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ORIGINAL INVESTIGATION

Age at onset in bipolar I affective disorder in the USA and Europe

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Abstract

Objective. To test for differences in reported age at onset (AAO) of bipolar I affective disorder in clinical samples drawn from Europe and the USA. *Methods*. Admixture analysis was used to identify the model best fitting the observed AAO distributions of two large samples of bipolar I patients from Europe and USA ($n = 3616$ and $n = 2275$, respectively). Theoretical AAO functions were compared between the two samples. *Results*. The model best fitting the observed distribution of AAO in both samples was a mixture of three Gaussian distributions. The theoretical AAO functions of bipolar I disorder differed significantly between the European and USA populations, with further analyses indicating that (i) the proportion of patients belonging to the early-onset subgroup was higher in the USA sample (63 vs. 25%) and (ii) mean age at onset (±SD) in the early-onset subgroup was lower for the USA sample (14.5 ± 4.9 vs. 19 ± 2.7 years). *Conclusions*. The models best describing the reported AAO distributions of European and USA bipolar I patients were remarkably stable. The intermediate- and late-onset subgroups had similar characteristics in the two samples. However, the theoretical AAO function differed significantly between the USA and European samples due to the higher proportion of patients in the early-onset subgroup and the lower mean age-at-onset in the USA sample.

Key words: *Bipolar I disorder, age at onset, adolescent, vulnerability factors, precipitating factors*

Introduction

Several recent clinical studies have suggested that the frequency of bipolar disorder in youth is much higher in the USA than in Europe. Onset during childhood and adolescence has been reported for up to 66% of bipolar patients in the USA (Perlis et al. 2004; Pavuluri et al. 2005; Kessler et al. 2005), with much lower percentages reported for European samples (Soutullo et al. 2005). Post et al. (2008) recently reported that bipolar disorder begins during childhood or adolescence in 61% of patients in the USA, but only 30% of patients in The Netherlands or Germany. Similar results were obtained for a Norwegian sample (38% of patients with an onset before the age of 18 years) (Larsson et al. 2010). However, the picture remains complex, for several reasons. First, these observations have not been uniformly replicated. In particular, Baldessarini et al. (2010) reported early onset of bipolar disorder to be more frequent in Europe, but this study included bipolar I and II patients in the sample (1456 European and 246 USA patients). Similarly, Beesdo et al. (2009) suggested a mean age

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of onset of bipolar disorder between 14 and 15 years in a German representative community sample of 3,021 subjects aged 14–24 years at baseline and prospectively assessed (up to 10 years follow-up). However, AAO evaluated using prospective follow-up studies cannot be directly compared to retrospectively reported AAO as evaluated in clinically ascertained samples. Prospective follow up studies provide a more valid evaluation of AAO, but diagnostic confidence is improved when studies incorporate course of illness markers and a range of sources of clinical information in the diagnostic assessment (Carlson 2011) and focus especially on the most reliable and valid bipolar diagnoses (namely bipolar I or II disorder). This is important, as evidence for the existence of cross-national differences in the age-specific incidence of bipolar disorders in youth remains conflicting. For example, in a recent meta-analysis, van Meter et al. (2011) concluded that there were no differences in the age-specific incidence of narrowly defined bipolar I and II disorders in children and adolescents recruited in the USA compared to non-USA epidemiological samples. However, when a broader definition of bipolar disorder was used (e.g., including bipolar NOS and paediatric bipolar cases), a higher incidence of bipolar disorder was observed in the USA samples by comparison of non-USA samples (van Meter et al. 2011).

Overall, it remains difficult to interpret the differences between Europe and the USA in terms of AAO of bipolar I disorder, and to determine whether these represent artefacts relating to methodological differences or clinical assessment biases or if they represent true differences in terms of risk or precipitating factors.

In recent years, several groups have suggested that bipolar I disorder aggregates into three age-at-onset groups (Bellivier et al. 2001, 2003; Lin et al. 2006; Manchia et al. 2008; Hamshere et al. 2009; Ortiz et al. 2011; Tozzi et al. 2011). Using admixture analyses, these independent studies have shown that the theoretical model best accounting for the observed distribution of AAO is consistent with the existence of three age-at-onset subgroups in bipolar I affective disorder. In these studies, the means and standard deviations (SDs) characterizing each subgroup were remarkably similar, suggesting that this model is highly robust (Hamshere et al. 2009; Ortiz et al. 2011; Tozzi et al. 2011). These results and others suggest that the age-at-onset subgroups of bipolar I disorder may be associated with specific risk factors (for a review, see Leboyer et al. 2005). One way to further explore the observed differences in AAO of bipolar I disorder between the USA and Europe in more detail is to focus on the early-onset subgroup identified in admixture analyses and to compare both the mean AAO of this group and the proportion of patients belonging to this subgroup between the two locations. Differences between Europe and the USA may be quantitative (similar mean AAO in the early-onset subgroups but with different proportions), qualitative (different ages at onset and different proportions) or both. For such a comparison of AAO between the USA and Europe, large samples drawn from naturalistic studies are needed to minimise selection bias.

The aim of this study was to compare the theoretical age-at-onset function of bipolar I disorder between large samples from the USA and Europe, and to explore specifically the characteristics of the early-onset subgroups of the two samples.

Methods

Sampling method

Adult patients with bipolar I disorder who gave an informed consent and for whom information was available concerning AAO were included. Age at onset was defined as the age at which the patient first met the DSM-IV criteria for a mood episode (either depressive, manic, hypomanic or mixed). At inclusion, patients met diagnostic criteria (DSM-IV) for bipolar I disorder.

European subjects were identified from two databases. We first selected a sample, part of an ongoing genetic study, in which all consecutive bipolar I patients ($n = 763$) admitted to one of four centres (Paris, Bordeaux, Geneva and Nancy) between 1994 and 2008 were asked to participate. We also used data drawn from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study. The EMBLEM study was a 2-year, pan-European, prospective observational study on the outcomes of pharmacological treatment in patients with bipolar I disorder who experienced a manic/mixed episode. Across 14 European countries (Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, The Netherlands, Norway, Portugal, Spain, Switzerland and the UK), 3459 adult inpatients and outpatients were enrolled, at the discretion of their treating psychiatrist. Further details of the EMBLEM study design, the samples and baseline characteristics of the patients have been published elsewhere (Haro et al. 2006; Goetz et al. 2007; Vieta et al. 2008).

The total initial sample consisted of 4222 European bipolar I subjects, from which 606 subjects were excluded from the analysis for the following reasons: missing data concerning age at first mood disorder episode, missing data for date of birth and inconsistencies in the definitions of age-at-onset

used for a given subject. Thus, 3616 bipolar I patients of European origin were included.

For the USA sample, a detailed description of the recruitment and diagnostic validation of the Stanley Center Bipolar Registry has been reported elsewhere (Cluss et al. 1999; Kupfer et al. 2002), and we will therefore provide only a brief description here. Subjects identifying themselves as having bipolar disorders were recruited through Stanley Center staff presentations at patient and family organization meetings and at meetings with healthcare professionals (in community mental health clinics, private psychiatry practices and general hospitals with psychiatric services, university psychiatric departments and state psychiatric hospitals), announcements in newspapers, on the radio and on television, and through a web site. The period of recruitment extended from 1995 to 1999. Subjects who signed an informed consent form (approved by the University of Pittsburgh Institutional Review Board) completed an interviewer administered and directed questionnaire. Demographic, clinical and treatment characteristics, including details of the first episode of illness, were obtained. For the most part, the self-identification of the subjects with bipolar disorder was based on their having been diagnosed with this condition by a psychiatrist. The validity of the diagnosis in these self-identified bipolar disorder subjects was verified in a subset of 100 randomly selected individuals assessed by trained psychiatric clinicians, in a face-to-face interview, using the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID) (First et al. 1995). These SCID diagnoses were verified by a supervising psychiatrist, or a senior research coordinator. The vast majority (93%) of these subjects met the criteria for a DSM-IV bipolar disorder (Cluss et al. 1999), demonstrating that most of the self-identified bipolar disorder subjects had accurately reported their diagnosis.

The analyses presented here are based on data for the 2839 registry participants living within a 150-mile radius of the Pittsburgh metropolitan region (Kupfer et al. 2002), because the diagnostic validity study was conducted for this group only (Cluss et al. 1999). The sample was further limited to 2308 participants for whom data concerning the first episode of illness had been obtained. Among those, only subjects with bipolar I disorder were included ($n = 2275$).

Statistical methods

We already used admixture analysis to identify the theoretical age-at-onset function best fitting the observed distribution in several analyses (Bellivier et al. 2001, 2003). The same method was used to identify the theoretical age-at-onset function in the two samples. Several models were estimated and compared, using maximum likelihood ratio tests. Each Gaussian mixture model was estimated with a stochastic EM algorithm (Celeux and Diebolt 1990). The number of components of each model was determined by maximum likelihood ratio tests. Four models were estimated: M1 and M2, fitting the European and USA samples, respectively, and M3, fitting the pooled data of the two samples. A comparison of M3 log-likelihood versus (M1 log-likelihood + M2 log-likelihood) was used to test the null hypothesis that European and North American populations had identical age-at-onset density functions. M4 was a specific model with a common mean and a common standard deviation for both populations, but with different weights. This specific model was constructed to test the hypothesis that European and American population had the same Gaussian components, but with different frequencies. This model was estimated with a slightly modified version of the program: the standard program is based on a stochastic EM algorithm (Celeux and Diebolt 1990). It allows the means and standard deviations of each subgroup to vary independently. For this test, constraints have been added: means and standard deviations of all subgroups were equal, and only the subgroup frequencies were allowed to vary between subgroups. M4 was also compared with (M1 + M2) in a maximum likelihood ratio test.

Results

Theoretical age-at-onset function for the USA and European samples

The European sample consisted of 3616 bipolar I patients (1603 male and 2013 female patients). Mean (±SD) age at interview was 44.02 ± 13.2 years, mean AAO was 28.8 ± 10.9 years and mean disease duration was 15.3 ± 11.2 years (Table I). The model that best fitted the observed distribution of AAO was a mixture of three subgroups with the following characteristics (mean ± SD (proportion)): 19 ± 2.7 years (24.8%), 27.2 ± 6.3 years (50.7%), 41.8 ± 10.7 years (24.5%)) (Table II, Figure 1).

The USA sample consisted of 2275 bipolar I patients (812 male and 1463 female patients). Mean (± SD) age at interview was 40.8 ± 11.7 years, mean AAO was 20.03 ± 10.4 years and mean duration of illness was 20.7 ± 12 years (Table I). The model that best fitted the observed distribution of AAO for the USA sample was also a mixture of three subgroups with the following characteristics (mean ± SD (proportion)): 14.5 ± 4.9 years (63%), 26.5 ± 7.6 years (28.5%), 39.5 ± 12.5 years (8.5%) (Table II, Figure 2).

Table I. Characteristics of the US and the European samples.

	EU sample ($n = 3616$)	US sample ($n = 2275$)	P value
Male/female ratio			
n	1603/2013	812/1463	$P < 0.0001$
proportions	44.34/55.66	35.69/64.31	
Age at interview			
Mean age (years)	44.02	40.8	$P < 0.0001$
SD	13.2	11.7	
Age at onset			
Mean age (years)	28.8	20.03	$P < 0.0001$
SD	10.9	10.4	
Disease duration			
Mean age (years)	15.3	20.7	$P < 0.0001$
SD	11.2	12	

Sex ratio, mean AAO, mean age at interview and mean duration of illness were significantly different between the two samples (Table I). Age-at-onset functions were significantly different between the USA and European samples ($\chi^2 = 1457$, df = 8, $P < 10^{-14}$). The proportions of subjects in each age-at-onset (AAO) subgroup differed significantly between the two samples ($\chi^2 = 874.9$, df = 2, $P < 10^{-10}$) (Table II). We also investigated whether the significance of the difference between the two AAO models resulted from differences in proportions only, or differences in both proportions and mean AAO for the theoretical subgroups. We showed that both the means of each subgroup and the proportion of subjects in each subgroup differed between the two samples ($\chi^2 = 323$, df = 6, $P < 10^{-3}$). These differences principally reflected differences in the early-onset subgroup (differences in means), the characteristics of the other two subgroups (intermediate and late onset) being very similar in the two samples (in terms of mean values obtained).

Table II. Models best fitting the observed distribution of age at onset in the European and North American samples.

	EU sample ($n = 3616$)	US sample ($n = 2275$)
Early-onset subgroup		
Mean age at onset (years)	19	14.5
SD	2.7	4.9
Proportion	24.8%	63%
Intermediate-onset subgroup		
Mean age at onset (years)	27.2	26.5
SD	6.3	7.6
Proportion	50.7%	28.5%
Late-onset subgroup		
Mean age at onset (years)	41.8	39.5
SD	10.7	12.5
Proportion	24.5%	8.5%

Comparison of the distribution of early-, intermediate- and late-onset subjects, defined according to the theoretical models: $\chi^2 = 874.9$, df = 2, $P < 10^{-10}$).

We calculated the probability of belonging to each subgroup for each patient. The patients were then grouped, with each patient assigned to the subgroup to which he or she had the highest probability of belonging. This process made it possible to identify suitable age cut offs for distinguishing between the early-, intermediate- and late-onset subgroups. In the USA sample, the cut offs between early- intermediate and intermediate-late onset were 22 and 40 years, respectively. In the European sample, the cut offs between early-intermediate and intermediate-late onset were 21 and 37 years, respectively.

Discussion

The theoretical age-at-onset function was similar between the European and USA samples with the best fitting model being a mixture of three subgroups with similar cut off points separating the early- and the intermediate-onset groups and the intermediate- and late-onset groups. This suggests that the underlying theoretical model is the same, and is consistent with several previous reports in populations of different origins demonstrating the existence of three age-at-onset subgroups in bipolar I disorder (Bellivier et al. 2001, 2003; Lin et al. 2006; Manchia et al. 2008; Hamshere et al. 2009; Ortiz et al. 2011; Tozzi et al. 2011). However, significant differences between the USA and European samples were observed for the early-onset subgroup (a higher proportion of subjects belonged to this group and the mean AAO was lower in the USA). The intermediate- and late-onset subgroups had similar characteristics in the two samples, suggesting that the factors accounting for these differences are (i) specific to the early-onset subgroup and (ii) both quantitative and qualitative.

Our finding that more than 60% of USA bipolar I patients belong to the early-onset subgroup is highly consistent with other results obtained for the USA population, as reported by Perlis et al. (2004) (66% of bipolar I patients with disease onset during childhood or adolescence), Lish et al. (1994) (59% of bipolar I patients with an onset before the age of 20) and Lin et al. (2006) (79% with an onset before the age of 21). The European rate – less than half that in the USA, with 28.5% of the sample of bipolar I patients belonging to the early-onset subgroup – is again highly consistent with previous results obtained in various European populations: 30.3% of patients with an onset before the age of 20 in the study by Baldessarini et al. (2010), 47% with an onset before the age of 22 in the study by Hamshere et al. (2009), 38% with an onset before the age of 18 in the study by Larsson et al. (2010), 36% with an onset before the age of 20 in the study by Manchia et al. (2008) and 27.9% with an onset before

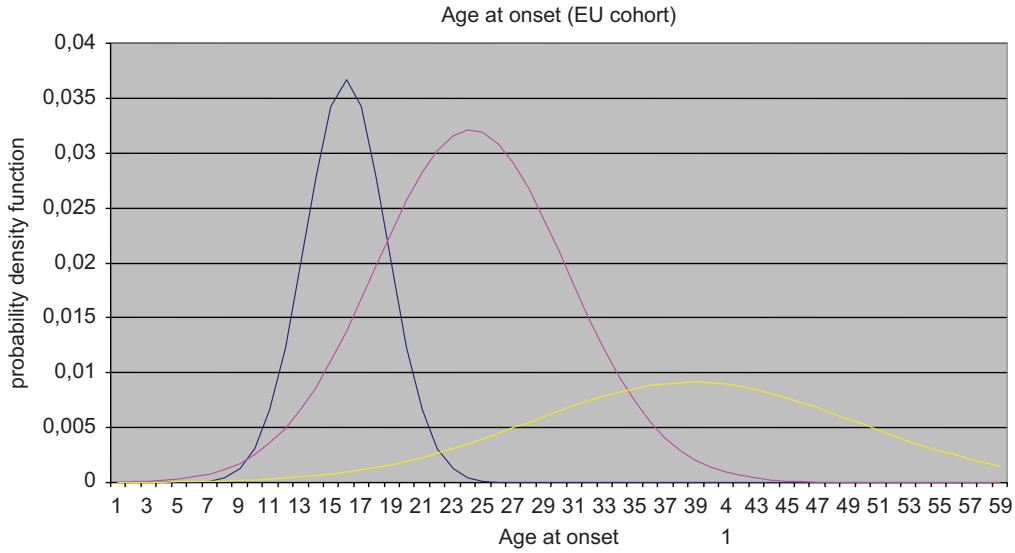

Figure 1. Theoretical age-at-onset function in the European sample.

the age of 21 in the study by Bellivier et al. (2003). There is one recent study that reported conflicting findings, with an earlier AAO in Europe than in the USA, but this discrepancy may be accounted for by differences in both the sampling (bipolar I and II patients were included) and recruitment strategy used in the USA (Baldessarini et al. 2010).

Several possible limitations should be discussed with regard to the interpretation of our results. Recall biases and errors in measurement during the retrospective assessment of AAO have been discussed at length in previous reports, but there is little reason to suspect that these alone could account for the differences observed between the USA and Europe. There is a theoretical possibility that the USA sample remembered age of first onset of psychiatric symptoms that were not affective disorders and retrospectively attributed all the symptoms to the onset of a mood episode rather than disorders that frequently precede mood episodes in those at risk of bipolar disorders such as conduct or sleep disorders (Kim-Cohen et al. 2003). However, against this notion is the fact that similar differences in AAO were obtained in studies using the same ascertainment strategy and assessment procedures for samples for the USA and Europe (Post et al. 2008, 2011). Moreover, these differences are consistent with those observed in prospective studies of childhood clinical

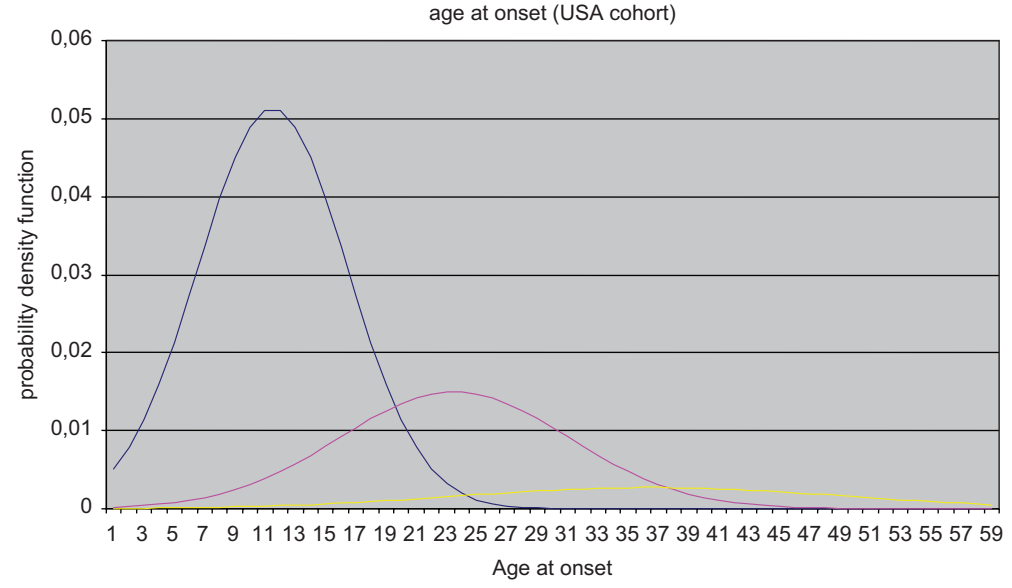

Figure 2. Theoretical age-at-onset function in the US sample.

psychiatric populations (Pavuluri et al. 2005; Soutullo et al. 2005) and in studies of populations at high risk (Reichart and Nolen 2004; Chang et al. 2000).

There may be differences in recall bias between the two samples due to differences in the mean age at interview leading to age-related forgetting (the risk of failing to recall the first episode experienced) or post-dating (attributing a later age of onset to the first episode). The European group were older at interview than the USA group (mean age 44 ± 13.2 vs. 40.8 ± 11.7 years) and mean AAO was lower in the USA sample than in the European sample (20 ± 10.4 vs. 28.8 ± 10.9 years), whereas the mean duration of the illness was much lower in the European sample (15.3 vs. 20.7 years). The possibility that this explains some of the findings cannot be totally excluded but again this would require that this phenomena was so prevalent in the European group that it masked other effects – we therefore suggest it is unlikely to truly explain the degree of difference. Furthermore, if there really was an effect of recall bias, it would also be expected to affect the intermediate- and late-onset subgroups, whereas this was only true for the early onset group. A birth cohort effect to explain the observed differences (da Silva Magalhaes et al. 2009) is unlikely for the same reason (namely that the shift of AAO would be expected to be observed for all subgroups).

Cultural differences or differences in how clinicians rate symptoms or accessibility to specialized mental health care, between the USA and the Europe, may contribute to the differences observed (Carlson 2011). In particular, it has been shown that clinician's and rater's culture may have an important impact on diagnostic accuracy of mania (Mackin et al. 2006). Psychometric properties of diagnostic tools may also vary across cultures (Mellsop et al. 2007). In addition, during the last decade in the USA, the huge reported increase of the proportion of outpatient attendees diagnosed with bipolar disorder in youth is compatible with over-diagnosis of some clinical presentations, e.g., affective instability being misclassified as bipolar disorder (Moreno et al. 2007). However, the recent USA findings do not explain the phenomena seen in the samples we recruited, as they had been service users for two to three decades prior to the studies of Moreno and others. We suggest that cultural factors and clinical ratings might influence the agreement for the diagnosis of an episode, but are less likely to influence agreement for a specific disorder, especially when lifetime history is rated using systematic structured interview schedules and trained assessors. In this study we are dealing with bipolar patients with several years of evolution and we think that both in the USA and in Europe, the diagnostic confidence of "bipolar I disorder" is high. As noted recently by Carlson (2011), possible selection bias and how representative are the populations studied, are important issues in cross-national comparative studies. For the USA sample, individuals referred themselves following a call for participation to The Stanley Center for Innovative Treatment of Bipolar Disorder through which the registry data were collected. They came from as far as 150 miles away from Pittsburgh and were not part of the specialist mood clinic population. For this reason, a major selection bias is unlikely and it is also notable that this sample is representative of the cases recruited to the Stanley Center Bipolar Registry from across the whole of the USA. For the European sample, both sources of recruitment included consecutive clinical referrals (out- or in-patients). For this reason, a major selection bias is also unlikely. Finally, ascertainment bias due to differences in the health care system between the USA and Europe may have occurred. However, such bias can only explain the differences in proportion of early onset patients, it cannot account for the shift of mean AAO observed in the early onset subgroup only. In addition, in presence of ascertainment bias, the three age-at-onset subgroups are supposed to differ between samples. In our hands, only the early onset subgroup was different between the USA and Europe. In summary, whilst acknowledging possible differences in patient's recall and some aspects of assessment and sampling procedures, such factors do not fully explain the differences observed; below we discuss potential clinical and developmental explanations of our findings.

If these differences between the USA and Europe are real, then they may have several possible causes. Early onset bipolar I disorder is more familial and is associated with a higher genetic risk in bipolar disorder. The USA population may therefore display greater genetic loading, for which several mechanisms may be proposed: a higher risk of affective illness in those who migrated from Europe to the USA, differences in health policy between the USA and Europe concerning women with bipolar I disorder having children, a higher rate of assortative mating (Post et al. 2008; Mathews and Reus 2001), the more rapid accumulation of vulnerability genes because of shorter intervals between reproductive generations. Various genetic mechanisms, such as anticipation (Lange and McInnis 2002), gene–environment interaction and gene–environment correlation, may also differ in importance between the USA and Europe. However, further investigations are necessary to prove or disprove the possible role of genetic mechanisms and the magnitude of any proposed genetic effect on these differences.

Environmental susceptibility factors associated with early onset in BP-I may also play different roles in the USA and Europe. Post et al. (2008, 2011) showed that the higher prevalence of childhood trauma in the USA was a factor that might potentially account for differences in AAO between Europe and the USA. As childhood trauma is associated with an earlier AAO of bipolar disorder (Leverich and Post 2006; Etain et al. 2008), our data are compatible with a differential implication of childhood trauma in the USA and in Europe. In a recent paper by Post et al. (2011), not only AAO and early environmental adversity were different between the USA and Europe but also rapid cycling, more than 20 prior episodes, comorbid anxiety and substance abuse disorders, and a positive parental history for an affective disorder. This further suggests important differences in the risk factor architecture between the USA and Europe. Other educational or stress factors and uncontrolled dietary factors may also be involved. Differences in precipitating factors may also result in differences in AAO in vulnerable subjects. These factors include the prescription of stimulants to children presenting with attention-deficit hyperactivity disorder (Reichart et al. 2004; Masi et al. 2006) as well as, higher rates of antidepressant use in children and adolescents in the USA. The higher frequency in the USA of substance misuse or differential drug use may have also played a role. Indeed, important regional differences in the frequency and the type of drug used may contribute to the differences observed on AAO as shown in a recent study (da Silva Magalhaes et al. 2009).

In summary, consistent results have been obtained suggesting that there are three age-at-onset subgroups in bipolar I disorder (theoretical age-at-onset function in independent samples and stability of the cut off ages). These findings indicate that the categorization of bipolar I disorder as a function of this onset variable is robust. This observation has several clinical and research implications. First, from a clinical point of view, AAO should be used as a specifier of bipolar I disorders in future diagnostic classifications, such as DMS-V, because it is probably a reliable indicator for delimiting different subgroups of patients with different clinical presentations, disease courses and therapeutic response profiles. It may also be useful for identifying important variables that could be used both in clinical treatment strategies and in public health preventive measures.

From the point of view of research, our findings deserve further investigation to provide clues to the reasons for the higher frequency of susceptibility and/or precipitating factors in the USA and, possibly, the higher frequency of protective factors in European populations. In that regard, epidemiological cross-national comparisons on bipolar disorders at a North American (e.g., USA versus Canada and/or versus Europe) or worldwide level should be conducted in the future to clarify if the differences in rates extend between and across continents. More generally, future studies should investigate whether age-at-onset subgroups can be explained by the involvement of specific susceptibility factors and/or factors influencing AAO (possibly independently of susceptibility to the disorder). Thus, future clinical and fundamental research studies and clinical trials should systematically consider AAO when exploring susceptibility/protective factors, clinical presentations, course, outcome and therapeutic profiles in bipolar I disorders.

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Statement of Interest

None to declare.

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