A number of convergent sources indicate that there is a substantial incidence of childhood-onset bipolar illness in the USA.1–5 Early onset is rarely observed in studies in many European countries,6 but it was unclear whether this is due to differences in methodology, clinical biases or a real difference in prevalence.

In the USA, Perlis and colleagues2 found that 28% of all adult patients with bipolar disorder reported an illness onset prior to age 13 years; and 66% reported an onset prior to age 20 years. In the Bipolar Collaborative Network (BCN) we found 16% with childhood onset had the longest delays to first treatment and showed a more difficult course as reported retrospectively and as rated prospectively.7

Three of the seven sites in the BCN were in Europe (Utrecht, The Netherlands; Freiburg and Munich, Germany). Four were in the USA: Los Angeles, Dallas, Cincinnati and Bethesda. We therefore had the opportunity to assess possible differences in age at onset and associated vulnerability factors using data emanating from the US compared with the European centres.

All patients gave oral and written informed consent to participate.5,6,9 Representative out-patients were recruited at each site as there were no exclusion criteria except major medical infirmity or active substance misuse requiring treatment elsewhere.

Patients were formally diagnosed using the Structured Clinical Interview for DSM–IV Axis I disorder (SCID).10 and they completed questionnaires about the nature and extent of their prior course of illness.6 The 543 patients were an average age of approximately 42 years at Network entry, with a mean of about 20 years of prior illness. To establish the age at onset of the first depression, patients were asked about their first depressive symptoms associated with dysphoria (i.e. a definition that would be likely to meet DSM–IV criteria), as well as their first hypomanic or manic symptoms (similar to those experienced in adulthood). In addition, the age of first psychopharmacological treatment for either mania or depression was recorded, as was a family history of psychiatric illness in first-degree relatives. In this cohort 337 patients had data on the age at onset of illness based on SCID interview which highly correlated with self-report (r=0.80). Age at onset was divided as in the study of Perlis and colleagues;2

The data were analysed using SPSS version 14.0.2 for Windows. We used t-tests to examine the differences between the USA and Europe on continuous measures and the chi-squared test was used with categorical measures.

Only 2% of patients had childhood-onset bipolar disorder in the three European sites (Fig. 1), compared with 22% in the four US sites (t=6.84, d.f.=591, P<0.0001). This was reflected in the higher mean age at onset of illness of 25.2 years (s.d.=9.9) for the European sites vs. 19.4 years (s.d.=9.7) for the US sites. Age at onset and duration of the untreated interval5 were inversely correlated (r=–0.46, P<0.0001), so the period of delay from onset to first treatment was shorter in the patients from Europe (4.7 years, s.d.=6.6) than in those from the USA (10.9 years, s.d.=10.6; t=6.99, d.f.=468, P<0.0001).

In examining possible risk factors, the US sample compared with the European sample had a significantly (P<0.001) higher incidence of a positive family history of bipolar disorder (51% v. 24%), major depressive disorder (63% v. 44%) and actual or attempted suicide (36% v. 19%), and of childhood physical (30% v. 14%) and sexual (30% v. 17%) abuse. These differences

![Fig. 1 Age at onset of bipolar disorder: comparison of US and European samples.](https://www.cambridge.org/core)
remained significant ($P<0.001$) whether or not all participants with childhood-onset disorder were eliminated from the analysis. Compared with the European patients, US patients also had a higher ($P<0.001$) incidence of rapid cycling (58% vs. 37%), dysphoric mania (67% vs. 41%) and comorbid substance misuse (47% vs 27%). Only a history of psychosis was more prevalent in the European cohort (66%) than in the US cohort (53%). Current age at Network entry, gender and age at onset of first treatment and hospitalisation were not different.

**Discussion**

Our finding indicating that 61% of the US patients had their onset of bipolar disorder prior to age 19 years – double the rate for the European sites (30%) – is highly similar to the 66% figure reported by Perlis and colleagues$^2$ or the 59% prior to age 20 years reported by Lish and colleagues$^1$ or the 59% prior to age 20 years reported by Perlis and colleagues$^2$ or the 59% prior to age 20 years reported by Perlis and colleagues$^2$ or the 59% prior to age 20 years reported by Perlis and colleagues$^2$ or the 59% prior to age 20 years reported by Perlis and colleagues$^2$ or the 59% prior to age 20 years reported by Perlis and colleagues$^2$ or the 59% prior to age 20 years reported by Perlis and colleagues$^2$ or the 59% prior to age 20 years reported by Perlis and colleagues$^2$ or the 59% prior to age 20 years reported by Perlis and colleagues$^2$. Only a history of psychosis was more prevalent (47% vs 27%).

A critical issue is whether this apparent incidence difference could be an artefact of recruitment bias, healthcare availability or variations in interpretation of the same questions by the patient or interviewer. However, at all sites patients were recruited almost exclusively from out-patient clinics and advertisements, and the average age and a variety of demographic variables, including gender and marital status, did not differ between the US and European sites. Whether the SCID clinician interview data or self-rated data were used, the distributions in the USA vs. Europe remained very different.

Retrospective assessments of age at onset of illness by SCID interview or self-report (although highly correlated) are both subject to errors in judgement and recall, and are probably more difficult for early episodes. However, there is little reason to suspect that these errors would occur differentially in Europe and the USA. Moreover, these retrospective data regarding different age at onset appear to be parallel by prospective cross-sectional evaluation of childhood clinical psychiatric populations$^{1,6}$ and in those at high risk.$^{11,12}$

Finally, the highly significant increase in both familial/genetic and psychosocial adversity risk factors in the USA compared with The Netherlands and Germany to some extent indirectly internally validates the age at onset data and is consistent with the well-replicated prospective reports of a high familial loading in childhood-onset bipolar illness cohorts$^2$. Nevertheless, questions about the differential incidence and the generality to other European countries$^{13}$ can only be definitively answered by large-scale epidemiological studies using the same diagnostic instruments.

If these data are valid, clinical and theoretical questions about causes and mechanisms are immediately raised. Explanations of how a greater genetic loading in the USA might occur could include: a higher risk of affective illness in those who migrated from Europe to the USA; increased assortative mating (as seen in our data); faster accumulation of vulnerability genes because of shorter times between reproductive generations; or differential rates of anticipation.$^{13}$ Environmentally based mechanisms could include an increased incidence of childhood adversity (as observed here); different degrees of psychosocial stress based on culture; environmental toxins; dietary differences; differential treatment of attention-deficit hyperactivity disorder with stimulants; or an increased rate of substance misuse (as observed).

Whatever the mechanisms, these preliminary findings deserve further exploration and could provide important hints about increased vulnerability factors in the USA and protective factors in some European populations. As such, they could help uncover important variables that could be utilised both in clinical treatment strategies and in public health preventive measures.$^{13}$

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**References**