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Subjects suffering from bipolar disorder taking lithium are less likely to report physical pain: a FACE-BD study

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Abstract

Background. Physical pain is a common issue in people with bipolar disorder (BD). It worsens mental health and quality of life, negatively impacts treatment response, and increases the risk of suicide. Lithium, which is prescribed in BD as a mood stabilizer, has shown promising effects on pain.

Methods. This naturalistic study included 760 subjects with BD (FACE-BD cohort) divided in two groups: with and without self-reported pain (evaluated with the EQ-5D-5L questionnaire). In this sample, 176 subjects were treated with lithium salts. The objectives of the study were to determine whether patients receiving lithium reported less pain, and whether this effect was associated with the recommended mood-stabilizing blood concentration of lithium.

Results. Subjects with lithium intake were less likely to report pain (odds ratio [OR] = 0.59, 95% confidence interval [CI], 0.35–0.95; $p = 0.036$) after controlling for sociodemographic variables, BD type, lifetime history of psychiatric disorders, suicide attempt, personality traits, current depression and anxiety levels, sleep quality, and psychomotor activity. Subjects taking lithium were even less likely to report pain when lithium concentration in blood was ≥0.5 mmol/l (OR = 0.45, 95% CI, 0.24–0.79; $p = 0.008$).

Conclusions. This is the first naturalistic study to show lithium's promising effect on pain in subjects suffering from BD after controlling for many confounding variables. This analgesic effect seems independent of BD severity and comorbid conditions. Randomized controlled trials are needed to confirm the analgesic effect of lithium salts and to determine whether lithium decreases pain in other vulnerable populations.

Introduction

Physical pain is highly prevalent in subjects suffering from bipolar disorder (BD) (~30%) [1]. Pain experienced by subjects suffering from BD seems to be mainly idiopathic (e.g. headache or chronic back pain) [1]. Pain worsens mental health and quality of life [2]. Indeed, subjects reporting pain have a longer time to remission [3], poorer treatment response [4], and higher suicidal rates [5]. Despite the large number of available pain-killer drugs, many subjects still report pain and experience high disability levels [6]. Opioids are among the most efficient analgesic drugs, but they have important side effects: substance use disorder, mood-altering effects, and higher suicide mortality [7–11].

Lithium is recommended and widely used in BD as a mood stabilizer. Some case reports show a promising effect of lithium on pain [12–14]. A randomized controlled trial (RCT) demonstrated that lithium reduces pain in subjects with spinal cord injury compared to placebo [15]. Moreover, lithium reduces pain in subjects with chronic cluster headaches [16, 17] and is recommended as a prophylactic treatment in this pathology [18]. Animal studies also support the lithium analgesic effect. In neuropathic rat models, lithium decreases thermal hyperalgesia, and mechanical and cold allodynia [19–22]. These effects are not observed when lithium is combined with naloxone, suggesting that it acts through the opioid system [20].

We hypothesized that (1) subjects suffering from BD and taking lithium are less likely to report physical pain (H1); and (2) subjects suffering from BD and with blood lithium concentration ≥ 0.5 mmol/l (that is the threshold recommended to observe the mood stabilizing effect) [23] are even less likely to report pain (H2).

Materials and methods

Study population

Participants were recruited from the FACE-BD cohort. This is a French prospective, naturalistic cohort of outpatients with BD enrolled at the advanced Centers of Expertise in Bipolar Disorder (CEBD) and coordinated by the FondaMental Foundation [24, 25]. Subjects are referred by a general practitioner or a psychiatrist to the expert center where they are evaluated and followed. Participants had a diagnosis of BD type I, II, or not otherwise specified, according to the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), were older than 18 years, and without ongoing severe mood episode at evaluation.

From all the subjects included in the database (n = 2,835), subjects with exhaustive baseline data (that is first evaluation at the CEBD) on pain levels, sex, age, depression level, sleep quality, and affectivity, lability, and intensity, impulsivity and hostility levels were selected (n = 977). Then, subjects treated with lithium but without available blood lithium measurements were excluded (n = 217). Therefore, the final sample included 760 subjects among whom 176 were treated with lithium salts. As treatment at baseline was the one prescribed by the referring physician (that is, current treating physician), the small number of participants taking lithium salts at inclusion could be explained by the current decrease in lithium prescriptions [26].

Assessments

From the database, the following data were extracted: sociodemographic variables (age, sex, marital status, education), current psychotropic medications, age at BD onset, number of thymic episodes, number of lifetime suicide attempts and psychiatric comorbidities (recorded by trained psychiatrists or psychologists using the SCID-I), quality of sleep (self-evaluated by the subjects with the Pittsburgh Sleep Quality Index), and potentially painful somatic comorbidities (e.g. multiple sclerosis, cancer, ulcer, rheumatoid arthritis).

Pain

Pain was self-evaluated with the EQ-5D-5L questionnaire [27, 28]. The EQ-5D-5L is a standardized quality-of-life scale developed by the

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European EuroQol group. This questionnaire has been validated in several countries, including France [29, 30]. It includes five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point Likert scale: no problem, slight problems, moderate problems, severe problems, and extreme problems. The standard reference period for the response is the respondent's "own health state today."

Using the reported EQ-5D-5L scores, subjects were classified in two groups in function of the presence or absence of moderate or severe problems for the pain/discomfort dimension [31]. The EQ-5D-5L pain dimension has good psychometric properties and has shown good responsiveness and discriminative validity in various diseases where pain is a major symptom [32–37]. It is correlated with the scores of specific pain measuring tools, such as pain visual analog scales and the Brief Pain Inventory [34, 38].

Lithium

Lithium plasma levels (mmol/l) were extracted from the database. For all participants, blood samples were collected 12 hours after the last lithium intake and after fasting.

Affective state

The scores of the following tests were extracted from the database: Young Mania Rating Scale (YMRS; manic state assessment), Quick Inventory of Depressive Symptoms (QIDS) scale (depression level), and Spielberger Anxiety Inventory (STAI Y-A; self-evaluation of anxiety state). Subscales of the Multidimensional Assessment of Thymic States (MAThyS) for subjects suffering from BD were used to evaluate emotional reactivity, cognition, motivation, psychomotor activity, and sensory perception.

Personality traits

Affective traits were self-assessed with the Affective Lability Scale (ALS), the Affect Intensity Measure (AIM), the Barrat Impulsiveness Scale (BIS-10), and the Buss-Durkee Hostility Inventory (BDHI). Two dimensions, overt and covert aggressiveness, were derived from the BDHI because its construction produces these two distinct loaded factors [39, 40].

Ethical concerns

A web-based application, e-bipolar©, was developed and is used to collect data for clinical monitoring and research purposes [25]. Access to this web-based system is carefully regulated and the application was approved by the French body overseeing the safety of computerized databases (that is, Commission Nationale de l'Informatique et des Libertés, CNIL) [25]. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects were approved by an ethics committee (CPP-Ile de France IX). All individuals provided written informed consent before entering the study.

Statistical analysis

Variables in the two groups (with and without pain) were compared by univariate analysis. Another univariate analysis was done to compare subjects with and without lithium intake. For quantitative variables, mean and standard deviation (SD) were used. For qualitative variables, number of occurrences and frequencies per class were used. Quantitative and quantitative variables were compared between groups with the *t*-test or Mann–Whitney test, and the chi-square or Fisher test, respectively.

To test whether pain was associated with lithium intake, two multivariate regression logistic models were used. Model 1 tested whether subjects with lithium intake were less likely to report pain compared with those without lithium intake. Model 2 tested whether subjects with blood lithium concentration ≥ 0.5 mmol/l were even less likely to report pain. To this aim, the sample was classified in three groups: (1) subjects without lithium intake, (2) subjects with blood lithium concentration < 0.5 mmol/l, (3) subjects with blood lithium concentration ≥ 0.5 mmol/l. All analyses were done with R, version 4.2.1 [41].

For each model, confounders were selected from the literature and from our univariate analysis ($p < 0.15$). The following variables were selected as potential confounders: age, sex, BD type, lifetime psychiatric disorders (anxiety, eating and substance use disorders), past history of suicide attempt, personality traits (affective lability and intensity, impulsivity, aggressiveness according to the ALS, AIM, BIS-10 and BDHI scores, respectively), depression and anxiety levels (QIDS and STAI Y-A scores), sleep quality (PSQI score), and MAThyS subscale scores. Their normal distribution was evaluated. The Box Cox transformation was used for the QIDS score to reduce the influence of positive skewness and of outliers. MAThyS subscores were categorized in three classes (that is terciles) because the relation between MAThyS sub-scores and pain was nonlinear [2].

To avoid overfitting, an automatic stepwise forward and backward selection was performedwith the MASS package [42]. Only variables with the best fit were retained, according to the Akaike information criterion (AIC). The odds ratios (OR) and their 95% confidence intervals (CI) were estimated. To discuss the risk accurately, odds ratios were transformed to averaged risk ratios according to Grant [43].

In sensitivity analyses, the following variables were added sequentially to the best model to test whether lithium intake was still associated with pain: psychotropic drugs (anticonvulsants, antipsychotics, anxiolytics, hypnotics, antidepressants) and variables associated in univariate analyses but with missing data (high-school diploma, single, age of first episode, number of depressive episodes, anxiety score, cancer, and ulcer). The number of observations without missing data are reported for each sensitivity analysis.

Results

Sample description

The sample included 463 (60.9%) women, and 339 (44.6%) subjects who had BD type 1. The mean age was 40.2 years (SD = 12.62), the mean QIDS score was 9.56 (SD = 5.75), suggesting a low level of depressive symptomatology, and the mean YMRS score was 2.34 (SD = 3.67), indicating the absence of hypomanic symptoms. According to the EQ-5D-5L score, 171 subjects (22.5%) reported pain. Depressive episodes, lifetime psychiatric comorbidities (anxiety, eating and substance abuse/dependence disorders), and history of suicide attempts were more frequent in subjects who reported pain than in those who did not. Moreover, the levels of depression and anxiety and also of affective lability and intensity, hostility, and impulsivity were higher, and sleep quality was lower in subjects who reported pain. The percentages of subjects taking anxiolytics and lithium salts were higher and lower, respectively, in the group who reported pain (Table 1). Few subjects had somatic comorbidities that were not associated with self-reported pain (Table 1).

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Table 1. Sociodemographic and clinical characteristics of the groups with and without pain

Variable		Without pain Mean (sd)/ Number (%)	With pain Mean (sd)/ Number (%)	Statistical analysis	*p*-value*
Sociodemographic					
n		589	171		
Age (years)		39.54 (12.83)	42.48 (11.63)	F = 7.24	0.007
Sex	Men	242 (41.1)	55 (32.2)	χ^2 = 4.1	0.04
	Women	347 (58.9)	116 (67.8)		
Single	No	270 (50.8)	82 (52.9)	χ^2 = 0.15	0.7
	Yes	362 (49.2)	73 (47.1)		
Education	No	193 (36.3)	62 (40.8)	χ^2 = 0.82	0.37
(High-school diploma)	Yes	338 (63.7)	90 (59.2)		
Clinical					
BD subtype	I	271 (46)	68 (39.8)	χ^2 = 2.19	0.34
	II	252 (42.8)	83 (48.5)		
	NOS	66 (11.2)	20 (11.7)		
Age at BD onset (years)		23.3 (9.14)	24.1 (9.7)	F = 0.91	0.34
Number of depressive episodes		5.01 (4.6)	6.4 (5.6)	F = 8.3	0.004
Number of manic episodes		1.0 (1.91)	1.02 (2.6)	F = 0.01	0.94
Number of hypomanic episodes		3.29 (4.93)	3.75 (4.98)	F = 0.81	0.37
Number of hospitalizations	0	141 (26.1)	46 (29.3)	χ^2 = 2.88	0.41
	1	113 (20.9)	32 (20.4)		
	2–3	165 (30.6)	38 (24.2)		
	> 3	121 (22.4)	41 (26.1)		
History of suicide attempt	No	402 (68.3)	100 (58.5)	χ^2 = 5.22	0.02
	Yes	187 (31.7)	71 (41.5)		
Lifetime substance use disorder	No	396 (67.2)	101 (59.1)	χ^2 = 3.55	0.06
(abuse/dependence)	Yes	193 (32.8)	70 (40.9)		
Lifetime anxiety disorder	No	362 (61.5)	80 (46.8)	χ^2 = 11.14	0.0008
	Yes	227 (38.5)	91 (53.2)		
Lifetime eating disorder	No	483 (82)	126 (73.7)	χ^2 = 5.25	0.02
	Yes	106 (18)	45 (26.3)		
Multiple sclerosis	No	570 (99.5)	164 (99.4)		1
	Yes	3 (0.5)	1 (0.5)		
Cancer	No	539 (97.6)	150 (95.5)		0.17
	Yes	13 (2.4)	7 (4.5)		
Inflammatory bowel disease	No	564 (99.1)	161 (99.4)		1
	Yes	5 (0.9)	1 (0.6)		
Rheumatoid arthritis	No	577 (99.8)	167 (100)		1
	Yes	1 (0.2)	0 (0)		
Peptic ulcer disease	No	584 (96.6)	153 (94.4)		0.29
	Yes	19 (3.4)	9 (5.6)		
QIDS-SR		8.7 (5.4)	12.5 (5.8)	F = 60.94	<0.0001
YMRS	0	323 (54.9)	80 (47.3)	χ^2 = 3.4	0.18
	(1–7)	213 (36.2)	69 (40.8)		
	>7	52 (8.8)	20 (11.8)		
PSQI (0–21)		6.46 (3.55)	9.42 (4.15)	F = 84.94	<0.0001
STAI Y-A (state) (0–60)		40.6 (13.94)	48.0 (13.8)	F = 37.14	<0.0001

Continued

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Table 1. *Continued*

Variable		Without pain Mean (sd)/ Number (%)	With pain Mean (sd)/ Number (%)	Statistical analysis	*p*-value*
MAThyS emotional (0–40)		21.22 (6.33)	23.15 (7.02)	F = 11.77	0.0006
MAThyS motivation (0–40)		17.56 (6.46)	16.64 (8.01)	F = 2.38	0.12
MAThyS cognition (0–40)		20.32 (5.8)	21.24 (6.67)	F = 3.13	0.08
MAThyS sensory perception (0–50)		25.91 (4.38)	26.34 (6.81)	F = 0.94	0.33
MAThyS psychomotor (0–30)		12.9 (5.21)	12.2 (6.27)	F = 2.05	0.15
AIM		3.66 (0.68)	3.9 (0.63)	F = 17.19	<0.0001
ALS		1.19 (0.66)	1.54 (0.67)	F = 38.62	<0.0001
BDHI Expressive component		20.2 (7.89)	23.23 (7.84)	F = 19.7	0.0001
BDHI Attitudinal component		7.09 (4.34)	8.75 (4.27)	F = 19.57	<0.0001
BIS-10		66.67 (11.01)	70.38 (12.87)	F = 14.24	<0.0001
Drugs					
Lithium carbonate	No	438 (74.5)	146 (85.4)	χ^2 = 8.43	0.004
	Yes	151 (25.6)	25 (14.6)		
Anticonvulsants	No	294 (49.9)	80 (46.8)	χ^2 = 0.4	0.53
	Yes	295 (50.1)	91 (53.2)		
Antipsychotics	No	334 (56.7)	103 (60.2)	χ^2 = 0.54	0.46
	Yes	255 (43.3)	68 (39.8)		
Anxiolytics	No	466 (79.1)	119 (69.6)	χ^2 = 6.26	0.01
	Yes	123 (20.9)	52 (30.4)		
Hypnotics	No	510 (86.6)	146 (85.4)	χ^2 = 0.08	0.78
	Yes	79 (13.4)	25(14.6)		
Antidepressants	No	362 (61.5)	93 (54.4)	χ^2 = 2.47	0.12
	Yes	227 (38.5)	78 (45.6)		

Note: **p*-values are not corrected for multiple comparison, nor adjusted for other variables.
Abbreviations: AIM, affect intensity measure; ALS, affective lability scale; BD, bipolar disorder; BDHI, Buss–Durkee Hostility Inventory; BIS-10, Barratt Impulsiveness Scale; MAThyS, multidimensional assessment of thymic states; NOS, not otherwise specified; PSQI, Pittsburgh Sleep Quality Index; QIDS-SR, quick inventory of depressive self-report; STAI Y-A, State–Trait Anxiety Inventory; YMRS, Young Mania Rating Scale.

Compared with subjects not treated with lithium salts, subjects taking lithium salts were more often men, with BD type I, had less frequent lifetime anxious and substance abuse/dependence disorders, took less often anticonvulsants, but reported a higher number of past psychiatric hospitalizations. They had lower levels of affective lability and intensity, hostility and impulsivity, and better sleep quality (Supplementary Table S1).

Multivariate analyses

In multivariate analysis (model 1), lithium intake was significantly and negatively associated with reporting pain, that is, subjects on lithium were significantly less likely to report pain (OR = 0.59, 95% CI, 0.35–0.95; $p = 0.036$) compared with the other subjects (Table 2). The risk of reporting pain was reduced by 36% in subjects on lithium (RR = 0.64, 95% CI, 0.41, 0.96). Model 1 with all confounding variables gave similar results (OR = 0.58, 95% CI, 0.34–0.95; $p = 0.035$) (Supplementary Table S2), as well as the sensitivity analyses (Supplementary Table S3).

Among the 176 subjects with lithium blood level data, 139 had a lithium concentration ≥ 0.5 mmol/l (that is therapeutic

Table 2. Odds ratios for the best model 1 selected based on the AIC

	OR [CI]	Statistic (z-value)	*p*-value
Lithium salts[a] [yes]	0.59 [0.35–0.95]	−2.1	0.036
Age	1.02 [1.01–1.04]	2.58	0.010
QIDS-SR (Box–Cox)	1.24 [1.11–1.38]	3.86	0.0001
PSQI	1.13 [1.07–1.19]	4.42	<0.0001
MAThyS Motivation[b]			
[16 – 20]	1.61 [0.99–2.66]	1.89	0.059
MAThyS Motivation[b]			
[21 – 40]	1.90 [1.11–3.28]	2.33	0.020
BDHI Expressive Component	1.02 [0.99–1.05]	1.68	0.09

[a]The reference for comparison is no lithium intake.
[b]The reference for comparison is the score [0–15] of the MAThyS motivation subscale.
Abbreviations: BDH, Buss–Durkee Hostility Inventory; MAThyS, multidimensional assessment of thymic states; PSQI, Pittsburgh sleep quality index; QIDS-SR, quick inventory of depressive self-report.

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Table 3. Odds ratios for the best model 2 selected based on the AIC

	OR [CI]	Statistic (z-value)	*p*-value
Lithium salts[a] [< 0.5 mmol/l]	1.15 [0.49–2.51]	0.34	0.735
Lithium salts[a] [≥ 0.5 mmol/l]	0.45 [0.24–0.79]	−2.64	0.008
Age	1.02 [1.00–1.04]	2.49	0.013
QIDS-SR	1.23 [1.11–1.38]	3.84	0.0001
PSQI	1.13 [1.07–1.19]	4.39	<0.0001
MAThyS Motivation[b]			
[16 –20]	1.63 [0.99–2.70]	1.93	0.053
MAThyS Motivation[b]			
[21 – 40]	1.85 [1.08–3.18]	2.33	0.026
BDHI Expressive Component	1.02 [0.99–1.05]	1.72	0.086

[a]The reference for comparison is no lithium intake.
[b]The reference for comparison is the score [0–15] of the MAThyS motivation subscale.
Abbreviations: BDHI, Buss–Durkee Hostility Inventory; MAThyS, multidimensional assessment of thymic states; PSQI, Pittsburgh Sleep Quality Index; QIDS-SR, quick inventory of depressive self-report.

concentration). The multivariate analysis (model 2) showed a significant and negative association between lithium concentration and reporting pain (OR = 0.45, 95% CI, 0.24–0.79; p = 0.008), but not in subjects with lithium <0.5 mmol/l (OR = 1.15, 95% CI, 0.49–2.51: p = 0.73) (Table 3). The risk of reporting pain was halved in subjects with lithium ≥0.5 mmol/l (RR = 0.5. 95% CI, 0.28, 0.83). Model 2 with all confounding variables gave the same results (OR = 0.45, 95% CI, 0.23–0.81; p = 0.01), and also the sensitivity analyses (Supplementary Table S4).

Discussion

In our study, individuals treated with lithium were less likely to report physical pain. Moreover, they were two times less likely to report pain when they had the recommended lithium blood level. This indicates that the recommended threshold of lithium efficiency for mood stabilization [23] is also effective for pain relief. These results remained significant after controlling for many variables, leading us to conclude that our results were not influenced by BD severity or emotional state. Subjects who reported pain also took more drugs, particularly antidepressants and anticonvulsants known to have analgesic effects. However, the intake of psychotropic medications (except lithium) was not associated with a reduced risk of reporting pain. Therefore, it is unlikely that the other psychotropic medications might explain lithium's positive effect on pain. This negative result may be explained by the naturalistic design of our study. Generally, the analgesic effects of antidepressants and anticonvulsants are reduced in psychiatric patients [44]. Future studies should investigate the analgesic effect of antidepressants and anticonvulsants in subjects suffering from BD and reporting pain.

Lithium could be a promising strategy for subjects suffering from BD reporting pain and could also be tested in subjects with chronic pain, independently of mood disorders. Case reports and animal studies suggest that lithium is efficient for different painful pathologies, such as fibromyalgia and neuropathic pain [12, 13, 20]. The current analgesic medications have limited efficiency [45–48] and opioids have serious side effects [7, 8, 11]. Moreover, developing new drugs to alleviate pain with acceptable adverse effects is a complex and long process [49–51]. Lithium is a well-known drug, cheap, with monitorable adverse effects [52]. Lithium effect occurs through multiple mechanisms at different levels, but its blood concentration needs to be >0.5 mmol/l to observe its full mood-stabilizing effect [53]. Lithium prevents the reduction of gray matter volume in brain, restores the balance between excitatory and inhibitory neurotransmission in neurons, and promotes the synthesis of neuroprotective proteins [54]. All these mechanisms are impaired also in pain (e.g. neuropathic pain) [55–57], and could be improved with lithium. For example, painful pathologies are associated with hyperalgesia due to N-methyl-D-aspartate (NMDA) receptor activity [58]. Chronic lithium intake reduces NMDA receptor activity, promotes glutamate reuptake, and restores the normal excitatory activity [54].

Some limitations must be highlighted. First, the EQ-5D-5L questionnaire is a validated measure of pain intensity, but does not provide any useful information on pain location, duration, and frequency. Thus, we could not determine whether lithium was effective on chronic pain. Second, due to the database format, we could not determine whether the pain reported by patients was related to specific medical conditions or was idiopathic. We also could not assess the effect of lithium on specific painful pathologies. Fibromyalgia and headache are frequently reported by subjects suffering from BD, and lithium could be efficient particularly for these pathologies [59–61]. Third, some variables could have confounded the effect of lithium on pain, such as opioid intake or other somatic comorbidities not recorded in the database. Fourth, the cross-sectional design of our study does not allow highlighting of causal relationships. Lithium could have been prescribed to people with lower depression levels and lower emotional instability, thus favoring the selection of individuals who were less likely to report pain. RCTs are necessary to rule out these potential confounding variables and to confirm our results.

The study has some strengths. We included many variables that could have confounded the effect of lithium on pain, particularly potential painful commodities, and we had the blood lithium concentration. Moreover, we assessed lithium's effect on pain in naturalistic conditions and this gives an ecological validity to our results.

In conclusion, this is the first naturalistic study showing that lithium has a promising effect on pain in subjects suffering from BD. However, RCTs are necessary to confirm this result. It would be important to determine whether lithium could also decrease pain in subjects reporting chronic pain and in subjects vulnerable to pain.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1192/j.eurpsy.2023.2476.

Data availability statement. The datasets generated and/or analyzed during the current study are not publicly available due to the sensitive and identifiable nature of health data but are available from the corresponding author upon reasonable request.

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Author contribution. Olié E., Courtet Ph., Dubois J., and Risch N. formulated the hypotheses, designed the study, interpreted the results, and wrote the article. Dubois J and Risch N performed statistical analyses. Etain B, Aouizerate B, Bellivier F, Belzeaux R, Dubertret C, Haffen E, Januel D, Lefrere Antoine, Walter M, Rey R, Schwan R, Samalin L, Roux P, Polosan M, Leboyer M, Olié E and Courtet P and FACE BD collaborators participated in partcipants' inclusion and assessment. All authors contributed to revise the final manuscript. All authors approved the submitted version of the article.

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Competing interest. The authors and the FACE BD Collaborators declare none.

Ethical standard. The study was performed according to the Declaration of Helsinki. The protocol was approved by an ethics committee (CPP-Ile de France IX).

Transparency declaration. All of the authors declare that the manuscript is an honest, accurate, and transparent account of the study being reported; and that no important aspects of the study have been omitted.

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