbidity[b]	Not adjusted[a]	Adjusted for co-morbidity[b]	Not adjusted[a]	Adjusted for co-morbidity[b]
FS MDD	**34.8%**	OR 1.4 (1.0–2.0)*	**25.3%**		**32.1%**	
	OR 1.8 (1.3–2.5)		**OR 2.5 (1.7–3.8)**	**OR 1.9 (1.2–3.1)**	**OR 1.8 (1.3–2.4)**	**OR 1.5 (1.1–2.2)**
Subthreshold MDD	30.0%		**22.5%**		**33.1%**	
	OR 1.4 (1.0–2.1)*	OR 1.4 (0.9–2.1)	**OR 2.0 (1.3–3.3)**	**OR 1.9 (1.2–3.1)**	**OR 1.7 (1.2–2.4)**	**OR 1.7 (1.2–2.4)**
Non-MDD	22.3%		11.9%		22.1%	
FS Bipolar	46.8%		33.3%		33.3%	
	OR 2.1 (0.9–4.6)*	OR 1.6 (0.7–3.6)				
Subthreshold Bipolar	32.6%		**34.2%**		34.0%	
			OR 2.1 (1.3–3.5)	**OR 1.7 (1.0–2.9)**		
Non-Bipolar	30.0%		20.3%		30.1%	
FS Anxiety	**40.3%**		**31.3%**		**34.0%**	
	OR 2.2 (1.7–3.0)	**OR 2.1 (1.5–2.9)**	**OR 2.4 (1.7–3.4)**	**OR 2.0 (1.3–2.9)**	**OR 1.5 (1.1–2.1)**	OR 1.3 (0.9–1.9)
Subthreshold Anxiety	**35.7%**		**22.1%**		32.0%	
	OR 1.7 (1.3–2.4)	**OR 1.6 (1.2–2.2)**	**OR 1.5 (1.0–2.2)**	OR 1.3 (0.9–1.9)		
Non-Anxiety	24.1%		16.9%		28.1%	
FS Alcohol	30.8%		22.3%		**36.8%**	
					OR 1.9 (1.4–2.5)	OR 1.4 (1.0–1.9)*
Subthreshold Alcohol	**39.5%**		22.3%		**33.2%**	
	OR 1.8 (1.3–2.6)	**OR 1.7 (1.2–2.5)**			**OR 1.6 (1.2–2.3)**	**OR 1.6 (1.1–2.3)**
Non-Alcohol	27.3%		20.4%		24.3%	
FS Substance	31.5%		24.3%		**37.6%**	
					OR 1.8 (1.4–2.5)	OR 1.4 (0.9–1.4)*
Subthreshold Substance	35.2%		23.6%		**37.2%**	
					OR 1.6 (1.0–2.7)	OR 1.3 (0.8–2.0)
Non-Substance	30.1%		20.3%		27.6%	
FS Conduct	36.3%		28.0%		**39.2%**	
					OR 1.9 (1.0–3.5)	OR 1.3 (0.6–2.4)
Subthreshold Conduct	33.3%		**34.4%**		**33.3%**	
			OR 2.1 (1.3–3.6)	**OR 1.9 (1.1–3.2)**	**OR 1.5 (1.0–2.3)**	OR 1.1 (0.7–1.8)
Non-Conduct	30.1%		19.9%		29.6%	

MDD, Major depressive disorder; Anxiety, anxiety disorder; Alcohol, alcohol dependence; Bipolar, bipolar spectrum disorder; Substance, substance dependence; Conduct, conduct disorder or antisocial personality disorder.

Percentages are per cent of probands' relatives who have diagnosis. Comparison group for odds ratios (OR) is non-subthreshold, non-FS probands. Ninety-five per cent confidence intervals are presented next to OR. Dependent variable is family history of full syndrome *v.* non-subthreshold, non-FS (i.e. subthreshold relatives are excluded).

[a] OR are only adjusted for relative sex and whether relative is parent or sibling.

[b] OR are adjusted for sex, whether relative is parent or sibling, and proband conditions that are associated with independent variable and dependent variable (see text). OR that are in bold type are significant at $p<0.05$. * $p<0.10$.

we examined the effects of co-morbidity at both the subthreshold and FS levels on these associations.

With one exception, if a subthreshold condition was associated with a particular familial disorder, the FS form of that condition was associated with the same familial disorder. However, compared with subthreshold conditions, FS disorders were associated with more familial disorders and the magnitudes were generally larger. These findings indicate that the pattern of familial aggregation risk for subthreshold conditions is qualitatively similar to that of FS disorders (Kendler & Gardner, 1998; Lewinsohn *et al*. 2003), and that the two only differ by degree, rather than kind.

As expected, we found evidence for homotypic associations between most subthreshold disorders in probands and the corresponding FS disorder in their relatives. Homotypic associations were observed

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Table 2 (*b*). *Familial associations between full syndrome (FS) conditions in relatives and proband FS and subthreshold conditions*

	Full threshold diagnosis in relative					
Lifetime proband diagnoses (T1–T4)	Substance ($n=1686$)		Conduct/ASPD ($n=1615$)		Any Axis I Dx ($n=1731$)	
	Not adjusted for co-morbidity[a]	Adjusted for co-morbidity[b]	Not adjusted[a]	Adjusted for co-morbidity[b]	Not adjusted[a]	Adjusted for co-morbidity[b]
FS MDD	**19.1%**		**4.2%**		**58.7%**	
	OR 1.4 (1.0–2.1)	OR 1.3 (0.9–1.9)	**OR 2.4 (1.1–5.6)**	OR 1.4 (0.6–3.6)	**OR 1.9 (1.5–2.6)**	**OR 1.5 (1.1–2.0)**
Subthreshold MDD	18.3%		4.8%		**56.3%**	
			OR 2.2 (0.9–5.7)*	OR 2.2 (0.9–5.7)*	**OR 1.7 (1.2–2.3)**	**OR 1.6 (1.2–2.2)**
Non-MDD	14.8%		2.1%		42.2%	
FS Bipolar	22.6%		**9.4%**		62.5%	
			OR 5.1 (1.7–15.2)	OR 3.2 (0.9–11.3)*		
Subthreshold Bipolar	20.2%		6.9%		59.4%	
Non-Bipolar	17.6%		3.4%		53.7%	
FS Anxiety	18.1%		**4.9%**		**64.3%**	
			OR 2.4 (1.2–4.6)	**OR 2.1 (1.0–4.2)**	**OR 2.1 (1.6–2.7)**	**OR 1.7 (1.3–2.4)**
Subthreshold Anxiety	18.3%		**5.1%**		**55.5%**	
			OR 2.2 (1.1–4.5)	OR 1.7 (0.9–3.2)	**OR 1.4 (1.0–1.8)**	OR 1.2 (0.9–1.6)
Non-Anxiety	17.6%		2.7%		49.2%	
FS Alcohol	**20.6%**		4.0%		**59.3%**	
	OR 1.4 (1.0–2.0)	OR 1.0 (0.7–1.4)			**OR 1.5 (1.2-2.0)**	OR 1.1 (0.8–1.5)
Subthreshold Alcohol	19.5%		**5.8%**		**59.6%**	
			OR 2.2 (1.1–4.7)	OR 1.8 (0.8–4.2)	**OR 1.6 (1.2–2.2)**	**OR 1.5 (1.2–2.2)**
Non-Alcohol	15.1%		2.9%		48.1%	
FS Substance	**25.8%**		**5.4%**		**60.2%**	
	OR 2.1 (1.5–2.9)	**OR 2.0 (1.4–2.9)**	**OR 2.3 (1.2–4.3)**	OR 1.7 (0.8–3.5)	**OR 1.5 (1.2–2.0)**	OR 1.2 (0.9–1.7)
Subthreshold Substance	23.2%		5.2%		**61.5%**	
					OR 1.7 (1.0–3.0)	OR 1.3 (0.8–2.3)
Non-Substance	14.9%		3.2%		51.7%	
FS Conduct	**26.3%**		6.5%		**66.0%**	
	OR 1.8 (1.0–3.1)	OR 1.2 (0.6–2.3)			**OR 1.9 (1.2–3.0)**	OR 1.5 (0.9–2.4)
Subthreshold Conduct	23.9%		**8.1%**		59.7%	
	OR 1.6 (1.0–2.6)*	OR 1.3 (0.8–2.1)	**OR 3.6 (1.6–7.8)**	**OR 2.7 (1.1–6.7)**		
Non-Conduct	16.9%		3.3%		53.1%	

ASPD, Antisocial personality disorder; MDD, major depressive disorder; Bipolar, bipolar spectrum disorder; Anxiety, anxiety disorder; Alcohol, alcohol dependence; Substance, substance dependence; Conduct, conduct disorder or ASPD.

Percentages are per cent of probands' relatives who have diagnosis. Comparison group for odds ratios (OR) is non-subthreshold, non-FS probands. Ninety-five per cent confidence intervals are presented next to OR. Dependent variable is family history of full syndrome *v.* non-subthreshold, non-FS (i.e. subthreshold relatives are excluded).

[a] OR are only adjusted for relative sex and whether relative is parent or sibling.

[b] OR are adjusted for sex, whether relative is parent or sibling, and proband conditions that are associated with independent variable and dependent variable (see text). OR that are in bold type are significant at $p<0.05$. * $p<0.10$.

for subthreshold anxiety, alcohol use, and conduct disorders, although not for drug use disorders. In addition, the association between subthreshold MDD in probands and FS MDD in relatives only reached a trend level of significance. This was surprising, as in a previous paper using the OADP sample we reported a significant association between subthreshold MDD in probands and FS MDD in relatives (Lewinsohn *et al*. 2003). A major difference between the two reports is that in the earlier paper probands had only been followed through age 24, whereas the present report includes data from the age 30 follow-up. An important consequence of including the additional wave of data is that a number of probands with subthreshold MDD through age 24 developed FS MDD by age 30, and a number of probands with no history of subthreshold or FS MDD through age 24 developed subthreshold or FS MDD by age 30. This reduced the size of the

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Table 3. *Associations among proband subthreshold and full syndrome (FS) conditions*

	FS MDD ($n=413$)	Subthresh. MDD ($n=161$)	FS Bipolar ($n=28$)	Subthresh. Bipolar ($n=48$)	FS Anxiety ($n=185$)	Subthresh. Anxiety ($n=184$)	FS Alcohol ($n=273$)	Subthresh. Alcohol ($n=137$)	FS Substance ($n=185$)	Subthresh. Substance ($n=53$)	FS Conduct ($n=45$)	Subthresh. Conduct ($n=61$)
FS MDD	–	–	N.S.	**3.6 (1.2–10.2)**	**9.6 (5.2–17.7)**	**3.6 (2.2–5.8)**	**2.3 (1.5–3.5)**	N.S.	**2.2 (1.4–3.4)**	**3.4 (1.3–8.9)**	N.S.	**3.3 (1.4–7.8)**
Subthresh. MDD	–	–	N.S.	N.S.	**2.1 (1.0–4.3)**	N.S.	N.S.	N.S.	N.S.	**3.1 (1.1–8.8)**	N.S.	N.S.
FS Bipolar	18 (4.4%)	n.a.	–	–	**4.7 (1.7–12.7)**	**3.6 (1.3–10.1)**	N.S.	N.S.	**4.7 (2.1–10.5)**	N.S.	N.S.	**3.0 (1.1–8.3)**
Subthresh. Bipolar	35 (8.5%)	9 (5.6%)	–	–	**5.1 (2.4–10.7)**	**2.6 (1.1–5.8)**	N.S.	N.S.	N.S.	N.S.	**2.8 (1.1–7.1)**	**2.8 (1.2–6.4)**
FS Anxiety	149 (36.1%)	23 (14.3%)	12 (42.9%)	24 (50.%)	–	–	**2.0 (1.3–3.0)**	**1.7 (1.0–2.8)**	**1.8 (1.2–2.8)**	N.S.	N.S.	N.S.
Subthresh. Anxiety	120 (29.1%)	36 (22.4%)	10 (35.7%)	13 (27.1%)	–	–	**1.6 (1.1–2.4)**	**1.7 (1.1–2.8)**	**1.7 (1.1–2.5)**	**2.0 (1.0–4.0)**	N.S.	N.S.
FS Alcohol	178 (43.1%)	51 (31.7%)	15 (53.6%)	20 (41.7%)	83 (44.9%)	72 (39.1%)	–	–	**14.1 (8.7–22.9)**	**4.9 (2.5–9.7)**	**14.0 (4.9–39.8)**	**4.3 (2.3–8.2)**
Subthresh. Alcohol	81 (19.6%)	26 (16.1%)	5 (17.9%)	6 (12.5%)	36 (19.5%)	40 (21.7%)	–	–	**3.5 (1.9–6.2)**	**2.5 (1.1–5.7)**	N.S.	N.S.
FS Substance	125 (30.3%)	31 (19.3%)	16 (57.1%)	13 (27.1%)	57 (30.8%)	53 (28.8%)	133 (48.7%)	28 (20.4%)	–	–	**21.5 (9.4–49.3)**	**5.0 (2.8–8.9)**
Subthresh. Substance	34 (8.2%)	14 (8.7%)	2 (7.1%)	3 (6.3%)	16 (8.6%)	17 (9.2%)	27 (9.9%)	21 (8.8%)	–	–	N.S.	**4.2 (1.8–9.5)**
FS Conduct	29 (7.0%)	9 (5.6%)	3 (10.7%)	6 (12.5%)	9 (4.9%)	17 (9.2%)	36 (13.2%)	5 (3.6%)	38 (20.5%)	0 (0.0%)	–	–
Subthresh. Conduct	45 (10.9%)	10 (6.2%)	5 (17.9%)	8 (16.7%)	21 (11.4%)	15 (8.2%)	39 (14.3%)	8 (5.8%)	29 (15.7%)	9 (17.0%)	–	–

MDD, Major depressive disorder; Bipolar, bipolar disorder; Anxiety, anxiety disorder; Alcohol, alcohol use disorder; Substance, non-alcohol substance use disorder; Conduct, conduct disorder/ASPD; N.S., non-significant.

Number of cases and percentage of condition in column are given below diagonal. For example, of the 161 cases with subthreshold MDD, 23 (14.3%) also had an FS diagnosis of an anxiety disorder. Odds ratios (OR) are given above diagonal and comparison group for OR is non-subthreshold, non-FS probands. Ninety-five per cent confidence intervals are presented below odds ratios.

OR that are in bold type are significant at $p<0.05$.

sample, and may have eliminated some of the subthreshold MDD probands with the greatest familial vulnerability. After controlling for co-morbid subthreshold and full threshold disorders, the homotypic associations for alcohol use disorder and conduct/ASPD remained. However, the homotypic association for anxiety disorder and the trend homotypic association for MDD were no longer significant. A plausible explanation for these effects stems from the substantial phenotypic and genetic overlap between depressive disorders and many anxiety disorders (Kendler *et al*. 2003; Watson, 2005; Krueger & Markon, 2006). In controlling for co-morbidity, we may have partialled out the common factor underlying the two disorders, substantially reducing the magnitude of the effect for familial aggregation.

Heterotypic associations between subthreshold forms of one disorder and FS forms of other disorders have rarely been examined in the literature. Thus, it is noteworthy that we observed a number of significant heterotypic associations between subthreshold disorders in probands and FS disorders in relatives. Moreover, many of these effects were bidirectional. Subthreshold MDD in probands was associated with FS anxiety disorders in relatives, and subthreshold anxiety disorders in probands were associated with FS MDD in relatives. Similarly, subthreshold MDD in probands was associated with FS alcohol use disorders in relatives, and subthreshold alcohol use disorder in probands was associated with FS MDD in relatives. In addition, subthreshold alcohol use disorder in probands was associated with FS conduct/ASPD in relatives, and subthreshold conduct/ASPD in probands was associated with FS alcohol use disorders in relatives. These findings for subthreshold psychopathology are consistent with other studies documenting familial associations between FS MDD and both FS anxiety disorders (Middeldorp *et al*. 2005) and alcoholism (Kendler *et al*. 1993), as well as between FS alcoholism and conduct disorder and ASPD (Hicks *et al*. 2004). Thus, one interpretation is that for these pairs of disorders, familial co-aggregation is evident at both the FS and subthreshold levels.

Subthreshold drug use disorder in probands was associated with FS alcohol use disorder in relatives. This is also consistent with the literature documenting substantial co-transmission between FS drug and alcohol use disorders (Hicks *et al*. 2004). However, the converse was not observed; subthreshold alcohol use disorder was not associated with FS drug use disorder in relatives. Indeed, there were surprisingly few associations between any subthreshold disorders and FS drug use disorders in relatives.

The findings that subthreshold anxiety disorder in probands was associated with FS conduct disorder/ASPD in relatives, and subthreshold conduct disorder was associated with FS anxiety disorders in probands were intriguing. Anxiety disorders and conduct/ASPD are not generally viewed as closely related conditions and classical conceptualizations of psychopathy suggest that it is characterized by the absence of anxiety (Cleckley, 1941). However, recent conceptualizations have reported that anxiety may be associated with the behavioral aspects of psychopathy (as emphasized in the DSM criteria for conduct/ASPD) more than the affective-interpersonal components (Verona *et al*. 2001). Additionally, studies have found within-person longitudinal relationships between anxiety disorders and conduct problems (Kim-Cohen *et al*. 2003; Burke *et al*. 2005).

Finally, subthreshold bipolar disorder in probands was also associated with FS anxiety disorders in relatives. Owing to the small number of relatives with FS bipolar disorder, we could not examine the opposite association. However, this last finding extends the growing literature reporting substantial co-morbidity between bipolar and anxiety disorders (McIntyre *et al*. 2006) by indicating that this association is also evident in patterns of familial transmission.

The majority of heterotypic associations between subthreshold disorders in probands and FS disorders in relatives remained significant after adjusting for co-morbid subthreshold and FS disorders. However, controlling for co-morbidity did eliminate the significant associations between subthreshold anxiety disorder in probands and FS conduct disorder/ASPD in relatives; subthreshold alcoholism in probands and FS conduct disorder/ASPD in relatives; and subthreshold drug use disorder in probands and FS alcohol use disorders in relatives. This may mean that that these subthreshold conditions do not have unique heterotypic associations with the above FS disorders, although an examination of the confidence intervals suggests that adjusting for co-morbidity did not have dramatic effects on some of these associations. Alternatively, for some of these associations (e.g. conduct and alcohol), adjusting for co-morbidity could have removed common variance related to externalizing factors (Markon & Krueger, 2005).

This study had a number of strengths, including a large representative sample of probands who were assessed on up to four occasions over approximately 15 years, and direct assessments of relatives using semi-structured diagnostic interviews. However, it should be noted that the numbers in some groups were small, so we had to aggregate some specific disorders into higher-order categories (e.g. anxiety disorders), and some disorders were not prevalent enough in the sample to include in the analyses (e.g. eating disorders). Second, due to the multiple

comparisons, some of our findings (particularly our exploratory heterotypic associations), may have been due to a Type I error. Third, lifetime psychopathology was determined in one assessment for relatives, but four for probands, suggesting that group status was likely more reliable for probands. This, however, likely improved the validity of the analyses as probands were divided into three groups (FS, subthreshold, and non-subthreshold/non-FS) but relatives were only divided into two (FS and non-subthreshold/non-FS). Fourth, probands were only assessed through age 30 and may have thus not passed through the full period of risk for some disorders such as MDD (Kessler *et al*. 2005). For these disorders, our results may therefore only generalize to those with an early onset of subthreshold or FS disorder. Finally, although our definitions of subthreshold disorders were consistent with the literature, they are admittedly somewhat arbitrary.

In conclusion, these findings highlight the importance of broadening the scope of studies of subthreshold psychopathology to multiple disorders. Thus, in addition to demonstrating a number of homotypic associations between subthreshold psychopathology in probands and the corresponding FS disorders in relatives, we also found evidence for multiple heterotypic associations between one form of subthreshold disorder and other forms of FS disorders. Finally, this study suggests that subthreshold and FS disorders may not have qualitatively different familial liabilities and future diagnostic systems should perhaps consider lowering the diagnostic 'threshold' or possibly adopting dimensional or continuous conceptualizations for particular psychopathologies (Widiger & Samuel, 2005).

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Declaration of Interest

None.

Notes

[1] Four hundred and thirteen probands met criteria for FS MDD at some point during the follow-up, suggesting that our lifetime prevalence of MDD was considerably higher than in many other epidemiological surveys. However, most epidemiological studies are based on single-wave retrospective assessments of predominantly adult samples while the OADP is based on four prospective evaluations conducted over a 15-year period from mid-adolescence to early adulthood. Importantly, other prospective epidemiological studies have reported similar rates to ours (e.g. Moffitt *et al*. 2007) suggesting that retrospective surveys may underestimate lifetime disorder.

[2] Compared with male relatives, female relatives were more likely to have MDD (OR 2.2, 95% CI 1.7–2.8), anxiety (OR 2.8, 95% CI 2.0–3.8), and less likely to have alcohol use (OR 2.7, 95% CI 2.2–3.5), substance use (OR 1.5, 95% CI 1.1–1.9), and conduct/ASPD (OR 6.2, 95% CI 3.1–12.2). Compared with parents, siblings were more likely to have alcohol (OR 1.3, 95% CI 1.1–1.7), substance (OR 2.1, 95% CI 1.6–2.8), and conduct/ASPD (OR 2.2, 95% CI 1.3–3.8).

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