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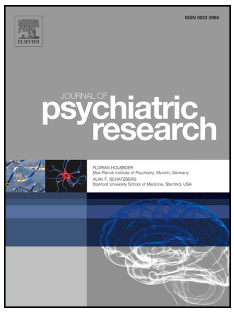


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**What clinical features precede the onset of bipolar disorder?**

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**Abstract**

Despite a growing number of reports, there is still limited knowledge of the clinical features that precede the onset of bipolar disorder (BD). To explore this, we investigated baseline data from a prospectively evaluated longitudinal cohort of subjects aged 12-30 years to compare: first, lifetime rates of clinical features between a) subjects at increased genetic risk for developing BD ('AR'), b) participants from families without mental illness ('controls'), and c) those with established BD; and, second, prior clinical features that predict the later onset of affective disorders in these same three groups. This is the first study to report such comparisons between these three groups (though certainly not the first to compare AR and control samples). 118 AR participants with a parent or sibling with BD (including 102 with a BD parent), 110 controls, and 44 BD subjects were assessed using semi-structured interviews. AR subjects had significantly increased lifetime risks for depressive, anxiety and behavioural disorders compared to controls. Unlike prior reports, preceding anxiety and behavioural disorders were not found to increase risk for later onset of affective disorders in the AR sample, perhaps due to limited sample size. However, preceding behavioural disorders did predict later onset of affective disorders in the BD sample. The findings that i) AR subjects had higher rates of depressive, anxiety and behavioural disorders compared to controls, and ii) prior behavioural disorders increased the risk to later development of affective disorders in the BD group, suggest the possibility of therapeutic targeting for these disorders in those at high genetic risk for BD.

**Keywords:** bipolar disorder, genetic, psychopathology, adolescent, at risk, high risk

## Introduction

There is a growing interest in identifying the earliest stages of bipolar disorder (BD) (Berk et al., 2014; Scott et al., 2013) so as to ultimately enable the capacity for developing early intervention programs for this condition (Mitchell et al., 2013a). As BD is a strongly genetic disorder (McGuffin et al., 2003; Mortensen et al., 2003) which usually presents in late adolescence or the early twenties (Merikangas et al., 2007), prospective longitudinal studies of cohorts at high genetic risk provide the potential means for identifying early features of this condition, in terms of both baseline differences compared to controls and, moreover, those features that are predictive of the later development of mania or hypomania.

There has been a growing but still relatively small number of reports of such high-risk BD studies, both cross-sectional and longitudinal. A recent major example which epitomises the expected rates of "conversion" to BD in such cohorts came from the Dutch high risk bipolar cohort (Mesman et al., 2013). That paper reported 13% of the offspring of parents with bipolar I or II disorders developing some form of BD spectrum by the 12-year follow-up.

The striking finding - from both the longitudinal reports and cross-sectional studies comparing high risk groups to controls – is the high rate and broad range of psychopathology reported in this population. The prospective Dutch study (Mesman et al., 2013) reported that by 12 years, 72% had developed at least one lifetime DSM-IV disorder. Fifty-four percent had experienced some mood disorder (mainly depression), 27% an anxiety disorder, 25% a substance use disorder (SUD), and 8% a disruptive behavioural disorder. Similarly, cross-sectional comparisons of populations of high-risk young people have also reported a greater prevalence of lifetime non-affective psychiatric diagnoses such as anxiety, disruptive behavioural disorders and SUDs when compared to control and major depressive disorder samples (Birmaher et al., 2009; Duffy et al., 2014; Hillegers et al., 2005; Leopold et al., 2014; Nurnberger et al., 2011; Shaw et al., 2005; Vandeleur et al., 2012; Wals et al., 2001; Whalley et al., 2011).

Another issue arising from recent studies is whether the risk to developing later depression or BD in these high risk families is increased by the prior occurrence of non-affective conditions. Two groups have reported that the prior onset of anxiety disorders, behavioural disorders and SUDs increase the risk for developing later affective disorders (Duffy et al., 2007; Duffy et al., 2010; Duffy et al., 2014; Nurnberger et al., 2011).

Most studies of BD high-risk subjects have compared findings against control subjects with no family history of severe mental illness. However, also comparing those at high-risk to those with established BD may provide complementary information on both the prior developmental trajectory and comorbid characteristics of the condition. To date, there has only been one such study (Goldstein et al., 2010) which compared rates of lifetime comorbid disorders in high-risk offspring without BD against high-risk offspring with BD. It demonstrated that those with BD have higher lifetime rates of anxiety disorders, oppositional defiant disorder or conduct disorder, and ADHD compared to those without BD.

This current study is novel in comparing rates and ages of onset of a range of psychiatric disorders between three groups: i) those genetically at-risk for developing BD who have not yet developed this condition (i.e. those with a first-degree relative with the disorder) – the 'AR' group; ii) those with no family of significant psychiatric history - 'controls'; and iii) those with established BD (with or without a family history of BD) – the 'BD' group. All subjects were within the age range of 12-30 years. As detailed above, there have been a number of prior studies which have compared AR and control samples.

The focus of this study was on clarifying the clinical features that precede the onset of bipolar disorder. We hypothesised that: i) AR subjects would have higher lifetime rates of depressive, anxiety and behavioural disorders compared to controls; and ii) within the AR and BD cohorts, onset of anxiety and behavioural disorders would precede the onset of their first major mood episode.

**Method**

The study was conducted with the approval of the University of New South Wales Human Research Ethics Committee (HREC Protocol 09/104) and the South Eastern Sydney Illawarra Health Service HREC (Protocol 09/097) in Sydney, Australia. Written informed consent from all participants was obtained and additional parental consent was obtained for participants under the age of 16. Recruited participants are involved in an ongoing longitudinal study with annual follow-up evaluations. The clinical protocol for those aged between 12 and 21 years of age was identical to that for a NIMH-funded collaborative prospective study of an at-risk cohort (Nurnberger et al., 2011), but there was no overlap between the sample described in this paper, and that of Nurnberger et al (2011).

***Ascertainment and assessments***

AR and BD participants were recruited from: families who had previously participated in a BD pedigree molecular genetics study or a specialised BD research clinic; clinicians; mental health consumer organisations; publicity through print and electronic media; and noticeboards in universities and local communities. (The majority of AR and BD subjects were recruited via print and electronic media publicity). Control subjects were recruited from print and electronic media, and noticeboards in universities and local communities.

AR subjects were defined as first degree relatives - children or siblings - of a proband with a confirmed DSM-IV-TR diagnosis of BD I or II. As confidence in the validity of the proband BD diagnosis was critical to this study, only those AR subjects with confirmed proband consensus best-estimate BD diagnoses based on the Diagnostic Interview for Genetic Studies (DIGS v. 4, Nurnberger et al., 1994), the Family Interview for Genetic Studies (FIGS, (Maxwell, 1992)) and medical records (where available) were included.

Controls were defined as those without a parent or sibling with BD I or II, recurrent major depression (MDD), schizoaffective disorder, schizophrenia, recurrent substance abuse or any past psychiatric hospitalisation; and those who did not have a second degree relative who had a past mood disorder hospitalisation or history of psychosis.

AR and control participants with a lifetime or current presence of psychiatric symptoms (apart from the occurrence of BD) were not excluded from the study; this ecological approach has been used by similar studies of individuals at high genetic risk for BD (Nurnberger et al, 2011).

All potentially interested subjects underwent an initial screening process which involved a brief family history of psychiatric diagnoses and general information about affected relatives. The Family Interview for Genetic Studies (FIGS) (Maxwell, 1992) was administered to all participants at baseline entry to determine any family history of affective disorders. For those aged between 12 and 21 (in all three groups), at least one parent had to be available to complete the FIGS and the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Aged Children – Present and Lifetime Version (K-SADS-BP) (Kaufman et al., 1997; Nurnberger et al., 2011) about their participating child. The K-SADS-BP was administered to both the parent and child; ratings from both the parent and child were then used to determine summary ratings for each symptom. The Diagnostic Interview for Genetic Studies, DIGS v. 4 (Nurnberger et al., 1994), was administered to all participants aged between 22 and 30, and the BD proband (parent or sibling) of all AR participants to confirm proband diagnosis. Similarly, parents of the control participants completed the DIGS to confirm eligibility into the study.

All clinical interviewers possessed at least an honours degree in psychology with some possessing postgraduate degrees in psychology-related fields. Interviewers were extensively trained by a clinical research manager from one of the collaborating US sites, the principal investigator and the study coordinator.

***Diagnostic procedure***

Using the Best Estimate Methodology (Leckman et al., 1982), lifetime diagnoses and age of onset were determined by the consensus of two independent raters (psychiatrists) who were blind to the family status of participants. This approach combined information from the DIGS or the K-SADS-BP, the FIGS, and medical records (where available) in order to determine whether the participant met diagnostic criteria for a lifetime DSM-IV-TR diagnosis and its age of onset. For each diagnosis, the

independent raters rated their diagnostic confidence based on a 4-point scale [1= diagnosis asserted without supporting symptoms; 2 possible; some criteria met (both informants) or all criteria met (one informant) with some supporting information; 3= probably; all criteria met, no supporting documentation; 4= definite; meets criteria and has supporting documentation]. For this paper, only diagnoses achieving a confidence level of 3 or 4 were considered.

***Data Analysis***

Between groups analyses of demographic and clinical characteristics between AR (with separate analyses for i) those with either parent or sibling probands, and ii) only those with a parent proband), control and BD groups were performed using ANOVA (Welch's statistic), chi-square and Fisher's exact tests (FETs) where appropriate. Generalized linear mixed models (GLMM) were then used to compare clinical characteristics between groups while adjusting for demographic variables (gender, age and ethnicity) and parental factors (parental status and parental diagnoses). GLMM is a subject-specific method which accounts for within-sample clustering, for example, families with more than one participating member. To investigate onset of various disorder we carried out survival analyses. Hazards for onset were modelled in a discrete-time framework using a complementary log-log link. Due to some difficulties in obtaining estimates using GLMM, we switched to generalized linear models using generalized estimating equations (GEE), a marginal method which corrects for within-sample correlations. The survival analyses investigated differences between groups (AR, control and BD) in the onset of major affective disorders (BD I; BD II; MDD; single major depressive episode), anxiety disorders (OCD; panic with and without agoraphobia; social phobia; specific phobia; GAD; agoraphobia), behavioural disorders (ADHD, inattentive type; ADHD, hyperactivity-impulsivity; conduct disorder; antisocial personality disorder; oppositional defiant disorder), and SUDs (abuse or dependence of: alcohol; nicotine; cannabis; cocaine; sedative; stimulant; opiate; other substance) respectively. Apart from subjects' status (i.e., AR, control or BD) the only other covariates in these models were years-of-age (linear trend plus quadratic and cubic where feasible) and gender. The estimates from these models were used to

form survival curves (modelled, not observed) illustrating the differences between groups in the onset of disorders. GEE was also used in subsequent within group analyses to determine the prognostic significance of the prior onset of anxiety disorder, behavioural disorder, and SUD on the onset of affective disorders.

**Results**

***Participants***

*The AR sample* comprised 118 participants; 72 were aged between 12 and 21 years old, and 46 were aged between 22 and 30 years old. For 87 AR subjects, the proband had BD I; and for 31, BD II. For 97 AR subjects, the proband was a parent; for 16 the proband was a sibling; and for 5, there was both a parent and a sibling with BD (in this case the parent was considered the primary proband). The sample was comprised of 70 families where the proband was a parent (45 families with a single participating offspring, 18 families with 2 participating offspring and 7 families with 3 or more participating offspring), 15 families where the proband was a sibling (14 families with a single participating sibling, 1 family with 2 active siblings and none with 3 siblings or more siblings), and 3 families where there was a parent and a sibling with bipolar disorder (1 family with a single participating family member, 2 families with 2 participating family members).

*The control sample* consisted of 110 participants. Forty-five controls were aged between 12 and 21 years, and 65 were aged between 22 and 30 years. The younger control sample (12-21 years-old) included one family which had two participating siblings. None of the older control participants (aged 22-30 years old) had siblings in this study.

*The BD sample* was comprised of 44 participants with a confirmed DSM-IV-TR diagnosis of BD I (n=27), BD II with recurrent depressive episodes (n=15), and BD II with a single depressive episode (n=2). No participants in the BD sample met criteria for a current episode of either depression or hypo/mania. Ten of the BD participants also had a first-degree relative with a confirmed diagnosis of BD I (n=7) or II (n=3). Ten BD participants were aged between 12 and 21 years of age, and 34 were aged between 22 and 30 years.

***Comparisons between AR, control and BD samples***

First, considering the AR sample with either parent or sibling probands, there were significant differences between the three groups in terms of age, ethnicity, years of education, occupation and home environment (Table 1) which were therefore controlled for in subsequent analyses. Control subjects (*M*=22.5 years) were older than the AR group (*M*=19.9), while in turn, the BD individuals (*M*=24) were older than the control and AR samples (Welch *F* (2,269) =15.66, *p*<.0001). There were significant differences in the proportions of those with Caucasian ethnicity between the groups, with 99.2% in the AR group, 86.4% in the BD sample and 69.1% amongst controls ($\chi^2$=40.27, *p*<.0001). The BD sample contained a significantly greater number of people who were either not employed or not a student (20.5%) when compared to the controls and AR subjects ($\chi^2$=18.59, *p*<.01). Over half of those in the AR and BD groups lived with at least one biological parent or relative compared to 35.5% of controls ($\chi^2$=19.91, *p*<.01).

[INSERT TABLE 1 ABOUT HERE]

With regard to family history, 86.4% of the AR sample had one parent with BD, with 69% of these parents having BD I. The remaining 13.6% only had a sibling with BD. In the BD sample, 22.7% (n=10) had one parent with BD with 70% (n=7) of these parents having BD I. 24.6% of the AR and 43.2% of BD subjects had at least one parent with MDD. 15.3% of the at-risk subjects and 18.2% of those with BD had at least one parent with an anxiety disorder. None of the parents of the BD group had a diagnosis of ADHD and only one parent of an at-risk subject had a diagnosis of ADHD. Only one parent of a BD individual had experienced psychosis while none of the at-risk parents met such criteria. None of the control parents met criteria for a lifetime diagnosis of an anxiety disorder, ADHD or psychosis.

When considering the AR group with only parent probands (n=102), the levels of significance for comparisons for both demographic and family history characteristics were the same as for those detailed in the prior two paragraphs for the AR group with parent or sibling probands.

The distribution of lifetime diagnoses and differences between the three groups (considering the AR group with either parent or sibling probands) is presented in Table 2, along with details on age of onset. 29.7% of the AR group were diagnosed as having a depressive disorder (MDD or a single major depressive episode) at some stage of their life compared to 12.7% of controls (FET; $p<.0001$). There were differences in rates of anxiety disorders across the three groups, with 22.9% of AR subjects and 52.3% of the BD sample meeting criteria for an anxiety disorder compared to 10% of controls ($\chi^2=32.31$, $p<.0001$). With respect to behavioural disorders, there were significant differences between both the AR and control groups (FET; $p<.001$) and the BD and control groups (FET; $p<.0001$). There were no significant differences between control and AR subjects in the rates of SUDs but there was a significantly higher proportion of individuals in the BD group (29.5%) who had a SUD ($\chi^2=22.71$, $p<.0001$). With regard to lifetime rates of psychiatric disorders, 5.5% of controls had two or more lifetime diagnoses compared to 17.8% of the AR group, and 65.9% of those with BD ($p<.0001$).

When considering the AR group with only parent probands, the levels of significance for comparisons for rates of lifetime diagnoses were the same as for those detailed in the prior paragraph for the AR group with parent or sibling probands.

[INSERT TABLE 2 ABOUT HERE]

Table 3 presents the adjusted odds ratios (ORs) derived from mixed models. With adjustment for the individual's gender, age, ethnicity and home environment (the current parental relationship status), the models supported results found in the between-group univariate analyses. These models demonstrated that being in the AR group (here firstly considering those with either parental or sibling probands) when compared to controls was associated with an increased risk for a depressive disorder (OR=2.6, 95% CI: 1.2-5.8, $p<.05$), any anxiety disorder (OR=2.7, 95% CI: 1.2-6.2, $p<.05$), a behavioural disorder (OR 3.9, 95% CI: 0.9-17.0, p = 0.07) and having at least two lifetime diagnoses (OR=3.2, 95% CI: 1.2-8.5, $p<.05$). The BD group showed greater associated risks for any anxiety disorder (OR=9.7, 95% CI: 3.9-24.2, $p<.0001$), any behavioural disorder (OR=7.9, 95% CI: 1.8-

35.0, *p*<.01), any SUD (OR=6.2, 95% CI: 2.1-18.3, *p*<.01) and having at least two lifetime diagnoses (OR=27.8, 95% CI: 9.7-79.8, *p*<.001) compared to controls. Analyses were conducted on for only those diagnosed with BD who had a family history of BD (n=27) and similar results were obtained.

When considering the AR group with only parent probands, there were a few differences in the significance levels of some of the comparisons compared to controls, though minimal differences in the odds ratios, suggesting a possible reduction in statistical power with reduced sample size. For anxiety disorders there was now only a trend towards statistical significance (OR=2.3, 95% CI: 1.0-5.5, *p*=0.07) while the comparison for behavioural disorders was no longer significant (OR 3.5, 95% CI: 0.8-16.0, p = NS).

[INSERT TABLE 3 ABOUT HERE]

Chi-square analyses did not show significant between-group differences in the number of participants currently from single-parent homes, and homes where both biological parents were present respectively. However, multilevel mixed models revealed that, on combining all groups (control, AR and BD), the odds of having an affective disorder (depression or BD) was 4.9 times greater for those living within a single biological parent home than for those living with both biological parents (OR=4.9, 95% CI: 1.4-16.7, *p*<.001). There was insufficient power to determine interaction effects between groups and the home environment.

For AR individuals, there were no differences in the rates of disorders between those whose BD proband was a parent or a sibling. Similarly, there were no differences in the rates of disorders between AR subjects with probands with BD I or II. Further analyses showed that other parental disorders - i.e. anxiety and substance use disorders - were not associated with an increased risk for any psychiatric disorders within the AR sample.

***Survival and hazard analyses***

Figure 1 (A) demonstrates a significant difference between all AR and control subjects (HR= 3.49, 95% CI: 1.86–6.55, *p*<.0001), and between BD and control subjects (HR= 21.91, 95% CI: 12.24–39.21, *p*<.0001) in the onset of any *lifetime* affective disorder. Significant linear, quadratic and cubic

trends were observed for the onset of any affective disorder. By definition, all BD subjects had developed an affective disorder. Figure 1 (B) shows a significant difference between the AR, control and BD groups in the onset of any lifetime anxiety disorder. Compared to controls, the AR group was more likely to have an onset of any anxiety disorder (HR= 2.76, 95% CI: 1.36–5.59), with the BD group showing an even greater ratio (HR= 6.35, 95% CI: 3.02–13.36). No differences were found between the AR and BD groups in the onset of lifetime behavioural disorders. No subjects in the control group had a diagnosis of a behavioural disorder. There was a significant difference in the onset of lifetime SUDs between the BD and control groups (HR= 5.29, 95% CI: 1.97–14.25, $p$<.01), but there were no significant differences between the AR and control groups. When considering the AR group with only parent probands, the levels of significance were the same as for those with parent or sibling probands.

[INSERT FIGURE 1 ABOUT HERE]

Within group analyses were conducted to test whether *prior* onset of an anxiety disorder, SUD or behavioural disorder increased risk for the later onset of affective disorders. Within the control group, prior onset of an anxiety disorder or a SUD was not associated with the onset of any affective disorder (note that there were no behavioural disorders in this group). Similarly, within the AR group alone, prior onset of an anxiety disorder, SUD or behavioural disorder was not associated with the later onset of any affective disorder. Within the BD group alone, prior onset of a behavioural disorder was associated with the later onset of an affective disorder (HR= 0.87, 95% CI: 0.70-0.97, $p$<.01), but prior onset of an anxiety disorder or SUD was not.

Analyses as above were also conducted for only those diagnosed with BD who had a family history of BD (n=27); similar results were obtained.

**Discussion**

The focus of this study was on clarifying the clinical features that precede the onset of BD, by examining, first, rates of clinical features in the AR group compared to controls, and second, clinical features that predicted later onset of affective disorders in the BD group.

First, this study extends previous reports in demonstrating that young subjects at high genetic risk for BD were also at significantly increased risk for developing a broad range of psychopathology (Birmaher et al., 2009; Duffy et al., 2010; Duffy et al., 2014; Hillegers et al., 2005; Leopold et al., 2014; Nurnberger et al., 2011; Vandeleur et al., 2012; Wals et al., 2001; Whalley et al., 2011). Specifically, we found that AR subjects were more likely to develop depressive, anxiety and behavioural disorders compared to controls. Furthermore, these subjects also had a three-fold greater risk for developing at least two lifetime diagnoses. However, rates of SUDs were not increased. There were no substantial differences between AR subjects with a parent or sibling proband and those with only a parent proband.

We also found that those with established BD had a greater risk for developing a range of psychopathology than either AR or control subjects. Those with BD were eight times more likely to have two or more lifetime disorders than AR subjects, with a more than three-fold increased risk of having an anxiety disorder and an almost five-fold increased risk of a SUD (though no significant difference in the rates of behavioural disorders). In the only other comparison of lifetime rates of comorbid disorders in AR and BD subjects of which we are aware, Goldstein et al (2010) found higher rates of anxiety and behavioural disorders in their BD group. Our finding of an intermediate rate of psychopathology in the AR group - between the BD and control samples - is consistent with this being a heterogeneous population, i.e. only a proportion will go on to later develop BD.

One of the issues of major contemporary interest in such AR populations is whether prior symptomatology increases the later risk for developing a major affective disorder such as depression or BD. Both Nurnberger et al (2011) and Duffy et al (2010) have demonstrated that prior anxiety disorders increase the likelihood of future major affective disorders in AR samples. Furthermore, Nurnberger et al (2011) have also shown that prior behavioural disorders also increase the risk for the later development of major affective illness. Notably, Nurnberger et al (2011) did not find such associations in their control group, suggesting that this relationship was specific to the AR sample.

Whilst we did not find that such prior conditions increased the risk of later depression in our at-risk sample we did find in our BD group that prior behavioural disorders predicted later onset of affective illness. These associations were not present within our control sample. We interpret this finding as a partial replication of the Nurnberger et al (2011) report concerning prior behavioural disorders as a risk factor to later affective conditions. It is difficult to reconcile our finding of a lack of predictive capacity of prior anxiety disorders with the reports of Nurnberger et al (2011) and Duffy et al (2014). As our sample was smaller than both of these studies, it is possible that our negative result was due to insufficient statistical power. Other possible explanations for this lack of association between preceding anxiety disorders and subsequent affective disorders may be the relatively young age of the AR cohort and the cross-sectional design utilising retrospectively collected data.

One of the unexpected, but nonetheless intriguing, findings was the impact of the current parental relationship upon the psychopathology of the young person – irrespective of the diagnostic grouping. The odds of an affective disorder were 4.9 times greater for those living in a single parent home than for those living with both biological parents. This is consistent with a finding from a Swiss high-risk study (Vandeleur et al., 2012) which found that lower rates of affective disorders in AR offspring were associated with living with both biological parents, and is in line with the broader literature on the increased rate of later mental illness in children who were exposed to parental marital disruption during their developmental years (Gilman et al., 2003; Strohschein et al., 2005; Cherlin et al., 1998). However, as our findings are cross-sectional we cannot exclude the alternative possibility that the disruption in the parental relationships may be due to the impact of severe affective illness in these families. Nonetheless, our findings highlight the importance of considering environmental (in this case, stability of the parental relationship) as well as genetic factors in the causative pathways towards the development of major affective illness in these high-risk families.

**Limitations**

First, as few participants met diagnostic criteria for some specific behavioural or anxiety disorders, such as ADHD, it was not possible to conduct predictive analyses examining particular disorders.

Second, as this was a cross-sectional study, information on the onset of disorders was based on retrospective recall with its inherent limitations. It should be noted here that this is also a limitation for most of the other studies that have addressed this issue. As the current study is following subjects prospectively, future reports will detail prospectively-obtained symptomatic and diagnostic data. Third, retrospective data was obtained from individuals of different ages with varying durations of illness history. We attempted to control for this by covarying for current age, though we accept the limitations of this. Fourth, the effect of the parental relationship was based on the current marital status, not on the status at the time of onset of the psychopathology. Fifth, we were not able to determine socio-economic status (SES) from the instruments used for this study, and were therefore unable to examine the effect of SES on rates of psychopathology. Sixth, the low rate of ADHD in the parents as determined by the DIGS of all groups suggests a limitation of assay sensitivity for this diagnosis using this measure**.**

**Conclusions**

We have demonstrated that those individuals at high genetic risk for developing BD were more likely to meet lifetime criteria for depressive, anxiety and behavioural disorders than controls. Though we did not replicate other reports that prior anxiety disorders predict later onset of affective disorders, the finding in our BD group that prior behavioural disorders predicted later onset of these conditions provided a partial replication of the report of Nurnberger et al (2011) in their AR sample. These findings suggest the potential for targeted preventive treatment of such prior conditions to reduce the later onset of affective disorders in subjects at increased genetic risk for BD.

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**Table 1.** Demographic and clinical comparison of at-risk, control and bipolar groups

| | Control (n=110) | At-risk (n=118) | Bipolar disorder (n=44) | Statistic | p-value | Pairwise Comparison |
|---|---|---|---|---|---|---|
| Demographic | | | | | | |
| Males, no. (%) | 49 (44.5) | 56 (47.5) | 17 (38.6) | $\chi^2 = 1.015$ | p= 0.61 | - |
| Age, mean (SD)[a] | 22.5 (3.7) | 19.9 (5.7) | 24 (4.2) | *F* = 15.66 | p<.0001 | ABC |
| Ethnicity, Caucasian (%) | 76 (69.1) | 117 (99.2) | 38 (86.4) | $\chi^2 = 40.27$ | p<.0001 | ABC |
| Years of education, mean (SD)[a] | 15.6 (2.4) | 12.8 (3.7) | 15.5 (2.8) | *F* = 24.33 | p<.0001 | AB |
| Occupation, unemployed and not a student (%) | 8 (7.3) | 3 (2.5) | 9 (20.5) | $\chi^2 = 18.59$ | p <.01 | BC |
| Currently living with at least 1 parent (%) | 39 (35.5) | 65 (55.1) | 20 (58.8) | $\chi^2 = 19.91$ | p<.01 | AC |
| Parental disorders[b] | | | | | | |
| Parent with any bipolar disorder, n. (%)[c] | 0 (0) | 102 (86.4) | 10 (22.7) | Exact | p<.0001 | ABC |
| BDI, n. (%) | 0 (0) | 67 (69.1) | 7 (70) | - | - | - |
| BDII, n. (%) | 0 (0) | 35 (30.9) | 3 (30) | - | - | - |
| Parent with recurrent major depressive disorder, n. (%) | 0 (0) | 29 (24.6 ) | 19 (43.2) | $\chi^2 = 47.21$ | p.< 0001 | ABC |
| Parent with anxiety disorder, n. (%) | 0 (0) | 18 (15.3) | 8 (18.2) | Exact | p.<0001 | AC |
| Parent with substance disorder, n. (%) | 2 (1.8) | 30 (25.4) | 7 (15.9) | $\chi^2 = 25.93$ | p.<0001 | AC |
| Parent with ADHD, n. (%) | 0 (0) | 1 (0.8) | 0 (0) | Exact | p= 1.00 | - |
| Parent with psychosis, n. (%) | 0 (0) | 0 (0) | 1 (2.3) | Exact | p= 0.16 | - |
| Both parent, no disorders, n. (%) | 106 (96.4) | 4 (3.4) | 18 (40.9) | $\chi^2 = 198.32$ | p.<0001 | ABC |

Abbreviations: Exact, Fisher exact test; ADHD, Attention Deficit Hyperactivity Disorder

[a] Welch F statistic was used
[b] At least one parent has the following disorder
[c] Remaining 13.6% of At-risk participants have a sibling with bipolar disorder
A = C versus AR; B = AR versus BD ; C = C versus BD

**Table 2.** Rates of lifetime disorders in at-risk, control and bipolar disorder groups

| **Psychiatric Disorders** | | **Control** | | **At-risk** | | **Bipolar disorder** | **Statistic** | **p-value** | **Pairwise Comparison** |
|---|---|---|---|---|---|---|---|---|---|
| | Age of Onset | (n=110) | Age of Onset | (n=118) | Age of Onset | (n=44) | | | |
| Any lifetime affective disorder, n. (%) | 22 (3.9) | 14 (12.7) | 19 (5.6) | 35 (29.7) | 15 (3.3) | 44 (100) | Exact | p.<0001 | ABC |
| Any lifetime anxiety disorder, n. (%) | 21 (5.6) | 11 (10) | 18 (6.7) | 27 (22.9) | 18 (8.6) | 23 (52.3) | $\chi^2 = 32.31$ | p.<0001 | ABC |
| Any lifetime behavioural disorder, n. (%)[a] | 22 (3.7) | 0 (0) | 20 (5.7) | 11 (9.3) | 24 (5.2) | 7 (15.9) | Exact | p.<0001 | AC |
| Any substance use disorder, n. (%) | 22 (3.9) | 6 (5.5) | 20 (5.7) | 8 (6.8) | 22 (5.4) | 13 (29.5) | $\chi^2 = 22.71$ | p.<0001 | BC |
| At least one lifetime diagnosis, n. (%) | | 27 (24.5) | | 63 (53.4) | | 44 (100) | Exact | p.<0001 | ABC |
| Two or more lifetime diagnoses, n. (%) | | 6 (5.5) | | 21 (17.8) | | 29 (65.9) | Exact | p.<0001 | ABC |
| No disorders, n. (%) | | 83 (75.5) | | 55 (46.6) | | 0 (0) | Exact | p.<0001 | ABC |
| At least one psychotropic medication, current, n. (%) | | 4 (3.6) | | 11 (9.3) | | 33 (75.0) | $\chi^2 = 120.07$ | p<.0001 | BC |

[a] Behavioural disorders included: Attention Deficit Hyperactivity Disorder, Conduct Disorder and Antisocial Personality Disorder

A = C versus AR; B = AR versus BD ; C = C versus BD

**Table 3.** Odds ratios and 95% confidence intervals for psychiatric disorders between At-risk, Control and Bipolar groups

| Disorders | At-risk v Control | Bipolar disorder v Control | Bipolar disorder v At-risk |
|---|---|---|---|
| Any affective disorder | 2.6 (1.2-5.6)* | - | - |
| Any anxiety disorder | 2.7 (1.2-6.3)* | 9.7 (3.9-24.2)*** | 3.6 (1.6-8.1)** |
| Any behavioural disorder [a] | 3.9 (0.9-17.0)[b] | 7.9 (1.8-35.0)** | 2 (0.6-6.7) |
| Any substance use disorder | 1.3 (0.5-3.9) | 6.2 (2.1-18.3)** | 4.7 (1.7-13)** |
| At least two lifetime diagnoses | 3.2 (1.2-8.5)* | 27.9 (9.7-79.8)*** | 8.8 (3.7-21)*** |

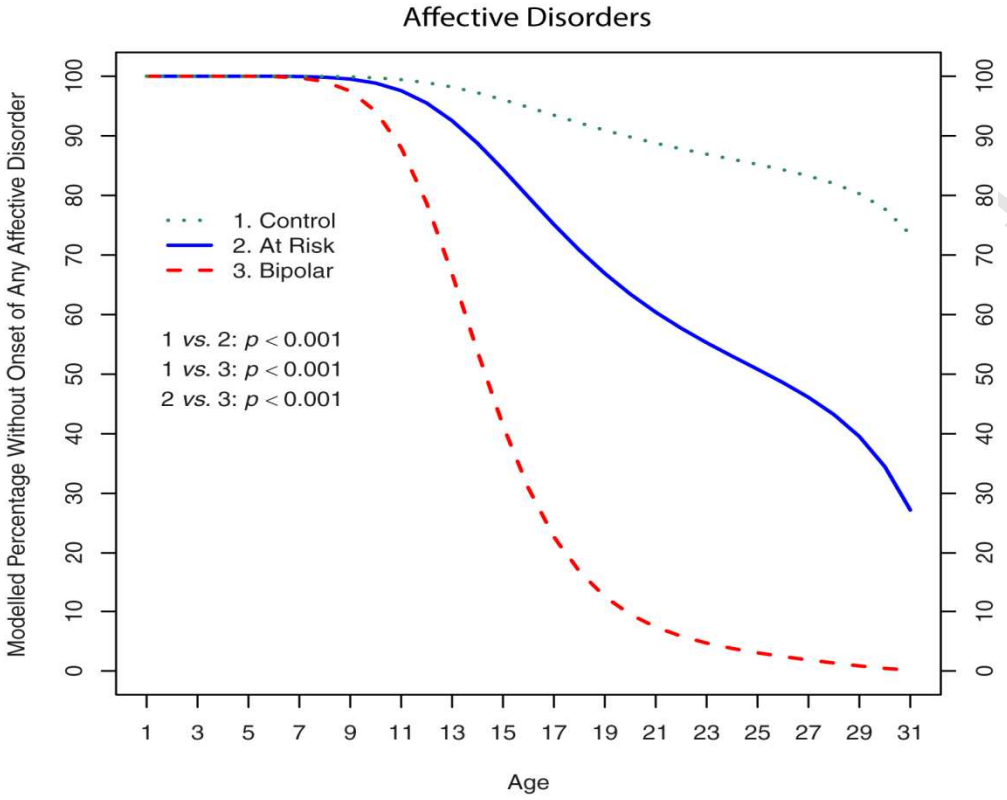
Adjusting for participant gender, age, ethnicity and home environment (parents)

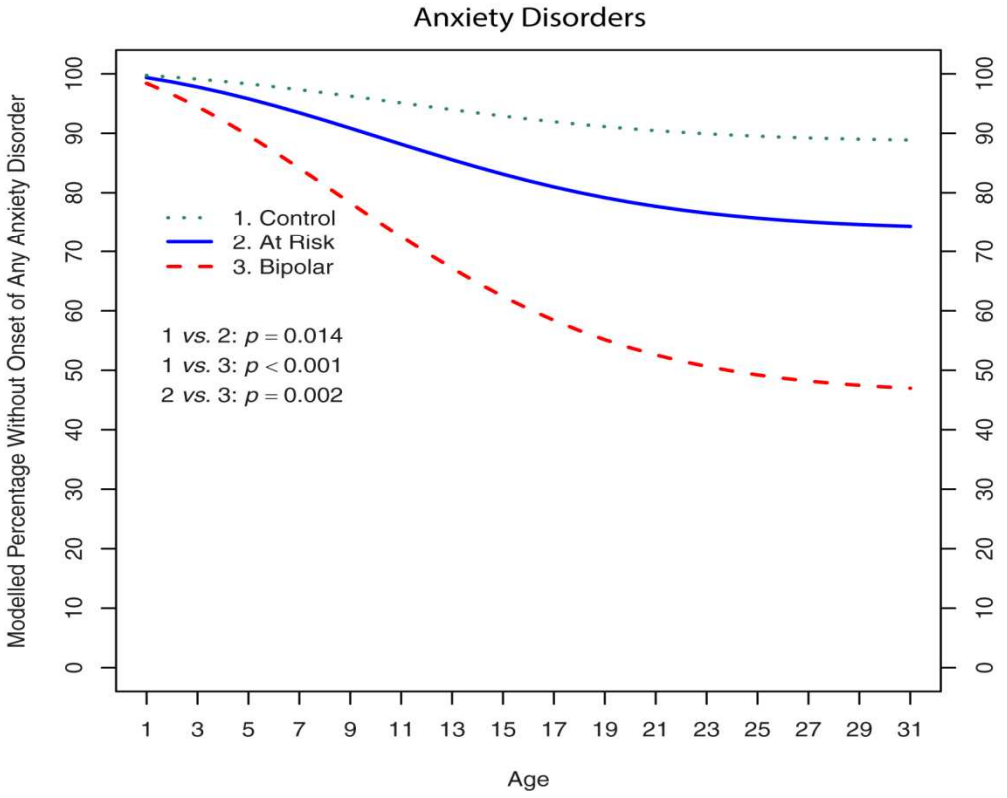
[a] Behavioural disorders included: Attention Deficit Hyperactivity Disorder, Conduct Disorder and Antisocial Personality Disorder

[b] p= 0.073

*p<0.05; **p<0.01; ***p<0.001

**Figure 1 Onset of disorders in at-risk, control and bipolar disorder groups. (A) Affective disorders; (B) Anxiety disorders**



- Young people at high genetic risk for bipolar disorder had significantly increased lifetime risks for depressive, anxiety and behavioural disorders compared to controls.
- Unlike prior reports, preceding anxiety and behavioural disorders were not found to increase risk for later onset of affective disorders in the at-risk sample, perhaps due to limited sample size.
- Preceding behavioural disorders did predict later onset of affective disorders in the bipolar disorder sample.
- The findings suggest the possibility of therapeutic targeting for depressive, anxiety and behavioural disorders in those at high genetic risk for bipolar disorder.

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