Clinical Correlates and Familial Aggregation of Age at Onset in Bipolar Disorder

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Objective: To assess whether age at onset variation reflects underlying genetic heterogeneity in bipolar disorder, the authors examined the clinical and familial characteristics of age at onset in bipolar disorder subjects from families with multiple affected members.

Method: A total of 211 families with 1,856 subjects were ascertained through bipolar I disorder probands. All the subjects were assessed with the Diagnostic Interview for Genetic Studies and assigned diagnoses by trained clinicians using best estimate procedures. Admixture analysis with the 211 bipolar disorder probands was used to decompose the age-at-onset distribution into a mixture of theoretical normal distributions. Logistic regression with general estimating equations was then used to examine clinical correlates and familial aggregation of age at onset in all 717 bipolar disorder subjects.

Results: The age-at-onset distribution consisted of a mixture of three normal distributions with means of 16.6 (SD=5.1), 26.0 (SD=1.4), and 34.7 (SD=6.6) years that comprised 79.7%, 7.2%, and 13.1% of the group, respectively. Cutoff points at ages 21 and 28 were derived from this analysis and used to define age-at-onset subgroups. Early-onset (age at onset ≤21) subjects had higher risks of drug abuse, alcohol abuse, rapid cycling, and suicide attempts. Affected subjects from a family with an early-onset proband were more likely than others to have an early onset (odds ratio=4.53, 95% CI=3.09–6.64). Subjects from a family with a proband whose age at onset was <28 were also more likely to have higher risks of drug abuse (odds ratio=11.62, 95% CI=2.16–62.66).

Conclusions: Age at onset is associated with clinical heterogeneity in bipolar disorder and aggregates, possibly along with drug abuse, within families. These findings are consistent with the conclusion that age at onset reflects underlying genetic heterogeneity in bipolar disorder. Thus, age at onset may conceivably be used to identify more homogeneous groups of bipolar disorder families and thereby facilitate the mapping of bipolar disorder susceptibility genes.

It has been shown that variation in age at onset reflects the underlying genetic heterogeneity of several complex diseases such as Alzheimer's disease (1–4) and breast cancer (5, 6). By using early age at onset to identify more homogeneous subgroups, investigators have been able to identify several genes that contribute to the etiology of these diseases.

Age at onset variation may similarly reflect underlying genetic heterogeneity in bipolar disorder. Recent studies have suggested that there may be a mixture of overlapping distributions of age at onset in bipolar disorder (7, 8), while other studies have shown that the clinical presentation of bipolar disorder, such as the occurrence of comorbid psychiatric disorders, may vary considerably with age at onset (9–12). In addition, some studies have reported that age at onset aggregates within bipolar disorder families (13, 14), and a segregation analysis has found that the transmission of bipolar disorder may differ in early- versus late-onset bipolar disorder (15).

We sought to extend these findings by using data from the NIMH Genetics Initiative for Bipolar Disorder to answer the following questions: 1) Can we replicate the finding that there is a mixture of overlapping age-at-onset distributions that define subgroups of bipolar disorder? 2) Does the clinical presentation of bipolar disorder differ across these age-at-onset subgroups? 3) Do the age-at-onset subgroups aggregate within families? 4) Does age at onset co-aggregate in families with other clinical features? Our goal was to assess the clinical evidence that variation in age at onset along with other clinical features reflects the underlying genetic heterogeneity of bipolar disorder and may be used to identify more homogeneous subgroups of families to facilitate mapping susceptibility genes that contribute to this disorder.

Method

Subjects

The subjects included in this study came from families collected as part of the NIMH Genetics Initiative for Bipolar Disor-

TABLE 1. Demographic and Clinical Characteristics of Affected First-Degree Relatives of Bipolar I Disorder Probands From 211 Families

Characteristic	Affected Subjects (N=717)		Age at Onset of Affected Subjects (years)	
	N	%	Mean	SD
Age at contact (years)[a]				
0–20	18	2.85	13.00	4.35
21–40	330	52.22	17.00	5.63
41–60	240	37.97	23.17	9.70
≥61	44	6.96	28.12	12.29
Gender[b]				
Male	295	41.14	21.6	10.00
Female	422	58.86	19.8	8.93
Diagnosis				
Schizoaffective disorder–bipolar type	52	7.25	20.17	9.37
Bipolar I disorder	510	71.13	20.77	9.71
Bipolar II disorder	155	21.62	19.90	8.45

[a] Mean age at onset significantly differed across categories (p<0.05, ANOVA). Note that 85 subjects had missing age-at-contact information.
[b] Mean age at onset significantly differed across categories (p<0.05, t test).

der. Details of the ascertainment and assessment of these subjects have been described in detail elsewhere (16). Briefly, a total of 211 families (1,856 subjects) were ascertained at one of four collaborating sites (Indiana University, Washington University, Johns Hopkins University, and the NIMH Intramural Research Program) using standardized criteria. Each family had to have a proband with bipolar I disorder and at least one first-degree relative affected with either bipolar I disorder or schizoaffective disorder–bipolar type. Subjects were assessed by trained mental health professionals using the Diagnostic Interview for Genetic Studies. Diagnoses were then assigned by psychiatrists on the basis of all available information—which included the Diagnostic Interview for Genetic Studies data, family history data, and medical records—using best estimate procedures with DSM-III-R criteria (for bipolar I disorder or schizoaffective disorder–bipolar type) and Research Diagnostic Criteria (for bipolar II disorder or recurrent unipolar depression). We examined a narrow phenotype model of affection status that included bipolar I disorder, schizoaffective disorder–bipolar type, and bipolar II disorder. We also analyzed a broad phenotype model that further included recurrent unipolar depression, but since the results were very similar we report here only the results with the narrow model. Age at onset was defined on the basis of self-report as the age at first episode of mania or depression that met diagnostic criteria. The Diagnostic Interview for Genetic Studies also provided detailed information about a range of auxiliary clinical features and comorbid psychiatric disorders diagnosed according to DSM-III-R criteria.

Statistical Analyses

We used analysis of variance to examine if age at onset differed by four age-at-contact groups and three phenotype subgroups and used a chi-square test to examine if age at onset differed by gender. Because the age-at-onset distribution of our sample was not normal, we logarithmically transformed the data for this descriptive analysis.

To determine whether the observed age-at-onset distribution could be decomposed into a mixture of theoretical normal distributions, we used admixture analysis with maximum likelihood estimation of the finite normal mixture (17). We tested a series of mixture models with the assumption of an increasing number of theoretical component distributions and used Akaike's information criterion to select the model that best fit the observed distribution most parsimoniously. We used only the 211 bipolar I disorder probands for this analysis, since the method cannot take into account intrafamilial correlation present in the full dataset of related subjects. Ignoring the intrafamilial correlation may bias the

estimates of the standard deviations of the theoretical age-at-onset distributions.

We used the results of the admixture analysis to derive age-at-onset cutoff points for dividing the affected subjects into subgroups. This was done by adding or subtracting one standard deviation from the estimated means of the theoretical component distributions. We then compared the prevalence rates of clinical correlates across the resulting subgroups. Clinical correlates of interest included comorbid disorders (such as drug abuse, alcohol abuse, panic disorder, obsessive-compulsive disorder, and eating disorders) and auxiliary clinical features (such as rapid cycling, suicide attempt, mood-congruent psychotic symptoms, and episode frequency). Differences in the rates of these features across age-at-onset subgroups were first examined by using chi-square tests and then with logistic regression that controlled for age at contact and gender. We controlled for age at contact and gender because both were associated with age at onset (Table 1) and possibly with the clinical features of interest. Therefore, both were potential confounders of the relationships we sought to examine and required adjustment. By controlling for age at contact, in particular, we tried to account for the fact that the manifestation of the clinical features we examined were potentially age dependent and the subjects were interviewed at different ages (i.e., observations on them were "censored"). Logistic regression models were fit using general estimating equations to account for the potential residual correlation in outcomes among affected subjects from the same families.

We then examined the familial aggregation of age at onset using a proband-predictive model with logistic regression. Here, we modeled dichotomous age at onset (≤21 versus >21) in siblings as a function of age at onset in the proband, controlling for continuous age at contact and gender of the siblings. We modeled age at onset in probands both as a dichotomous variable (≤21 versus >21) and as a dummy-coded categorical variable with three groups (≤21, 22–28, and >28 as the reference). General estimating equations were again used to account for residual correlation among siblings.

We used a modification of the proband-predictive model (18) to investigate potential co-aggregation of different clinical correlates with age at onset in these bipolar disorder families. Here, co-aggregation was assessed by examining whether age at onset in the proband predicted the clinical correlate of interest in the siblings after we controlled for the clinical correlate in the proband as well as age at onset, age at contact, and gender of the relative. These models were also fit by using logistic regression with general estimating equations. All proband-predictive models tested

TABLE 2. Clinical Correlates of Bipolar Disorder Subjects by Age at Onset

| | Prevalence (%) by Onset Age | | Age-at-Onset Subgroup Comparison[a] | | | | | |
| | | | ≤21 Versus >21 | | 22–28 Versus >28 | | ≤21 Versus >28 | |
Clinical Correlate	≤21 Years	>21 Years	Odds Ratio[b]	95% CI	Odds Ratio[b]	95% CI	Odds Ratio[b]	95% CI
Drug abuse	32.12	15.20	1.81	1.16–2.83	1.41	0.61–3.25	2.33	1.07–5.06
Alcohol abuse	44.54	28.80	1.62	1.10–2.37	1.78	0.95–3.30	2.38	1.33–4.22
Panic disorder	16.49	15.60	0.77	0.46–1.28	1.28	0.59–2.76	0.91	0.43–1.91
Obsessive-compulsive disorder	5.35	0.40	9.04	1.11–73.38				
Rapid cycling	52.28	27.14	2.32	1.57–3.43	1.12	0.57–2.19	2.49	1.35–4.60
Suicide attempt	37.64	20.58	1.85	1.27–2.70	1.37	0.69–2.74	2.29	1.31–4.01
Eating disorder	8.99	1.60	3.00	0.97–9.28	0.49	0.08–2.90	1.89	0.43–8.27
Psychosis	54.36	56.58	0.76	0.53–1.09	0.64	0.34–1.18	0.57	0.33–0.99
High episode frequency[c]	38.95	18.54	2.28	1.41–3.69	1.00	0.44–2.31	1.96	0.97–3.96

[a] For the three age-at-onset subgroups: age at onset ≤21 years, N=467; age at onset 22–28 years, N=138; age at onset >28 years, N=112.
[b] Estimated after adjusting for age at contact and gender.
[c] Greater than the mean of 2.7 episodes per year.

controlled for age at contact and sex for the aforementioned reasons.

All analyses were carried out by using the software Stata, release 8 (College Station, Tex., Stata Corp.). Results from logistic regression models are reported as odds ratios with 95% confidence intervals (CIs). The reported p values were not corrected for multiple testing. Many of the clinical features we examined were selected because prior considerations suggested these features may be relevant to age at onset, and we prefer to rely on replication of findings in independent samples rather than use corrections that may be overly conservative.

Results

Table 1 shows the characteristics of the 717 subjects diagnosed with bipolar disorder in this study. The mean age at onset was significantly younger for female relative to male subjects, and the mean age at onset increased in relation to the age of contact. The mean ages at onset for subjects with schizoaffective disorder–bipolar type, bipolar I disorder, and bipolar II disorder were very similar.

The distribution of age at onset in the probands from the 211 families was skewed. Admixture analysis yielded a best fitting model (based on Akaike's information criterion) that suggested the observed distribution could be decomposed into a mixture of three normal distributions (Figure 1). The three component age-at-onset distributions had means of 16.6 (SD=5.1), 26.0 (SD=1.4), and 34.7 (SD=6.6) years and comprised 79.7%, 7.2%, and 13.1% of the group, respectively. On the basis of these results, we divided the group into three age-at-onset subgroups with cutoff points at ages 21 (mean of the youngest group plus one standard deviation) and 28 (mean of the oldest group minus one standard deviation). Alternatively, since the youngest group occupied a substantially greater proportion than the sum of the other two groups, we combined the second and third age-at-onset subgroups to dichotomize early- and late-onset subjects at a cutoff point of age 21.

Table 2 shows the prevalence rates of each clinical correlate among the affected subjects by age at onset. Relative to subjects with a late onset, those with early-onset bipolar disorder were found to have significantly higher rates of drug abuse (z=4.73, p<0.001), alcohol abuse (z=4.08, p<0.001), obsessive-compulsive disorder (z=2.59, p<0.001), rapid cycling (z=5.81, p<0.001), suicide attempt (z=4.40, p<0.001), and episode frequency (z=3.90, p<0.001), with a higher rate of eating disorders that was nearly significant. Typically, the onset of the comorbid disorders occurred after the onset of bipolar disorder. For example, in over two-thirds of the cases the onset of drug or alcohol abuse was after the onset of bipolar disorder. Logistic regression analyses confirmed that early-onset subjects were at a higher risk of having these clinical correlates even after gender and age at contact were controlled. In general, subjects with an age at onset between 22 and 28 had similar, albeit slightly higher, risks relative to subjects with an age at onset >28. There were no apparent differences among the age-at-onset subgroups in the rates of panic disorder or mood-congruent psychosis. Conversely, early-onset subjects tended to have lower rates of psychosis, especially when comparing those with an onset of bipolar disorder ≤21 versus >28.

We used proband-predictive logistic regression models to examine whether age at onset aggregated in these families. Specifically, we tested if age at onset in the probands predicted age at onset in the siblings after age at contact and gender were controlled (Table 3). Affected siblings of early-onset probands were over four times more likely than others to have an early onset. When we trichotomized age at onset in the probands (model 2), we found that compared with siblings of probands in the oldest age-at-onset group (>28), those in the youngest age-at-onset group (≤21) were significantly more likely to have an early onset. By contrast, siblings of probands in the middle age-at-onset group were no more or less likely to have an early onset.

We then compared the prevalence rates of different clinical features among siblings of early- versus late-onset probands (Table 4). The rates of suicide attempts and alcohol abuse were marginally higher in siblings of early-onset probands. However, the most compelling difference was

TABLE 3. Predictors of Early Age at Onset in Affected Siblings of Bipolar I Disorder Probands[a]

| | Early Age at Onset in Affected Sibling | | | |
| | Analytic Model 1 | | Analytic Model 2 | |
Predictor Variable	Odds Ratio	95% CI	Odds Ratio	95% CI
Sibling age at contact	0.94	0.92–0.95	0.94	0.92–0.95
Sibling gender	1.24	0.86–1.81	1.23	0.85–1.79
Proband age at onset (years)				
Dichotomous classification				
≤21	4.53	3.09–6.64		
>21	reference			
Trichotomous classification				
≤21			5.88	3.33–10.34
22–28			1.49	0.79–2.80
>28			reference	

[a] Age at onset in the siblings was modeled as a dichotomous outcome (≤21 versus >21 years).

observed for drug abuse. Prevalence rates of the other clinical features did not differ significantly among siblings of early- versus late-onset probands.

On the basis of these initial comparisons, we used a modification of the proband-predictive logistic regression model to more closely examine the familial co-aggregation of age at onset and drug abuse. Specifically, we tested whether age at onset in the probands predicted drug abuse in the siblings after we controlled for drug abuse in the probands as well as age at onset, age at contact, and gender of the siblings (Table 5). In model 1 with dichotomous onset classification, proband age at onset did not appear to predict drug abuse in the siblings (odds ratio= 0.96, 95% CI=0.44–2.09). However, in model 2 which had a trichotomous classification of proband age at onset, a significant association with drug abuse in the siblings was revealed. Compared with siblings of probands in the oldest age-at-onset group, those in the youngest age-at-onset group were over 10 times more likely to have drug abuse, and those in the middle age-at-onset group were over 18 times more likely. Because of the similar increase in risk, we collapsed the middle and youngest age-at-onset categories and found that siblings of probands with age at onset ≤28 were over 11 times more likely to have drug abuse (odds ratio=11.62, 95% CI=2.16–62.56) than siblings of probands with age at onset >28.

We reran the aforementioned models and controlled for disease duration (age at contact minus age at onset) instead of age at contact. Like age at contact, disease duration was correlated with age at onset (Pearson correlation r=–0.16, p<0.001) and may have also been an important potential confounder of the relationships we observed. However, the results with disease duration controlled were not meaningfully different (data not shown).

Discussion

We found that the skewed distribution of age at onset in our bipolar I disorder subjects could be decomposed by admixture analysis into three normal distributions with means of 16.6 (SD=5.1), 26.0 (SD=1.34), and 34.7 (SD=6.6)

FIGURE 1. Three Theoretical Distributions of Age at Illness Onset for Bipolar I Disorder Probands From 211 Families
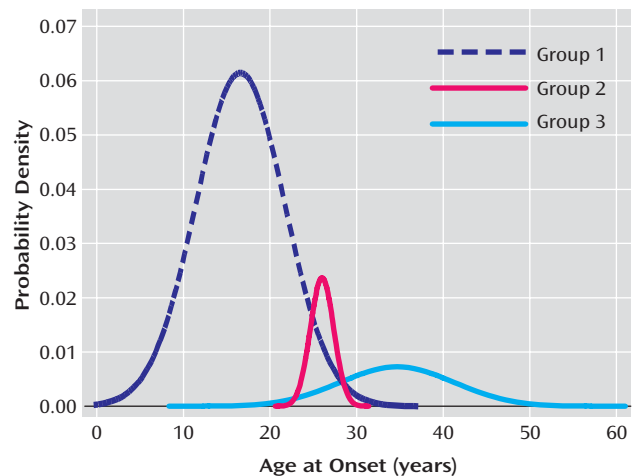
years that comprised 79.7%, 7.2%, and 13.1% of the group, respectively. Although there were differences in the estimated means and proportions of the component distributions, our findings were largely consistent with those reported by Bellivier et al. (7, 8) in their studies of age at onset with two independent samples.

We used the results from our admixture analysis to empirically define cutoff points at ages 21 and 28 for distinguishing age-at-onset subgroups. We then examined if the clinical presentations of bipolar disorder differed across the age-at-onset subgroups. Consistent with previous studies, we found that early-onset subjects (age at onset ≤21) had higher risks of clinical features such as comorbid substance abuse (19, 20), suicidality (11, 20–23), rapid cycling (11, 24), and increased episode frequency (25). We also found that early-onset subjects were at greater risk for eating disorders (although this difference did not quite reach significance after gender and age at contact were controlled), an association that to our knowledge has not been previously examined. In general, subjects with an

TABLE 4. Clinical Correlates in Affected Siblings of Early- Versus Late-Onset Bipolar I Disorder Probands

	Prevalence (%) Among Siblings		Analysis	
Proband Clinical Correlate	Early-Onset Probands (N=381)	Late-Onset Probands (N=166)	χ^2	p
Drug abuse	28.08	19.28	4.73	0.03
Alcohol abuse	36.48	28.31	3.44	0.07
Panic disorder	11.55	15.56	1.29	0.26
Obsessive-compulsive disorder	2.10	0.60	1.60	0.21
Rapid cycling	40.00	42.62	0.12	0.73
Suicide attempt	18.83	12.42	3.33	0.07
Eating disorder	4.99	3.61	0.45	0.48
High episode frequency[a]	34.04	35.85	0.27	0.83

[a] Greater than the mean of 2.7 episodes per year.

TABLE 5. Predictors of Drug Abuse in Affected Siblings of Bipolar I Disorder Probands

	Drug Abuse in Affected Sibling			
	Analytic Model 1		Analytic Model 2	
Predictor Variable	Odds Ratio	95% CI	Odds Ratio	95% CI
Sibling age at onset	0.96	0.92–1.00	0.96	0.92–1.00
Sibling age at contact	0.99	0.96–1.00	0.99	0.96–1.00
Sibling gender	0.53	0.27–1.04	0.51	0.26–1.02
Proband drug abuse	2.43	1.18–4.97	2.33	1.11–4.90
Proband age at onset (years)				
Dichotomous classification				
≤21	0.96	0.44–2.09		
>21	reference			
Trichotomous classification				
≤21			10.21	1.91–54.37
22–28			18.35	3.02–111.35
>28			reference	

age at onset between 22 and 28 years were relatively similar in presentation to late-onset subjects (age at onset >28), albeit with slightly higher risks of the various features examined. These findings appear to suggest that early-onset bipolar disorder has a more severe course leading to the manifestation of numerous clinical complications. However, in contrast to previous studies, we did not find any association between early-onset bipolar disorder and higher risks of comorbid panic disorder (10, 26). Furthermore, we found that early-onset bipolar disorder tended to be associated with lower rates of mood-congruent psychotic symptoms. Such findings contradict some earlier studies of mood-congruent psychosis (27).

As noted by Bellivier and colleagues (7), "if age at onset is a marker for biologically different subtypes of bipolar disorder, then age-at-onset subgroups should have separate normal distributions with different means, variances, and population proportions as well as different clinical characteristics." Our results, therefore, would appear to support the conclusion that age at onset is a clinical marker of biological heterogeneity in bipolar disorder.

In order to assess whether the suggested biological heterogeneity of bipolar disorder may be due to genetic heterogeneity, we examined whether the age-at-onset subgroups aggregated in these bipolar disorder families. Using a proband predictive model, we showed that affected siblings of early-onset probands were over four times more likely than others to have an early onset as

well, even after we controlled for age at contact, which was highly correlated with the self-reported age at onset in this sample. Several previous studies have reported similar observations, which suggests that age at onset aggregates in families. Such findings are consistent with the notion that age at onset is a heritable trait within bipolar disorder reflecting the underlying genetic heterogeneity of the disorder. However, it should be noted that the findings do not prove this, since familial aggregation may be due to non-genetic as well as genetic factors.

We further noted that siblings of early-onset probands tended to have higher risks of certain psychiatric disturbances, including alcoholism, drug abuse, and suicidality. It is interesting that several previous studies also found that these same disturbances occurred more frequently in relatives of early-onset subjects (19, 28–30). Because our results were most compelling with drug abuse, we sought to examine more closely the evidence that it co-aggregates with age at onset in our families. Using a modification of the proband-predictive model, we found that siblings of probands with an age at onset <21 were over 10 times more likely to have drug abuse problems than siblings of probands with an age at onset >28. This association persisted even after we controlled for age at onset in the siblings and drug abuse in the probands, which could confound the relationship. In contrast to our other findings, the siblings of probands with ages at onset between 22–28 were more similar to the early-onset than the late-onset

groups. It is unclear why this is the case. Nevertheless, the findings suggest age at onset and drug abuse may share a common genetic etiology that warrants further investigation.

The current study has several limitations. Most notably, age at onset was assessed by retrospective self-report. The most accurate way to assess age at onset would be to prospectively follow normal subjects until they develop bipolar disorder. However, this is impractical in most situations. By default, the next best approach is self-report. The quality of such data is potentially degraded by recall or information bias. Indeed, it is arguable whether subjects can accurately tell whether their disorder started when they were 16 or 18 years old. Consequently, the true variation in age at onset of bipolar disorder may not be validly captured by a self-reported continuous variable. It seems more reasonable to assume that subjects are better able to distinguish whether their disorder started when they were 16 versus 30 years old. In this case, capturing age at onset in broad categories may be the best that can be validly differentiated.

The difficulty with a categorical variable is determining where to make the cutoff points between age-at-onset subgroups. Previous studies have used a variety of cutoff points (10, 15, 31), often with little justification. We decided to empirically define the cutoff points using the "points of rarity" in the observed age-at-onset distribution. Such an approach has a certain intuitive appeal, but it too may lead to misclassification of subjects, especially among those who have an age at onset where the subgroups may overlap. Misclassification of this sort would tend to introduce noise into the analyses and likely bias observed associations toward the null. Despite this, we were still able to observe robust patterns of differences between the age-at-onset subgroups.

The current study also has several important strengths. The families used in this study were ascertained through a common set of criteria, and the subjects were all assessed with the Diagnostic Interview for Genetic Studies, a widely used and well-validated instrument that collects information on a wide range of psychopathology. Furthermore, diagnoses of mood disorders and other comorbid conditions were assigned by experienced clinicians using best estimate procedures, thus minimizing concerns about misclassification of affection status. Finally, the study group was sufficiently large to allow examination of a variety of hypotheses related to the clinical and familial features of age at onset in bipolar disorder.

In summary, we found that 1) the distribution of age at onset in bipolar disorder revealed several subgroups of patients, 2) the clinical presentation varied significantly across these subgroups, and 3) the subgroups aggregated within families. These results, which are consistent with several other lines of evidence, provide further support for the conclusion that variation in age at onset is an important clinical marker of the underlying genetic heterogene-

ity in bipolar disorder. Thus, age at onset may conceivably be used to identify more homogeneous groups of bipolar disorder families and thereby facilitate the mapping of bipolar disorder susceptibility genes. Some investigators have started to consider age at onset in genetic studies of bipolar disorder (32–34), but the current findings suggest further investigation is warranted. Finally, our novel finding that drug abuse may co-aggregate with early age at onset requires further investigation.

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