Key findings on bipolar disorders from the longitudinal FondaMental Advanced Center of Expertise-Bipolar Disorder (FACE-BD) cohort

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Abstract

Background: The FACE-BD cohort is an observational cohort of individuals with bipolar disorders (BD) who benefited from a systematic evaluation with evidence-based treatment recommendations and who were followed-up every year for 3 years in France. The objectives were to describe the lifetime course of BD, associated psychiatric and somatic comorbidities, and cognition profile. This cohort aims to identify clinical/biological signatures of outcomes, trajectories of functioning and transition between clinical stages. This article summarizes 10 years of findings of the FACE-BD cohort.

Method & Results: We included 4422 individuals, all having a baseline assessment, among which 61.2% had at least one follow-up visit at either one, two or three years. A subsample of 1200 individuals had at least one biological sample (serum, plasma, DNA). Assessments include family history of psychiatric disorders, psychiatric diagnosis, current mood symptoms, functioning, hospitalizations, suicidal attempts, physical health, routine blood tests, treatment history, psychological dimensions, medico-economic data and a cognitive assessment. Studies from this cohort illustrate that individuals with BD display multiple coexistent psychiatric associated conditions including sleep disturbances, anxiety disorders, substance use disorders and suicide attempts as well as a high prevalence of metabolic syndrome. During follow-up, we observed a 55% reduction of the number of days of hospitalization and a significant improvement in functioning.

Conclusions: The FACE-BD cohort provides a strong research infrastructure for clinical research in BD and has a unique position among international cohorts because of its comprehensive clinical assessment and sustainable funding from the French Ministry of Health.

Keywords: Bipolar disorders, cohort, longitudinal, course, biomarkers, environment

Introduction

Bipolar disorder (BD) is the 16th leading cause of disability[1] and is associated with a reduction of ~10 years of life expectancy compared to the general population. BD has thereby a high impact on health care utilization, societal costs, and public health. Despite this fact, research focused on individuals with BD has consistently been, and remains, underfunded compared to other research fields.

Longitudinal cohorts with repeated assessment of clinical, psychological, cognitive, and functional measures are needed to better understand the complexity of BD and examine the dynamics of the course of the disorder. In 2010, this has led the FondaMental Foundation (www.fondation-fondamental.com) to build a health and research infrastructure by setting-up a network of 10 centres of expertise for BD, which are located in the main cities in France (Besancon, Bordeaux, Clermont-Ferrand, Creteil, Grenoble, Marseille, Monaco, Montpellier, Nancy, Paris and its suburban cities). FondaMental is a non-profit foundation, created in 2007 under the auspices of the French Ministry of Research and supported by the Ministry of Health to improve mental health care organization, to foster clinical and fundamental research, as well as to inform and educate the lay public about psychiatric disorders. A pivotal goal was to create and coordinate a network of centers of expertise in BD, which aims to provide extensive and standardized assessments for individuals with BD, including psychiatric, somatic, psychological, cognitive and functional assessments. Such assessments are then utilized to more precisely describe the most prominent difficulties encountered by individuals with BD and to establish a personalized care plan based on proof-of-concept international recommendations[1]. The assessment and follow-up data collected on individuals with BD in the FondaMental Foundation centers allowed the set-up of a follow up cohort, named the "FondaMental Advanced Centers of Expertise-Bipolar Disorder (FACE-BD)" cohort. The first individual has been included in 2009 and the FACE-BD cohort was officially launched in 2013.

The main goals of the FACE-BD cohort are to: 1) describe the lifetime course of BD and its psychiatric and somatic comorbidities (baseline data); 2) finely characterize the inter-episode phases for residual mood symptoms, emotion regulation, sleep disturbances, cognitive profile and functioning; 3) identify clinical/biological signatures predictive of outcomes (hospitalizations, relapses, and suicide attempts), of trajectories of functioning and of transition between clinical stages; 4) evaluate the cost effectiveness of implementing this new care organization in France.

This article summarizes 10 years of clinical research using the FACE-BD cohort [2].

Which individuals are included in the FACE-BD cohort?

FACE-BD is an open, ongoing cohort of individuals with BD who are clinically assessed at inclusion and annually followed-up for at least 3 years. In January 2021, the FACE-BD cohort comprised of 4421 participants, all having had a baseline assessment. Referrals are received from either general practitioner (11.7%), psychiatrists (45.0% private practice – 38.0% public or hospital-based practice), or by self-referral/patient associations (5.3%).

While individuals are assessed at each expert centre at baseline, 6 month and then every year, routine care and treatment prescriptions are still undertaken by the treating psychiatrists (and GPs). Evidence-based recommendations for both pharmacological treatments and non-pharmacological interventions are sent to the psychiatrists and GPs following each visit. Each individual and his/her psychiatrist are encouraged to use a shared-decision approach, and to discuss together which interventions they are willing to implement (in terms of medications and psychosocial interventions). As a whole, 89% of psychiatrists completely or partially followed the pharmacological recommendations, and 11% did not follow the recommendations. Regarding non-pharmacological treatment, 80% of psychiatrists completely or partially followed the recommendations, and 20% did not follow the recommendations. Reasons for not following the recommendations include for instance the patient's refusal, the psychiatrist's disagreement with the recommendations, tolerance issues, or the inability to implement some recommendations (for instance when a recommended psychosocial intervention is not available in the catchment area the individual is living in).

Inclusion criteria require individuals to meet DSM-IV criteria for any BD subtype (I, II, or not otherwise specified, NOS). Exclusion criteria are restricted to ongoing severe mood episode, dementia-related disorders or mental retardation. Most individuals are women (61.8%). DSM-IV subtypes are BD-I (45.4%, n=2006), BD-II (43.3 %, n=1914), BD-NOS (11.3%, n=501). The mean age at inclusion is 40.5 years old (sd=13.0), and 48.8% of individuals are married or in a stable relationship. Most participants (71.0%) have a high school diploma. Unemployment rate at assessment was 21.1%, being significantly higher than the national average (around 8-10%). The demographic, socioeconomic and clinical characteristics of the sample are described in tables 1 and 2.

How often have individuals been followed up?

Individuals are followed-up annually for at least 3 years. Among the 4421 individuals included at baseline, 2496 had at least one follow-up visit at either one, two or three years with a retention rate of 61.2%. The mean duration of follow-up is 26.5 month (sd=17) (median=25). The mean number of assessments is 3 (sd=1.9) (median=3).

Individuals lost at follow-up, compared to those remaining in the cohort, were younger and more frequently diagnosed with BD-NOS, had higher depressive symptoms, lower functioning, and greater levels of comorbidities (tobacco misuse, substance misuse, and sleep disturbances) at initial assessment. Individuals lost at follow-up were also treated at baseline with a higher number of psychiatric medications [3].

What are the measures used in the FACE-BD cohort?

All collected data are entered into a specifically developed, web-based application, "e-Bipolar". Access to e-Bipolar is strictly and carefully regulated, with approval obtained from the French data protection agency (CNIL DR-2011-069). All data collected in each center are anonymized and exported annually into a national database. Table 3 shows the main measures used during the assessment and follow-up.

At baseline, individuals are assessed by a multidisciplinary team, trained for the diagnosis and management of BD, including nurses, psychiatrists, psychologists and neuro-psychologists [2]. The assessment tools and the generated measures during follow up are described in table 3. Assessments include the following domains:

- Physical examination: weight, height, BMI (Body Mass Index), abdominal perimeter, electrocardiogram, blood pressure, routine blood tests,
- Somatic comorbidities, assessed from a list of 35 possible comorbidities, including neurological, cardiovascular, endocrine, metabolic, skin, urinary tract, liver and digestive disorders, allergic and auto-immune-inflammatory disorders, cancer and chronic infectious disorders,
- Family history of mood disorders, alcohol misuse, dementia and metabolic syndrome,
- Psychiatric diagnosis (SCID, DSM-IV criteria), including BD, anxiety disorders, substance use disorders (SUD), eating disorders,
- Mood symptoms: depressive and manic symptoms (self and observer-rated measures), anxiety symptoms, emotional and behavioral activation/inhibition,
- Life style: sleep disturbances and circadian rhythms, vigilance, diet, physical activity, tobacco dependence,
- Global functioning,
- Suicide ideation and suicidal attempts,
- Treatment history (drug and psycho-social), including plasma levels of anticonvulsants and lithium carbonate, as well as adherence to medication and side effects,

- Psychological dimensions: affect intensity, affective lability, impulsivity, hostility, childhood trauma, childhood ADHD symptoms (at baseline only),
- Cognition: verbal memory, working memory, executive functions, processing speed, attention and reasoning (at baseline and at two years),
- Biological samples: serum, plasma, DNA, RNA, PBMC (for a subsample only).

The following measures of outcomes are systematically recorded during follow-up: mood recurrences and relapses, hospitalizations, suicidal ideation and attempts, functioning, physical health (physical examination and blood routine test), use of health services, sick-leave.

Individuals may also be included in specific research programs based on collaborations between centers and several research teams involved in epidemiology, genetics, immunology, brain-imaging, ecological momentary assessment. These research programs take advantage of the extensive clinical assessment and the generated comprehensive phenotypic assessment.

Key findings and publications

Baseline clinical characteristics

The first description of the cohort was published in 2015 in a sample of 839 participants [4]. To date, 4421 individuals have been included and their clinical description is consistent with our previously published works. At inclusion, most of individuals (76.2%) were not in an acute mood episode, but were considered as having a sub-syndromal remission. Residual symptoms were prevalent with a mean MADRS score of 10.8 (9.2) and a mean YMRS score of 2.5 (3.8). Impaired functioning was observed in 48% of individuals. Sixty percent of these individuals had sleep disturbances (PSQI score >5) and 50% were overweight or obese.

This clinical description shows that individuals experienced at baseline a wide range of dysfunction across different measures (including mood residual symptoms, sleep disturbances, functional impairment ...), which require screening, treatment and follow-up. We have modelled the links between these measures at baseline (sleep, functioning, affective/mood symptoms, metabolic health). We identified associations between: 1) emotional reactivity, sleep disturbances and functioning[5]; 2) sleep disturbances and childhood trauma[6]; 3) emotional reactivity, cardiometabolic risk, elevated inflammation (C-reactive protein [CRP] and allostatic load) and functioning [7–10].

Psychiatric comorbidities and suicide attempts

Psychiatric comorbidities are highly prevalent in BD. Data from the FACE-BD cohort confirmed that individuals have multiple coexisting psychiatric conditions. Around 44% have comorbid anxiety

disorders and 32.8% have comorbid substance misuse, with 25% showing alcohol misuse and 20% showing cannabis misuse.

Cigarette smoking was a very frequent comorbidity (49%) in this cohort, with current smokers more likely to have additional substance use disorders and to be diagnosed with BD-I[11]. Individuals with severe tobacco dependence have a threefold higher incidence of suicide attempts [12].

Lifetime history of suicide attempts is highly frequent in BD, with 38% of individuals having attempted suicide over their lifetime. Individuals reporting poor sleep quality had more suicide attempts and suicidal ideation than good sleepers [6]. In depressed participants, baseline clinical features (e.g. depression severity, childhood trauma, global functioning) were more severe in participants with, versus without, suicidal depression [13].

All of these psychiatric comorbidities are potentially linked to psychopathological dimensions of vulnerability, including emotional dysregulation and impulsivity/hostility. Both suicide attempts and SUD were linked to impulsivity [14]. We demonstrated that the links between childhood trauma and suicide attempt were mainly mediated by affective intensity/lability while the links between childhood trauma and SUD were mainly mediated by impulsivity/hostility [15].

In summary, these findings confirmed the high prevalence of psychiatric comorbidities, in particular substance use disorders, as well as suicide attempts in individuals with BD [16,17]. We further demonstrate the existence of some dimensional mediators making the links between early life stress and these associated conditions, that has been further replicated[18].

Medical comorbidities

Physical health is a major concern in BD. Physical comorbidities are common, especially metabolic syndrome (MetS), but also a number of other medical conditions, which are suggested to contribute to decreased life expectancy in BD. In this cohort, only 8.4% of individuals with BD presented with no medical disorder, whilst 53.0% had at least two medical comorbidities at baseline. The most frequent medical comorbidities were hypercholesterolemia (49%), hypertriglyceridemia (22%), headache/migraine (20%), allergies (other than asthma) (19.7%), and hypertension (19%).

MetS prevalence is particularly high in individuals with BD (20% in this cohort versus 10% in the French general population). MetS is under-treated with more than 70% of the individuals with BD and MetS receiving no specific treatment [19]. We also estimated the prevalence of non-alcoholic fatty liver disease (NAFLD) on blood samples using the fatty liver index (FLI), showing a NAFLD prevalence of 28.4% which is two time higher than in the general population in France. NAFLD was independently associated with older age, male gender, sleep disturbances, and current use of atypical antipsychotics or anxiolytics, being overweight and having MetS [20].

Metabolic health was worse in individuals with an evening chronotype who also had higher levels of triglycerides [21] and a higher atherogenic index of plasma (the log transformed ratio of triglycerides to HDL-cholesterol). Individuals with a seasonal pattern of recurrences (33% of participants) also

showed higher levels of obesity, fasting glucose, triglycerides and systolic blood pressure [22]. Low-grade of peripheral inflammation, as defined by Hs-CRP>3mg/L, was found in one third of individuals with BD, with CRP elevations being associated with cardiovascular risk factors (specifically perivisceral fat) and with impaired general cognitive functioning [23].

In summary, findings are consistent with the available literature showing a high prevalence of somatic and cardio-vascular comorbidities in BD[24,25]. Importantly, the network provided new data regarding the NAFLD prevalence in this cohort[20], which has not been studied so far in BD and was reported as a high level in this cohort (40% of men and 21% of women).

Psychotropic medications

Management of psychotropic medications is still challenging in BD. This arises from a number of reasons, including prescribers in France having a tendency not to follow current prescribing international guidelines. Also, the response to medications may be suboptimal in many individuals, often attributed to treatment resistance, poor adherence and high levels of side effects. Such factors are likely to reflect the need to improve targeted biological treatment of an individual's pathophysiology, which may vary over the course of neuroprogression and clinical staging.

Of the 4421 individuals within the FACE-BD database, the mean number of psychotropic medications received at inclusion was 2.2 (±1.2). The most frequently prescribed classes of mood stabilizers were anticonvulsants (51%), followed by atypical antipsychotics (39.8%) and lithium carbonate (33.2%). Importantly, a high percentage of participants (39%) were receiving antidepressants at baseline, which contravenes international guidelines.

At inclusion, 47.8% of individuals were poorly adherent to medication [26,27]. Residual depressive symptoms and side effects were the main determinants of poor adherence, with gender, a smaller number of previous mood episodes and a shorter duration of BD also contributing to poor adherence [26,27], as does a non-planning impulsivity trait.

In summary, we identified that most individuals were currently treated with medication regimes that may not follow available guidelines for BD. Adherence to medication is still a challenge for many individuals with BD, possible being determined by multiple factors that may offer avenues for targeted interventions. One future challenge for data analysis is to disentangle the different trajectories of medication changes during the follow-up to extract those changes that may predict better outcomes.

Cognition

One of the strengths of the FACE-BD cohort is the comprehensive and systematic cognitive assessment at baseline and at year 2. This assessment is particularly important since a substantial proportion of individuals with BD have cognitive complaints and/or cognitive deficits that may impact many aspects of functioning. In addition, cognitive deficits can be targeted by cognitive and functional remediation as part of the care plan.

The study of a sub-sample of the cohort (based on strict inclusion criteria for analyses, mainly euthymia) have identified cognitive alterations in BD. Using a clustering analysis including six domains of cognition (motor speed, attention, executive functions, verbal memory, working memory, intellectual functioning), four clusters of participants were identified. The four clusters were defined by good performances to all tests (13%); low performances on all tests (29%), with two further groups showing intermediate clusters (57%)[28]. When using different classification criteria, the prevalence of cognitive impairment ranged from 4% (when at least two impaired cognitive domains were evident) to 66.8% (at least one measure of any cognitive domain <1.5 SD below the normative mean). The method with satisfactory psychometric properties, good convergent and concurrent validity suggested a prevalence of 12.4% for cognitive impairment in euthymic individuals with BD [29]. A path analyses modelled the relationships between residual depressive symptoms, six cognitive domains and functioning [30]. Only verbal and working memories were significantly associated with better functioning while residual depressive symptoms were associated with poorer functioning. No significant relationship was found between residual depressive symptoms and any cognitive component.

In summary, our results confirm the existence of several distinct cognitive profiles in individuals with BD[31,32]. However, we report a lower prevalence of cognitive impairment as compared to levels observed in previous studies[33,34], suggesting that only a subgroup of individuals with BD (12.4% and using stringent criteria for the definition of cognitive impairment and euthymia) would indeed experience a cognitive impairment.

Prediction of outcomes: BD course and trajectories

Follow-up data in the FACE-BD cohort allow the prediction of outcomes (i.e. recurrences, suicide attempts or hospitalizations) and the modelling of trajectories (functioning, adherence or cognition).

We reported results of outcomes after 2 years of follow-up of the first 984 adult patients[3]. When comparing 1 year before inclusion versus during the follow-up period, we observed significant decreases - above 50% - in the number of mood episodes, the number of hospitalizations and the duration of hospitalizations. The decrease in number of days being hospitalized during follow-up may be explained by a better adherence to medication (see paragraph below about trajectories of adherence), a better adequation with evidence-based medication regime (see section about psychotropic medications), but also by participation (at least for some individuals) to psychoeducation groups that are organized in each centre[35]. In addition, individuals showed a significant improvement in functioning, this improvement being associated with a reduction of mood symptoms and of active psychiatric comorbidities, an improvement of sleep quality and a better treatment adherence.

Regarding adherence to medication, we identified three distinct trajectories: one trajectory starts poorly and keeps deteriorating (4.8%); one trajectory starts poorly but improves (9%); and the last one

starts well and keeps improving (86.2%). A good tolerance to psychotropic medications, low depressive symptoms, and prescription of anticonvulsants were associated with better adherence [36].

Regarding suicidality, individuals with high affect lability were more likely to report suicidal ideation during follow-up [37], whilst anhedonia predicted suicide events in the subgroup of participants who were depressed at baseline [38].

As a major episode is typically observed every two years over the course of BD, prediction of mood recurrences is important to tailor the care plan. We studied the time to a first mood recurrence in 630 individuals with BD-I and 505 with BD-II over a 3 years follow-up. The first recurrence of any polarity occurred earlier in BD-II than in BD-I. In BD-I, the time to a first mood recurrence was associated with depressive symptoms, lifetime rapid cycling, global behavioral activation and the number of psychotropic medications at baseline. In BD-II, the time to a first recurrence was associated with a younger age at BD onset and a higher number of lifetime mood episodes [39].

We also identified different trajectories of global functioning during the follow-up. A stable trajectory of impaired functioning was associated with unemployment, depressive symptoms, sleep disturbances, overweight, and childhood maltreatment, as well as higher numbers of prescribed psychotropic medications and of previous hospitalizations [40]. The longitudinal relationships between cognition and functioning in BD at two years supports a causal model in which cognition moderately predicts, and is causally primary, to functional outcome at the subsequent 1year time-point, whereas psychosocial functioning does not predict later cognitive performance. Subthreshold depressive symptoms concurrently affected functioning at each measurement time-point [41].

In summary, we confirmed that more than a half of individuals with BD will experience a mood recurrence during the follow-up period[42] and that functional impairment is frequent in BD, these latter results being consistent with those obtained in cross-sectional studies[43–45], but replicated here with a longitudinal design. Importantly, we have further suggested that the time to recurrence was poorly accurately predictable when using clinical variables extracted from the interview. As noted more than a decade ago by Treuer and Tohen[46], "forecasting the course of BD is challenging and still largely relies on clinical characteristics that together make only a modest contribution to the prediction of recurrences". Conversely, we have shown that, as compared to the prediction of recurrence, the prediction of trajectories of functioning might be accurate and highly informed by the clinical assessment. Future studies are planned to explore what are the main determinants of the reduction observed in terms of hospitalized days, which may partly due to better adequation with evidence-based medication regime, better adherence to medication, and participation to psychoeducation groups that are provided in each centre. As mentioned above, one future challenge for data analysis is to disentangle the different trajectories of medication changes during the follow-up to extract those changes that may predict better outcomes.

Cost analysis

We used a cross-sectional design to estimate the cost of BD per year among individuals in the cohort. Direct health care costs (i.e. full time hospitalization, day care hospitalization, consultations with a psychiatrist, medications) were calculated for each patient (n= 1116). Direct health care costs were €7565 per patient annually (Laidi et al. submitted). The cost of full-time hospitalization, consultations and medication represented respectively 80%, 13% and 7% of direct healthcare costs. In the subsample of individuals followed-up for two years, a decrease of direct healthcare cost was estimated to be between 30-50%, indicating the cost-effectiveness of this network.

Lessons learned, challenges and future directions

FACE-BD is the first large cohort to be set-up in France with an initial in-depth phenotyping and a long-term follow-up of individuals with BD. It provides specific information on the trajectories of BD in the clinical, cognitive, biological and economic domains. This cohort is based on a national network of Expert Centers, which provide a standardized evaluation and implementation of research projects. The database is centralized, providing a good quality and an easy access for research purpose.

Lessons learned: We demonstrate that the implementation of such a network at the national level is feasible. Each centre has established strong links to local health services and clinicians (psychiatrists but also general practitioners) who provide the first point of contact with health services for most individuals with BD. The centres offer wide access for all individuals with BD with few barriers for referral and no major biases towards treatment-refractory cases. In order 1) to ensure harmonization of clinical assessments and scoring procedures, 2) to provide regular reviews of evidence-based recommendations and clinical guidelines, 3) to set-up an effective implementation of psychosocial interventions (such as group psychoeducation) and 4) to promote research efforts, monthly meetings are organized, at which all centers attend to (including psychiatrists, psychologists, neuropsychologists). Moreover, two-days schools are organized twice a year (spring and autumn) to foster dense and intense collaborations and experience-sharing between centers. Regarding the use of the database, the valorization is organized in several complementary work-packages with one leading center per work-package. As a consequence, the FACE-BD cohort, involving several clinical teams from all over the country, has a positive effect in the development and coordination of clinical research in BD in France.

Challenges: Nevertheless, Expert centers are third line facilities. It has consequences in term of potential recruitment bias and representativeness of the collected sample which has to be taken into account when considering the generalizability of the results. Although supported by funding from the Ministry of Health, the sustainability of the network depends of the support of policy makers and public health priorities. BD may be characterized by a low level of adherence to follow-up, this may

have consequences in terms of attrition rate in the cohort (around 40%) and need a close monitoring. The increase in recruitment rates during previous years may induce issues for the clinicians who need to ensure at the same time both new inclusions and follow-up visits.

Futures directions: Futures directions will include extension of the network with a greater national coverage. The implementation of molecular tools (such as "omics") and brain imaging is also a challenge to be able in the next future to develop new biomarkers that would complement the clinical assessments to better predict outcomes and trajectories and to help moving forward personalized medicine. Finally, recent modifications in French health laws may provide opportunities to link these cohort data with medical administrative database which could allow exhaustive collection of resources use, professional and health status and will be very relevant for medical costs issues.

Access to data of the FACE-BD cohort

Sharing data within the network and as part of collaborations are strong values of our network. A charter describing data access, rules (composition of the submission file, evaluation of the request, and transmission of the data) and publication policies (authorship, acknowledgements) have been established and are available on our web site (www.fondation-fondamental.org).

An external request from academic labs who are not members of the FondaMental network, requires a Confidential Disclosure Agreement (CDA) and a Material Transfer Agreement (MTA) to be signed. For external requests from private companies, a CDA and a partnership agreement have to be signed. If approved by our Scientific Committee, these extractions of data can be used, analyzed and results can be published under the supervision of the Scientific Committee and in association with the network coordinators.

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M. Leboyer, PM Llorca, E. Olie and B. Etain: Conceptualization, Funding acquisition, Project administration, Writing - original draft. **All others authors:** Conceptualization, Writing - review & editing. All authors have approved the final article

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Table 1: Demographic, socioeconomic and clinical characteristics of the FACE-BD sample at inclusion

	All FACE-BD cohort N=4421
***Demographic* characteristics**	
Age at inclusion (years), mean (sd)	40.5 (13.0)
< 30	1077 (24.4)
30 - 40	1198 (27.1)
40 - 50	1045 (23.6)
>50	1101 (24.9)
Gender n (%)	
Male	1688 (38.2)
Female	2733 (61.8)
***Socio-economic* characteristics**	
Education (years), mean (sd)	14.1 (2.9)
Marital status n (%)	
Maried	1763 (48.8)
Separated/divorced	423 (11.7)
Widowed	23 (0.6)
Single	1405 (38.9)
Occupational status n (%)	
Unemployed	1875 (52.5)
Employed	1694 (47.5)
Baseline clinical factors	
Bipolar subtype n (%)	
Type I	2006 (45.4)
Type II	1914 (43.3)
Type NOS	501 (11.3)
Duration of illness (years), mean (sd)	16.8 (11.2)
Age at onset (years), mean (sd)	23.7 (9.6)
Number of lifetime episodes, mean (sd)	8.9 (9.6)
Rapid cycling, n (%)	614 (17.0)
Lifetime comorbidities	
Anxiety disorders n (%)	1706 (45.1)
Substance misuse (alcohol, cannabis, drugs) n (%)	1432 (37.4)
History of suicide attempt n (%)	1608 (39.0)
Somatic comorbidities	
Body Mass Index, mean (sd)	25.8 (5.4)
<25	2101 (51.0)
25-30	1251 (30.4)
>30	767 (18.6)
Sleep quality, mean (sd)	7.3 (3.8)
Sleep disturbances n (%)	2596 (63.1)
Current smokers, n (%)	1906 (46.3)
Childhood maltreatment, mean (sd)	43.0 (14.7)
Pharmacological treatments (based on 2760 individuals)	
Adherence to medication, mean (sd)	6.9 (2.0)
Lithium, n (%)	1037 (33.1)
Second generation antipsychotics, n (%)	1269 (40.5)
First generation antipsychotics, n (%)	785 (25.0)
Antidepressants, n (%)	1221 (38.9)
Anticonvulsants, n (%)	1569 (50.0)
Anxiolytics/hypnotics, n (%)	944 (30.1)

Table 2: Descriptive measures of depression, mania and health-related quality of life at baseline

	All FACE-BD cohort N=4421
Mood symptoms	
Depressive symptoms (MADRS), mean (sd)	10.8 (9.2)
Depressive symptoms (QIDS-16), mean (sd)	10.2 (6.1)
Manic symptoms (YMRS), mean (sd)	2.5 (3.8)
Manic symptoms (ASRM), mean (sd)	3.0 (3.6)
Functioning and quality of life	
Global functioning (FAST), mean (sd)	21.6 (14.7)
≤ 20 n (%)	2116 (51.6)
> 20 n (%)	1983 (48.4)
Global functioning (GAF), mean (sd)	65.7 (14.0)
Severe (≤50) n (%)	607 (15.9)
Moderate (≤60) n (%)	1014 (26.6)
Mild (≤70) n (%)	943 (24.7)
No (>70) n (%)	1250 (32.8)
Quality of life %(EQ5D), mean (sd)	63.5 (21.4)

MADRS: Montgomery and Asberg Depressive Rating scale; QIDS: Quick Inventory of *Depressive* Symptomatology (self-report); YMRS: Young Mania Rating Scale, ASRM: Altman Self-Rating Mania(self-report); GAF: Global Assessment of Functioning scale, FAST: Functioning Assessment Short Test

Table 3: Overview of the assessment package employed by the FACE-BD cohort.

Phenotypic class	Measures/Process	Timing in the cohort
BD diagnosis and course	DSM-IV criteria, SCID	Baseline
BD diagnostic interview	Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID)	Baseline
BD lifetime characterization	SCID	Baseline
Current symptomatology		
Manic symptoms	Young Mania Rating Scale (YRMS)	Baseline, 6 month, annually
	Altman Mania Rating Scale (AMRS)	Baseline, 6 month, annually
Depressive symptoms	Montgomery Asberg Depression Rating Scale (MADRS)	Baseline, 6 month, annually
	Inventory of Depressive Symptoms-Self-Rating (QIDS-SR 16)	Baseline, 6 month, annually
Anxiety	Spielberger Anxiety Scale (STAY-A)	Baseline, 6 month, annually
Multi-dimensional assessment	Multi-dimensional Assessment of Thymic States (MATHYS)	Baseline, 6 month, annually
Functioning and severity of disorder		
Global functioning	Global Assessment of Functioning scale	Baseline, 6 month, annually
Social functioning	Functioning Assessment Short Test (FAST)	Baseline, 6 month, annually
Severity of the illness	Clinical Global Impressions Scale (CGI)	Baseline, 6 month, annually
Psychiatric comorbidities and childhood trauma		
Current and past comorbidities	SCID	Baseline, 6 month, annually
Childhood history of ADHD	Wender Utah Rating Scale (WURS)	Baseline
Childhood history of trauma	Childhood Trauma Questionnaire (CTQ)	Baseline
Suicidal behaviour		
Personal history of suicide attempts	Suicide Intent Scale (SIS)	Baseline
Characterization of most violent and lethal attempt	Risk Rescue Rating Scale	Baseline
Assessment of suicidal feelings	Measure of suicidal Ideation (ISF)	Baseline, 6 month, annually
Medical burden and risk factors		
Medical comorbidity	e-bipolar© (checklist adapted from Pittsburgh medical inventory)	Baseline, 6 month, annually
	Fageström questionnaire	
Smoker status/nicotine dependence	Weight, height, BMI, blood pressure, waist measurement, ECG	Baseline, 6 month, annually
Physical examination	Liver, thyroid and renal functions, lipids, blood glucose, blood count,	Baseline, 6 month, annually
Biochemistry screen	CRP, serum level of mood stabilizer	Baseline, 6 month, annually
Sleep disturbances and vigilance		
Quality of sleep	Pittsburgh Sleep Quality Index (PSQI)	Baseline, 6 month, annually
Vigilance scale	Epworth Vigilance Scale	Baseline, 6 month, annually
Treatment		
Pharmacological		
Current and past psychotropic agents and/or somatic treatment	e-bipolar© checklist organized by drug classes (adapted from the Theriaque list)	Baseline, 6 month, annually
Adherence	Medication Adherence Rating Scale (MARS) and serum level of mood	Baseline, 6 month, annually
Side effects	disorders	
Psychosocial Interventions	Prise-M	Baseline, 6 month, annually
	e-bipolar© checklist (CBT, Psychoeducation, IPSRT, etc.)	Baseline, 6 month, annually
Inter-episode assessment		
Emotional reactivity	Affect Intensity Measure (AIM), Affective Lability Scale (ALS)	Baseline
Impulsivity/hostility	Barrat Impulsiveness Scale version 10 (BIS-10), Buss and Durkee Hostility Inventory (BDHI)	Baseline
Chronotype	Composite Scale of Morningness (CSM), circadian type inventory (CTI)	Baseline
Family history		
Psychiatric comorbidities and suicide behaviour	History in 1st degree relatives (mood disorders, schizophrenia, alcohol and substance misuse, suicide and suicide attempts, and dementia)	Baseline
Risk factors for metabolic syndrome	History in 1st degree relatives of diabetes, hypertension, obesity and dyslipidaemia	Baseline
Cognitive functioning		
Premorbid IQ and current level	WAIS-III (Vocabulary and Matrix reasoning)	Baseline, every two years
Verbal episodic memory	California Verbal Learning Test (CVLT)	Baseline, every two years
Working memory	WAIS-III (Digit Span)	Baseline, every two years
Processing speed	WAIS-III (Digit Symbol Substitution and Symbol Search)	Baseline, every two years
Attention	CPT II/CPT III	Baseline, every two years
Executive functions	Verbal Fluency, Stroop, Trail-Making (A and B) Tests	Baseline, every two years