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Age-at-onset subsets of bipolar I disorders: A critical insight into admixture analyses

Claire Montlahuc^{1,2} | Emmanuel Curis^{1,3,4} | Sarah Flora Jonas^{3,4} | Frank Bellivier^{5,6,7} | Sylvie Chevret^{1,2}

¹Service de Biostatistique et Information médicale, Hôpital Saint Louis, AP-HP, Paris, France

²ECSTRA Team (Epidémiologie Clinique et Statistiques pour la Recherche en Santé), UMR 1153 INSERM, Université Paris Diderot, Sorbonne Paris Cité, Paris, France

³Laboratoire de biomathématiques, faculté de pharmacie, université Paris Descartes, Sorbonne Paris Cité, Paris, France

⁴VariaPsy UMR-S 1144, Université Paris Descartes, Sorbonne Paris Cité, Paris, France

⁵VariaPsy UMR-S 1144, Université Paris Diderot, Sorbonne Paris Cité, Paris, France

⁶Département de Psychiatrie et de Médecine Addictologique, GH Saint-Louis – Lariboisière – F. Widal, AP-HP, Paris, France

⁷Fondation FondaMental, CHU de Créteil, Créteil, France

Correspondence

Claire Montlahuc, Hôpital Saint Louis, 1 avenue Claude Vellefaux, 75010 Paris, France.
Email: claire.montlahuc@univ-paris-diderot.fr

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Abstract

Gaussian mixture analysis is frequently used to model the age-at-onset (AAO) in bipolar I disorder and identify homogeneous subsets of patients. This study aimed to examine whether, using admixture analysis of AAO, cross-sectional designs (which cause right truncation), unreliable diagnosis for individuals younger than 10 years old (which causes left truncation) and the selection criterion used for admixture analysis impact the number of identified subsets. A simulation study was performed. Different criteria – the likelihood ratio test (LRT), the Akaike information criterion (AIC), and the Bayesian information criterion (BIC) – were compared using no, left and/or right truncation simulated data. The error rate of each criterion (percentage of erroneous number of detected subsets) was estimated. An application to two real databases, including 2,876 and 1,393 patients, is provided. Without data truncation and regardless of the distribution of AAO, the LRT and the AIC had much higher error rates (12% and 33%, respectively) than the BIC (1%). For a homogeneous population, the error rate increased with the introduction of left truncation. This study shows that the number of subsets identified using admixture analysis may depend on the sample size, the selection criterion, and the study design.

KEYWORDS

admixture, age-at-onset, bipolar disorder, cross-sectional design, subsets

1 | INTRODUCTION

In psychiatric disorders such as type I bipolar disorder, the age-at-onset (AAO) is frequently used to identify homogeneous subsets of patients that share similar risk factors or pathophysiological processes (Leboyer, Henry, Paillere-Martinot, & Bellivier, 2005). To determine whether the type I bipolar population is homogeneous in regard to AAO, Bellivier, Golmard, Henry, Leboyer, and Schürhoff (2001) proposed an admixture analysis approach. The basic idea of admixture analysis is that the AAO distribution in the patient population is a mixture of distinct distributions (commonly assumed to be Gaussian) of AAO, one for each underlying subset, weighted by the relative prevalence of each subset, resulting in the so-called “Gaussian mixture model” (GMM) analysis. Several techniques can be used to determine the number of subsets in the mixture. In psychiatric applications, used techniques are primarily based on the likelihood ratio test

(LRT), which is assumed to be chi-square distributed. This widely used approach (Azorin et al., 2013; Bellivier et al., 2003, 2014; González Pinto et al., 2009; Hamshere et al., 2009; Manchia et al., 2008) consistently identified three different subsets in terms of the AAO of type I disorders, with slight differences in terms of mean and prevalence of these subsets (Figure 1).

Exploring AAO subsets of bipolar I patients aims, among other things, at determining patient profiles or predicting treatment response according to these subgroups; identifying them accurately and correctly is therefore a major issue. Furthermore some studies use AAO cutoff points defined in previously published admixture analyses studies to analyze age at onset subsets (Propper et al., 2015). However, several methodological issues regarding this method remain understudied. First, all the aforementioned studies used cross-sectional designs, including patients whose bipolar disorder has already been declared and diagnosed, with retrospective assessments of AAO.

FIGURE 1 Admixture analysis of age-at-onset (AAO) in type I bipolar disorder: a literature review

Although the advantage of cross-sectional studies is that diagnostic confidence is very high, such a study design might lead to sampling bias that influences the estimate of the AAO distribution. In particular, because the sample is composed only of patients with confirmed diagnosis, individuals who have not declared the disease and those who have not been diagnosed with the disease yet obviously cannot be included in the study. Therefore, the AAO is lower than the age-at-interview (AAI) by construction, leading to so-called “right data truncation”, with an over-representation of low AAO and an under-representation of late AAO (Figure 2). Moreover, episodes of bipolar disorder before the age of ten years old are difficult to diagnose accurately, particularly during retrospective interviews of adult patients (Bellivier et al., 2001; Carlson, 2011; Moreno et al., 2007); this difficulty results in left data truncation (Figure 2).

Second, the use of an asymptotic chi-square distribution for the LRT statistics has been criticized (McLachlan, 1987). Other approaches based on the Akaike information criterion (AIC) or the Bayesian information criterion (BIC) also exist that could be used.

Third, in admixture analyses, any distribution can be described as a Gaussian mixture (GM) with an infinite number of subsets. Therefore, the determined number of subsets may represent a trade-off among the sample size, the departure of the distribution from normality and the method used to detect the number of subsets with no link with the real number of subsets in the population.

Thus, the use of admixture analyses for studying type I bipolar disorder raises modeling and theoretical issues. Two of them are investigated in this article: (1) left and right truncations, as described earlier, that distort the observed distribution; (2) the criterion used to determine the number of subsets. The main objective of this study was to explore how these methodological issues influence the number of subsets identified in published papers that use admixture analyses to model the AAO distribution of type I bipolar disorders.

Using simulated data, we tested the number of subsets detected in different scenarios: no, left, right, and left and right truncations. For each scenario, three different methods to identify the number of subsets were compared: the LRT with an asymptotic three-degrees-of-freedom (3-df) chi-square distribution, the AIC, and the BIC. Two applications using real AAO data from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study and from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study are also presented.

2 | METHODS

2.1 | Gaussian mixture model (GMM)

Consider a population made of K distinct subsets, with the AAO of subset k ($k = 1, \dots, K$) distributed according to a Gaussian distribution with expectation μ_k and standard deviation σ_k , and let π_k be the prevalence of subset k (with $\sum_{k=1}^K \pi_k = 1$). In this population, the AAO is distributed as a GM with a probability density f given by the sum of Gaussian density of each subset weighted by their prevalence: $f(a) = \sum_{k=1}^K \pi_k N_k(a; \mu_k, \sigma_k)$, where a is the AAO and N_k is the Gaussian density of subset k . To achieve this, we have to, on the one hand, identify the number K of subsets of the mixture and on the other hand estimate the parameters of each underlying subsets.

When K is known, the most frequent method used to estimate the parameters (π_k, μ_k, σ_k) of each underlying subset is maximizing the likelihood using expectation-maximization (EM) algorithms. However, the situation in which the number K of subsets is known seldom occurs. Thus, its determination constitutes the first and main problem that arises in studies of mixture distributions. In the cited works regarding type I bipolar disorders, this determination was primarily

FIGURE 2 Right (a) and left (b) data truncation in cross-sectional studies that included bipolar disorder patients. (a) Patient A is included in the database; his age-at-onset (AAO) (18 years) is lower than his age-at-interview (AAI) (30 years). Patient B is not included in the database; his AAO (62 years) is greater than his AAI (56 years). (b) Patient A is included in the database; his AAO is greater than 10 years

made using either the LRT between models with K and $K + 1$ subsets, with p -values computed from a 3-df chi-square distribution, or by minimizing the AIC, that also relies on the data likelihood but includes a penalty that is an increasing function of the number of estimated parameters. However, both methods are known to perform badly for GMM (Delmas, 2003; Peel & McLachlan, 2000) for theoretical reasons and because of the small sample sizes. An alternate, simple, and common approach is the BIC, where the penalty term also incorporates the sample size.

2.2 | Simulation study

Assessing whether data truncation may influence the admixture analysis was done through a simulation study. The AAO law was first defined for the population, assumed to follow a GM with $K = 1$ (homogeneous, usual Gaussian distribution), $K = 2$, or $K = 3$ underlying subsets. The parameters of these GMs were chosen to mimic previous literature results as indicated in Table 1. The resulting law was used to randomly generate AAO for N patients ($N = 100,000$). For each patient, a random AAI was also generated using a uniform distribution over [15–70] given the observed age distribution of the French population.

Then, four scenarios of data truncation were applied: (1) no truncation; (2) left truncation obtained by replacing all patients with AAO < 10 years with newly generated patients until all patients had AAO > 10 years; (3) right truncation obtained by replacing all patients whose AAO > AAI; and (4) both left and right truncations obtained by combining (2) and (3). Scenario (4) was assumed to be the closest to the Bipolar I cross-sectional studies published in the literature so far. Finally, $M = 10,000$ independent random samples of ($n = 150, 200, 250, 300, 350, 400, 500$, up to 2,000) patients were drawn from these N patients. The sample sizes correspond to the sample sizes found in articles addressing AAO.

In each of these M samples, admixture analysis (using GMM) was performed, using an EM algorithm to estimate the parameters of each subsets of the AAO distribution, assuming 1, 2, 3 or 4 subsets. The detected number of subsets, K' , was based on either one of three criteria, the LRT with an asymptotic 3-df chi-square distribution, the AIC, or the BIC, then compared to the actual number of subsets of the theoretical AAO distribution, K . The focus was on detecting the correct number of subsets, that is selecting $K' = K$. The error rate of a given method was defined as the percent of erroneous number of subsets detected by the method, either higher or lower than the actual number of subsets in the 10,000 samples. All analyses were performed using the R statistical software package version 3.0.2 (available at: <http://www.R-project.org>) with the R function “normalmixEM” from the package mixtools (Benaglia, Chauveau, Hunter, & Young, 2009).

2.3 | Application

2.3.1 | EMBLEM database

We used data from the EMBLEM study, which is a prospective observational study conducted across 14 European countries and designed to estimate the outcomes of pharmacological treatment in patients with bipolar I disorder who had been diagnosed with at least one manic or mixed episode. A total of 3,459 adult patients were enrolled. The AAO was determined retrospectively and defined by the age at which the first mood episode (manic, hypomanic or depressive) occurred.

TABLE 1 Error rate in detecting the number of admixture subsets according to criterion used for various simulated scenarios based on samples of 1,000 patients

Age-at-onset distribution	Criteria for admixture analysis		
	LRT 3-df	BIC	AIC
Gaussian homogeneous population $\mu = 29, \sigma = 11$			
No truncation	12.2%	1.0%	33.9%
Left truncation	96.9%	92.6%	100%
Right truncation	10.8%	1.0%	32.5%
Left and right truncations	97.3%	92.5%	100%
Gaussian mixture of two subsets $\mu_1 = 18, \sigma_1 = 3, \mu_2 = 40, \sigma_2 = 10, \pi_1 = 0.5$			
No truncation	12.5%	0.2%	31.7%
Left truncation	14.4%	0.1%	35.8%
Right truncation	12.9%	0.1%	34.1%
Left and right truncations	15.8%	0.1%	40.3%
$\pi_1 = 0.66$			
No truncation	12.0%	0.1%	31.4%
Left truncation	16.0%	0.2%	40.5%
Right truncation	12.0%	0.2%	32.9%
Left and right truncations	15.0%	0.15%	39.6%
Gaussian mixture of two subsets $\mu_1 = 18, \sigma_1 = 3, \mu_2 = 25, \sigma_2 = 6, \pi_1 = 0.5$			
No truncation	13.8%	0.5%	34.5%
Left truncation	22.9%	0.5%	51.2%
Right truncation	13.8%	0.5%	34.4%
Left and right truncations	23.0%	0.5%	51.2%
$\pi_1 = 0.66$			
No truncation	14.0%	0.3%	34.1%
Left truncation	21.5%	0.3%	50.9%
Right truncation	13.0%	0.2%	33.6%
Left and right truncations	21.7%	0.3%	50.9%
Gaussian mixture of three subsets $\mu_1 = 18, \sigma_1 = 3, \mu_2 = 25, \sigma_2 = 6, \mu_3 = 40, \sigma_3 = 10, \pi_1 = 0.2, \pi_2 = 0.3, \pi_3 = 0.5$			
No truncation	22.4%	60.5%	31.9%
Left truncation	22.7%	34.7%	35.7%
Right truncation	22.7%	61.0%	32.5%
Left and right truncations	23.6%	35.8%	37.5%
Gaussian mixture of three subsets $\mu_1 = 15, \sigma_1 = 3, \mu_2 = 35, \sigma_2 = 7, \mu_3 = 60, \sigma_3 = 11, \pi_1 = 0.2, \pi_2 = 0.3, \pi_3 = 0.5$			
No truncation	17.8%	3.9%	25.4%
Left truncation	18.8%	3.9%	25.9%
Right truncation	90.5%	64.4%	92.7%
Left and right truncations	91.3%	65.5%	93.5%

Note: AIC, Akaike information criterion; BIC, Bayesian information criterion; df, degree of freedom; LRT, likelihood ratio test.

Further details regarding the EMBLEM study have been published elsewhere (Goetz et al., 2007; Haro et al., 2006; Vieta et al., 2008).

2.3.2 | NESARC database

The Wave 1 of the NESARC database is a nationally representative face-to-face survey of 43,093 respondents aged 18 years and older

conducted in 2001 and 2002. The objective of the NESARC database was to describe prevalence and comorbidity of DSM-IV alcohol and drug use disorders and independent mood and anxiety disorders. The AAO was determined retrospectively and defined by the age at which the first mood episode (manic, hypomanic or depressive) occurred, that is the minimum age between first manic or hypomanic episode and first depression episode. Further details regarding the NESARC study are described elsewhere (Grant et al., 2003, 2004). A total of 2,419 bipolar patients including 1,411 had a bipolar I disorder, were enrolled.

3 | RESULTS

The simulation results are summarized in Table 1. Figure 3 ($K = 1$), and Figure S1, Supporting Information ($K = 2$) and Figure S2, Supporting Information ($K = 3$), show for each truncation scenario (none, left, right,

both) and according to different sample sizes the error rate of each given method to select the number of subsets.

3.1 | No truncation

In the absence of truncation, that is, in the ideal case when the data indeed come from a GM distribution, the number of detected subsets depends on the selection criterion: the chi-square LRT statistic and the AIC performed poorly in detecting the actual number of subsets compared with the BIC (regardless of whether the actual distribution was homogeneous or not). In both cases, the error rate of the chi-square LRT statistic was approximately 12%, whereas that of AIC reached approximately 33% (Table 1; Figure 3 and Figure S1, Supporting Information). In contrast, the BIC error rate was at most 1%. When the LRT criterion was wrong in detecting more than one subset, it indicates mostly that a two subsets model fitted better (around 90% of the

FIGURE 3 Distribution of the number of detected subsets and the false positive error rate in detecting the number of mixture subsets according to the criterion and the sample size when the age-at-onset (AAO) is distributed as a Gaussian homogeneous population ($K = 1$, $\mu = 29$, $\sigma = 11$)

cases), whereas the AIC detected two subsets in around 45% of the cases, three in 32% of the cases and even four in 23% of the cases. These results were not markedly affected by the sample size (Figure 3). When the true distribution was homogeneous but the estimation procedure falsely selected two subsets, these two subsets always framed the actual density, as illustrated by their mean values (approximately, 22 for the first subset and 35 for the second subset, which should be compared with 29, the mean of the actual homogeneous distribution; Figure S3, Supporting Information). When the true distribution of AAO was composed of two subsets, the incorrect number of subsets was mostly greater than the actual number of subsets, whatever the criterion used (Figure S1, Supporting Information).

When the true distribution of AAO was heterogeneous and composed of three subsets, the BIC performed less well than the AIC or the 3-df chi-square LRT when the sample size was less than 500. Whereas the BIC tended to underestimate the number of subsets, the AIC tended to overestimate the number of subsets. For the BIC, the error rate decreased with the sample size, whereas the AIC was less influenced by the sample size (Figure S1, Supporting Information).

3.2 | Left and right truncations

Introducing data truncations heavily modified previous results. With regard to a homogeneous population ($K = 1$), left truncation had much more important effects than right truncation. In addition, when the sample size exceeds 500, the use of the LRT or AIC yielded the false conclusion of a heterogeneous population in more than 90% of the cases and the estimated number of underlying subsets increased with the sample size reaching for example for the AIC, four detected subsets instead of one, in around 80% of the cases when the sample size equals 2,000 (Figure 3).

With regard to a heterogeneous population, comparable results were found when considering two Gaussian subsets, although the error rates were lower, most likely because with this model, the probability of $AAO < 10$ years is smaller, thus diminishing the left-truncation effects. However, all criteria error rates were still more influenced by left truncation than by right truncation (Figure S1, Supporting Information).

When the AAO was distributed as a GM of three subsets, left truncation did not markedly modify the error rate of the chi-square LRT statistic and the AIC. The error rate of the BIC decreased to approximately 1% when left truncation was applied and the sample size was equal to 2,000. For all criteria, right truncation did not modify the results relative to the no-truncation case (Figure S2, Supporting Information). Just as when no truncation applied, the BIC tended to underestimate the actual number of subsets in the GM, while the AIC tended to overestimate it.

3.3 | Applications

3.3.1 | EMBLEM database

Of the 3,459 patients, 583 (16.8%) patients were excluded because of missing AAO values. Among the 2,876 remaining patients with bipolar I disorder, the median AAI was 43 years [interquartile range (IQR): 35–54], and the median AAO was 28 years [IQR: 21–35]. Figure 4 shows the observed distribution of AAO (Figure 4A) and the

best-fitting AAO mixture model according to the selection criterion (Figure 4B). Both the AIC and the LRT detected four subsets with similar mean $\pm$ standard deviation (and prevalence of the subset), namely 19.3 ± 2.4 years (22.0%), 27.1 ± 4.9 years (42.4%), 38.1 ± 2.9 years (5.0%) and 39.9 ± 12.1 years (30.5%). In contrast, using the BIC, the model that best fitted the observed AAO was a GM with three subsets: 19.5 ± 2.4 years (21.2%), 27.5 ± 5.7 years (45.3%), and 39.6 ± 11.7 years (33.6%). Note that the difference in the number of detected subsets appeared related to the intermediate subset (located at 27.5 years), separated into two subsets by the LRT and the AIC (at 27.1 and 38.1 years, respectively), whereas the extreme subsets (one located at 19 years and the other at 40 years) appeared relatively independent of the criterion used.

3.3.2 | NESARC database

Of the 1,411 subjects with a bipolar I disorder, 18 (1.3%) were excluded due to missing AAO values. Among the 1,393 remaining subjects, the median AAI was 36 years [IQR: 26–48], and the median AAO was 20 years [IQR: 15–29]. As mentioned with the EMBLEM database, the AIC criterion and the LRT detected four subsets with the following parameters: the mean $\pm$ standard deviation, (proportion of the population) values were 17.3 ± 6.6 years (55.0%), 15.8 ± 1.9 years (9.9%), 32.6 ± 10.6 years (33.8%) and 67.7 ± 7.7 years (1.3%). Using the BIC, the model that best fitted the observed AAO was a GM with three subsets: 16.4 ± 5.7 years (60.3%), 31.1 ± 9.9 years (37.1%), and 58.7 ± 11.8 years (2.6%) (Figure 4D). When subjects younger than 10 years old ($n = 106$, 7.6%) were excluded, the admixture analysis based on the AIC criterion even detected five subsets.

4 | DISCUSSION

Our study investigated the admixture analysis for AAO in bipolar type I disorders. We showed that characteristics of the data due to a cross-sectional design or lack of reliable diagnosis accuracy in childhood that result in right and left data truncation are likely to have a major impact on the number of detected subsets.

Such admixture analyses based on cross-sectional designs have been widely applied in other settings, notably type II bipolar disorders (Bauer et al., 2010; Ortiz et al., 2011; Tozzi et al., 2011), suicide attempts (Blasco-Fontecilla et al., 2012; Slama et al., 2009), obsessive compulsive disorders (Anholt et al., 2014; Delorme et al., 2005; De Luca, Gershenson, Burroughs, Javadi, & Richter, 2011), panic disorders (Tibi et al., 2013), schizophrenia (De Luca et al., 2012; Liu, Norman, Manchanda, & De Luca, 2013; Panariello et al., 2010; Schürhoff et al., 2004; Vinokur, Levine, Roe, Krivoy, & Fischel, 2014), and major depressive disorders (Zhu et al., 2012). Given that large prospective follow-up studies are difficult to conduct and must address non-specific premorbid psychopathologies and diagnostic uncertainty, cross-sectional designs are particularly popular in psychiatry. In contrast with the influence of right truncation induced by this cross-sectional sampling, which remains somewhat low, at least in our model, the left truncation of patients aged less than 10 years old was more influential on the results of the admixture analysis. This result suggests that such a situation violates the assumption of an underlying mixture of Gaussian

FIGURE 4 Distributions of age-at-onset (AAO) in bipolar I affective disorder: (a) observed distribution of AAO in the EMBLEM study; (b) theoretical distribution of AAO in the EMBLEM study; (c) observed distribution of AAO in the NESARC study; (d) theoretical distribution of AAO in the NESARC study

subsets because the first subset is left-truncated as a result of the low likelihood of diagnosis in childhood (Delmas, 2003; McLachlan, 1987). Whether this impossibility is a consequence of our limited ability to accurately diagnose bipolar disorders in youth or refers to the low frequency of this disease in children remains an open issue.

From a practical point of view, our study shows that both of the most frequently used criteria to select the number of subsets in this setting, namely the 3-df chi-square LRT and the AIC, tend to overestimate this number. Given that the 3-df chi-square LRT is the leading method in admixture analysis among populations with bipolar I disorder, these results raise an issue regarding previously published findings. Our results suggest that the BIC should be preferred especially if the sample size is small and two subsets are suspected, as also reported by a recent study of admixture analysis in the same setting (Li et al., 2014) and in other settings (Preacher, Zhang, Kim, & Mels, 2013).

Some limits to our study can be noted. First, we used some heterogeneous GM distributions in various scenarios with different parameters for the location and dispersion (for example, choosing the larger of two differences between mean parameters of two subsets, thus possibly making it easier to detect distinct subsets) among the infinitely

potential distributions; other choices may have possibly modified the results; note that with AAO in bipolar I disorder, possibly the most difficult case occurs when there is only a small difference between the mean parameters of distinct subsets. Secondly, we generated left and right data truncation using a uniform distribution of AAI that was assumed to be close to the distribution of age of the French population (except for children younger than 10 years old, excluded from the sampling); nevertheless, the data truncation phenomenon in studying bipolar I disorder is possibly more complex than those simulated in this paper. Of note, estimation of AAO distributions in disorders with variable onset have been studied (Heimbuch, Matthysse, & Kidd, 1980) but only taking into account right truncation and assuming a Gaussian distribution and never to our knowledge assuming GMMs nor left truncation which appears to have a stronger impact on the number of detected subsets than right truncation. Moreover, we showed that, when left and right truncations scenario – data structure scenario which seems to be the closest scenario to the one of studies in bipolar I disorder – was applied, truncation had an impact on the number of detected subsets. Third, we considered only Gaussian AAO distributions, either homogeneous or not, though this assumption may not

hold. Further research is needed to explore which AAO distribution is the most appropriate. Moreover, determining retrospectively AAO is not straightforward and can suffer from recall bias and inaccurate determination of AAO; for example in other domain such as cigarette smoking reported age of onset can suffer from “forward telescoping” (Johnson & Schultz, 2005). Nevertheless, existence of these biases, should not change the result of the paper, which is that admixture analysis of AAO is more sensitive to the sample size, the characteristics of the data and the criterion used to define the number of subsets than on the underlying number of subsets. These biases, distorting the underlying distribution, only worsen the situation. As shown by the considerable number of articles on this topic, the question of identifying subsets of bipolar I disorder subjects remains particularly relevant to help with the identification of specific pathophysiological processes in bipolar I disorders. The majority of studies in the literature were consistent with the identification of three subsets of patients regarding AAO of bipolar I disorders; however, we need to carefully interpret these results because they could be more closely related to the sample size, the sampling design, or the choice of criterion rather than the existence of three truly different clinical-phenotype subsets of patients. González Pinto et al. (2009) already pointed the fact that even if they found, using admixture analyses, three subgroups of patients regarding AAO, clinical analysis showed that the early and intermediate onset groups had no significant differences for any of the clinical variables studied, which according to them was in favor of the existence of two different AAO groups instead of three. Moreover, Consoli et al. (2007) identified a GM of two AAO subgroups using admixture analysis which may be explained in part by the population sample which was different from other studies including patients with Cotard's syndrome with comorbid bipolar disorder but probably also by the very small sample of the study ($n = 27$), in fact too small to allow fitting any model with more than two subsets. Our simulated results indeed already showed that the number of detected subsets depends on the sample size (Consoli et al., 2007). Thus, future studies that model AAO in bipolar I disorder using admixture analyses should critically consider the interpretation of their results, especially regarding the number of identified subsets. They should also discuss the criterion used to determine the number of subsets and the potential impact of the structure of the data (such as data truncation). Finally—and unfortunately—it appears unreasonable to conduct birth cohorts to avoid any truncation of data because bipolar disorder is rare, and the AAO varies widely among patients. Thus, methods to account for data truncation in this setting should be developed.

In summary, this study noted that for admixture analyses applied to psychiatric settings, the use of the LRT with a chi-square distribution and the use of AIC as selection criteria should be avoided. It also suggests that rather than a sampling procedure based on a cross-sectional survey, the lack of diagnosis in childhood may artificially result in heterogeneity.

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DECLARATION OF INTEREST STATEMENT

The authors have no competing interests.

REFERENCES

- Anholt, G. E., Aderka, I. M., van Balkom, A. J. L. M., Smit, J. H., Schruers, K., van der Wee, N. J. A., ... van Oppen, P. (2014). Age of onset in obsessive-compulsive disorder: Admixture analysis with a large sample. *Psychological Medicine*, 44(1), 185–194. doi:10.1017/S0033291713000470
- Azorin, J.-M., Bellivier, F., Kaladjian, A., Adida, M., Belzeaux, R., Fakra, E., ... Golmard, J.-L. (2013). Characteristics and profiles of bipolar I patients according to age-at-onset: Findings from an admixture analysis. *Journal of Affective Disorders*, 150(3), 993–1000. doi:10.1016/j.jad.2013.05.026
- Bauer, M., Glenn, T., Rasgon, N., Marsh, W., Sagduyu, K., Munoz, R., ... Whybrow, P. C. (2010). Association between age of onset and mood in bipolar disorder: Comparison of subgroups identified by cluster analysis and clinical observation. *Journal of Psychiatric Research*, 44(15), 1170–1175. doi:10.1016/j.jpsychires.2010.04.009
- Bellivier, F., Etain, B., Malafosse, A., Henry, C., Kahn, J.-P., Elgrabli-Wajsbrot, O., ... Leboyer, M. (2014). Age at onset in bipolar I affective disorder in the USA and Europe. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*, 15(5), 369–376. doi:10.3109/15622975.2011.639801
- Bellivier, F., Golmard, J. L., Henry, C., Leboyer, M., & Schürhoff, F. (2001). Admixture analysis of age at onset in bipolar I affective disorder. *Archives of General Psychiatry*, 58(5), 510–512.
- Bellivier, F., Golmard, J.-L., Rietschel, M., Schulze, T. G., Malafosse, A., Preisig, M., ... Leboyer, M. (2003). Age at onset in bipolar I affective disorder: Further evidence for three subgroups. *The American Journal of Psychiatry*, 160(5), 999–1001.
- Benaglia, T., Chauveau, D., Hunter, D., & Young, D. (2009). mixtools: An R package for analyzing finite mixture models. *Journal of Statistical Software*, 32, 1–29.
- Blasco-Fontecilla, H., Alegria, A. A., Delgado-Gomez, D., Legido-Gil, T., Saiz-Ruiz, J., Oquendo, M. A., & Baca-Garcia, E. (2012). Age of first suicide attempt in men and women: An admixture analysis. *The Scientific World Journal*, 2012, 825189. doi:10.1100/2012/825189
- Carlson, G. A. (2011). Will the child with mania please stand up? *The British Journal of Psychiatry: the Journal of Mental Science*, 198(3), 171–172. doi:10.1192/bjp.bp.110.084517
- Consoli, A., Soultanian, C., Tanguy, M.-L., Laurent, C., Perisse, D., ... Cohen, D. (2007). Cotard's syndrome in adolescents and young adults is associated with an increased risk of bipolar disorder. *Bipolar Disorders*, 9(6), 665–668. doi:10.1111/j.1399-5618.2007.00420.x
- De Luca, V., Gershenson, V., Burroughs, E., Javaid, N., & Richter, M. A. (2011). Age at onset in Canadian OCD patients: Mixture analysis and systematic comparison with other studies. *Journal of Affective Disorders*, 133(1–2), 300–304. doi:10.1016/j.jad.2011.03.041
- De Luca, V., Zai, C., de Souza, R., Polsinelli, G., Teo, C., Shinkai, T., ... Kennedy, J. L. (2012). Admixture analysis of age at onset in schizophrenia: Genetic association study of 45 candidate loci. *Schizophrenia Research*, 134(2–3), 288–290. doi:10.1016/j.schres.2011.11.011
- Delmas, C. (2003). On likelihood ratio tests in Gaussian mixture models. *Sankhyā: The Indian Journal of Statistics (2003–2007)*, 65(3), 513–531.
- Delorme, R., Golmard, J.-L., Chabane, N., Millet, B., Krebs, M.-O., Mouren-Simeoni, M. C., & Leboyer, M. (2005). Admixture analysis of

- age at onset in obsessive-compulsive disorder. *Psychological Medicine*, 35(2), 237–243.
- Goetz, I., Tohen, M., Reed, C., Lorenzo, M., Vieta, E., & EMBLEM Advisory Board (2007). Functional impairment in patients with mania: baseline results of the EMBLEM study. *Bipolar Disorders*, 9(1–2), 45–52. doi:10.1111/j.1399-5618.2007.00325.x
- González Pinto, A., Barbeito, S., José Díaz, F., Vega, P., Mosquera, F., López, P., ... de León, J. (2009). Age at onset in bipolar I disorder: Two may be better than three subgroups. *Revista de Psiquiatría y Salud Mental (English Edition)*, 2(1), 29–34. doi:10.1016/S1888-9891(09)70711-6
- Grant, B. F., Dawson, D. A., Stinson, F. S., Chou, P. S., Kay, W., & Pickering, R. (2003). The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV): Reliability of alcohol consumption, tobacco use, family history of depression and psychiatric diagnostic modules in a general population sample. *Drug and Alcohol Dependence*, 71(1), 7–16
- Grant, B. F., Stinson, F. S., Dawson, D. A., Chou, S. P., Dufour, M. C., Compton, W., ... Kaplan, K. (2004). Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of General Psychiatry*, 61(8), 807–816. doi:10.1001/archpsyc.61.8.807
- Hamshere, M. L., Gordon-Smith, K., Forty, L., Jones, L., Caesar, S., Fraser, C., ... Smith, D. J. (2009). Age-at-onset in bipolar-I disorder: Mixture analysis of 1369 cases identifies three distinct clinical sub-groups. *Journal of Affective Disorders*, 116(1–2), 23–29. doi:10.1016/j.jad.2008.10.021
- Haro, J. M., van Os, J., Vieta, E., Reed, C., Lorenzo, M., Goetz, I., & EMBLEM Advisory Board (2006). Evidence for three distinct classes of “typical”, “psychotic” and “dual” mania: Results from the EMBLEM study. *Acta Psychiatrica Scandinavica*, 113(2), 112–120. doi:10.1111/j.1600-0447.2005.00692.x
- Heimbuch, R. C., Matthysse, S., & Kidd, K. K. (1980). Estimating age-of-onset distributions for disorders with variable onset. *American Journal of Human Genetics*, 32(4), 564–574.
- Johnson, E. O., & Schultz, L. (2005). Forward telescoping bias in reported age of onset: An example from cigarette smoking. *International Journal of Methods in Psychiatric Research*, 14(3), 119–129.
- Leboyer, M., Henry, C., Paillere-Martinot, M.-L., & Bellivier, F. (2005). Age at onset in bipolar affective disorders: A review. *Bipolar Disorders*, 7(2), 111–118.
- Li, R., Perneczky, R., Yakushev, I., Förster, S., Kurz, A., Drzezga, A., ... Alzheimer's Disease Neuroimaging Initiative (2014). Gaussian mixture models and model selection for [18F] fluorodeoxyglucose positron emission tomography classification in Alzheimer's disease. *PloS One*, 10(4), e0122731. doi:10.1371/journal.pone.0122731
- Liu, J. J., Norman, R. M. G., Manchanda, R., & De Luca, V. (2013). Admixture analysis of age at onset in schizophrenia: Evidence of three subgroups in a first-episode sample. *General Hospital Psychiatry*, 35(6), 664–667. doi:10.1016/j.genhosppsych.2013.07.002
- Manchia, M., Lampus, S., Chillotti, C., Sardu, C., Ardu, R., Severino, G., & Del Zompo, M. (2008). Age at onset in Sardinian bipolar I patients: Evidence for three subgroups. *Bipolar Disorders*, 10(3), 443–446. doi:10.1111/j.1399-5618.2007.00572.x
- McLachlan, G. J. (1987). On bootstrapping the likelihood ratio test statistic for the number of components in a normal mixture. *Journal of the Royal Statistical Society. Series C (Applied Statistics)*, 36(3), 318–324. doi:10.2307/2347790
- Moreno, C., Laje, G., Blanco, C., Jiang, H., Schmidt, A. B., & Olfson, M. (2007). National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Archives of General Psychiatry*, 64(9), 1032–1039. doi:10.1001/archpsyc.64.9.1032
- Ortiz, A., Bradler, K., Slaney, C., Garnham, J., Ruzickova, M., O'Donovan, C., ... Alda, M. (2011). An admixture analysis of the age at index episodes in bipolar disorder. *Psychiatry Research*, 188(1), 34–39. doi:10.1016/j.psychres.2010.10.033
- Panariello, F., O'Driscoll, L., de Souza, R. P., Tiwari, A., Manchia, M., Kennedy, J., & De Luca, V. (2010). Age at onset in Canadian schizophrenia patients: Admixture analysis. *Schizophrenia Research*, 122(1–3), 278–279. doi:10.1016/j.schres.2009.10.024
- Peel, D., & McLachlan, G. J. (2000). Robust mixture modelling using the t distribution. *Statistics and Computing*, 10(4), 339–348.
- Preacher, K. J., Zhang, G., Kim, C., & Mels, G. (2013). Choosing the optimal number of factors in exploratory factor analysis: A model selection perspective. *Multivariate Behavioral Research*, 48(1), 28–56. doi:10.1080/00273171.2012.710386
- Propper, L., Ortiz, A., Slaney, C., Garnham, J., Ruzickova, M., Calkin, C. V., ... Alda, M. (2015). Early-onset and very-early-onset bipolar disorder: Distinct or similar clinical conditions? *Bipolar Disorders*, 17(8), 814–820. doi:10.1111/bdi.12346
- Schürhoff, F., Golmard, J.-L., Szöke, A., Bellivier, F., Berthier, A., Méary, A., ... Leboyer, M. (2004). Admixture analysis of age at onset in schizophrenia. *Schizophrenia Research*, 71(1), 35–41. doi:10.1016/j.schres.2004.02.002
- Slama, F., Courtet, P., Golmard, J. L., Mathieu, F., Guillaume, S., Yon, L., ... Bellivier, F. (2009). Admixture analysis of age at first suicide attempt. *Journal of Psychiatric Research*, 43(10), 895–900. doi:10.1016/j.jpsychires.2009.01.007
- Tibi, L., van Oppen, P., Aderka, I. M., van Balkom, A. J. L. M., Batelaan, N. M., Spinhoven, P., ... Anholt, G. E. (2013). Examining determinants of early and late age at onset in panic disorder: An admixture analysis. *Journal of Psychiatric Research*, 47(12), 1870–1875. doi:10.1016/j.jpsychires.2013.09.001
- Tozzi, F., Manchia, M., Galwey, N. W., Severino, G., Del Zompo, M., Day, R., ... Muglia, P. (2011). Admixture analysis of age at onset in bipolar disorder. *Psychiatry Research*, 185(1–2), 27–32. doi:10.1016/j.psychres.2009.11.025
- Vieta, E., Panicali, F., Goetz, I., Reed, C., Comes, M., Tohen, M., & EMBLEM Advisory Board (2008). Olanzapine monotherapy and olanzapine combination therapy in the treatment of mania: 12-week results from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) observational study. *Journal of Affective Disorders*, 106(1–2), 63–72. doi:10.1016/j.jad.2007.05.009
- Vinokur, D., Levine, S. Z., Roe, D., Krivoy, A., & Fischel, T. (2014). Age of onset group characteristics in forensic patients with schizophrenia. *European Psychiatry: The Journal of the Association of European Psychiatrists*, 29(3), 149–152. doi:10.1016/j.eurpsy.2012.11.006
- Zhu, T., De Luca, V., Gallagher, L. A., Woldeyohannes, H. O., Soczynska, J. K., Szymkowicz, S., ... McIntyre, R. S. (2012). Admixture analysis of age at onset in major depressive disorder. *General Hospital Psychiatry*, 34(6), 686–691. doi:10.1016/j.genhosppsych.2012.06.010

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