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Cohort Profile

Cohort Profile Update: The Heinz C. Prechter Longitudinal Study of Bipolar Disorder

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Key Features

- Since its inception in 2006, the Heinz C. Prechter Longitudinal Study of Bipolar Disorder has continued to actively enrol and follow a cohort of individuals with bipolar disorder and unaffected psychiatric controls with deep phenotyping and ongoing monitoring of symptom severity. There are 1393 individuals in the cohort and 899 who continue to actively provide ongoing bimonthly outcomes assessments. The average follow-up period is 9 years (range 0–7 years).

- The study includes data from seven ontological classes of phenotypes: disease, neuropsychology, personality, motivated behaviour, sleep and circadian rhythms, life story and treatment outcomes patterns.

- The database of measures has been standardized and harmonized along with collected biological samples that can be shared and further utilized to research bipolar disorder.

- In addition to further longitudinal outcomes and symptom severity measures, new measures include wearable device data, mobile technology assessments, voice-derived emotion annotation, induced pluripotent stem cells and diverse molecular omics data.

- All clinical, longitudinal, biological and deoxyribonucleic acid samples are available through the Heinz C. Prechter Genetic Repository, distributed by the University of Michigan Central Biorepository. Initial diagnostic evaluation, omics data and longitudinal measures and outcome data, including coded subsets of the PRIORI speech data set, are available via request at the following e-mail address: mmcinnis@umich.edu, prechter-data-request@med.umich.edu conditional on data-use agreement.

The original cohort

The Heinz C. Prechter Longitudinal Study of Bipolar Disorder is an open cohort of bipolar disorder (BD) that began in 2006 and continues to enrol new participants. The study includes individuals with BD and unaffected controls, both with deep phenotyping using a dimensional and multidisciplinary approach. The rationale for the establishment of this cohort was the recognized need for deep clinical phenotypic data with longitudinal symptoms and outcomes data. The complexity of BD along with the dynamic and variable nature of the clinical phenotype, which includes variability in

the frequency of changing clinical states over time, was a further impetus for the longitudinal approach.

Participants are opportunistically recruited into the cohort through advertisements on the web and in newspapers, outpatient specialty psychiatric clinics, community mental health centres, community outreach events and in the inpatient psychiatric unit at the University of Michigan from 2006, continuing until the present. Inclusion criteria into the cohort include: (i) BD I diagnosis with history of mania or schizoaffective disorder, manic type; or (ii) BD II diagnosis with history of major depressive episode or hypomania; and (iii) ≥18 years of

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age and willingness to participate in a longitudinal study. Participants were excluded during screening for enrolment if they had schizophrenia or schizoaffective disorder, depressive type; active substance dependence (that would impair their ability to provide accurate information); medical illnesses associated with depression (e.g. Cushing's disease, stroke, etc.); or substantial intellectual impairment (IQ < 70). However, individuals initially ascertained as having BD but over time, following detailed clinical assessment, were found to have other diagnoses, e.g. non-affective disorder, other affective disorder and major depression disorder, have been retained and continue to be followed. Healthy and unaffected controls were recruited through community and campus advertising and included if they had no history of Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV) axis I psychiatric illness and no family history of psychiatric diagnosis; no attempt was made to match for sex or age. Recruitment of controls was discontinued at $n = 288$ but they remain in the follow-up cohort, roughly matched by age and sex. The control group is representative of the geographical unaffected population. Further, as the number of follow-up measures increases in the BD cohort, each individual participant effectively becomes their own control by comparing current measures with previous.

Compared with other large BD cohorts[1,2] this cohort covers a longer time of ≤17 years and collects more frequent measures (every 2 months). Phenotyping is organized into multiple phenotypic classes that include disease, neurocognitive, personality, motivated behaviours, sleep and circadian rhythms, life story and treatment outcome patterns. Since the initial publication of the descriptive baseline data[3] from 1111 participants, we have focused on the curation and harmonization of the longitudinal data for efficient sharing and analyses related to longitudinal outcomes while continuing a rolling enrolment focusing on diversifying the race and ethnicity of the cohort. There have been 282 additional participants enrolled. Over the years, there have been 254 participants who have chosen not to continue, 176 who have not responded within 3 years of their last completed measure, 15 who have completely withdrawn all data from the study and an additional 64 deaths. Currently there are 899 active participants with an average of almost 10 years of participation. In aggregate, there are ~182 000 individual bimonthly self-report clinical assessment measures, 30 000 individual biannual assessments, 84 000 individual annual self-report or clinician-assessed measures, ~1400 individual baseline neuropsychology assessments with 428 and 120 individual 5-year assessments and 10-year neuropsychology assessments, respectively. New individuals are added with the goal of maintaining an 'actively' followed cohort of between 900 and 1000 participants. Emphasis is currently placed on those with recent onset and minority individuals. Herein we (i) update the demographic description of the cohort and the current and new data collected that are available for sharing under institutional data-use agreements and (ii) review recent findings from the cohort, including a summary of participant satisfaction surveys, and provide links to the programme website for further details and bibliography. With this cohort update, we emphasize the ongoing and evolving longitudinal data collection that is accessible for sharing.

What is the reason for the new data collection?

The data set includes the initial baseline assessments and adds the longitudinal monitoring data from baseline enrolment,

continuing from January 2006 through to 31 December 2022. The updated demographics for the Heinz C. Prechter Bipolar Longitudinal Study of Bipolar Disorder are listed in Table 1. The starting year for a given instrument (some assessment instruments were added after the study began), the frequency of collection, the number of participants, the number of collected measures and the average percent completion rate are shown in Figure 1 and Tables 2 and 3.

In addition to the availability of the ongoing, growing longitudinal clinical assessment data collected in the cohort, concomitant efforts have emphasized standardizing and harmonizing all data elements. Further, efforts are ongoing to maintain the engagement of participants as well as to expand and diversify the ethnic and racial backgrounds of the cohort participants. Participants are routinely notified and invited to participate in auxiliary studies in BD and, as these studies progress, the data generated typically become part of the collective Prechter data set.

The COVID Impact Scale was implemented in 2020 and continues to be collected bimonthly to study the effects of the Sars-CoV-2 pandemic. A participant feedback survey is now collected on a rolling annual anniversary to monitor participant engagement and satisfaction, often making emendations as needed. From this feedback, for example, the self-report assessment line-up was reordered to improve the completion rate, sexual orientation categories were clarified and dated insensitive questionnaires removed, including the Barratt Impulsiveness Scale, Brown-Goodwin Aggression history, Buss-Durkee Inventory and the Brief Social Phobia Scale. Cohort participants have embraced mobile technology to collect research data. Mobile monitoring that includes ecological momentary assessment (EMA), a digital self-report survey of mood for BD (DigiBP)[4] and an integrated self-management application based on a well-established approach (LifeGoals)[5] has been undertaken. Additionally, the PRIORI (Predicting Individual Outcomes for Rapid Intervention) project, focused on the analysis of speech and acoustic patterns,[6] has expanded to include multiple human annotations of speech segments to estimate levels of activation and valence in speech for training machine-learning models in analyses of mood and emotion. The PRIORI emotion data set is available for sharing.

What will be the new areas of research?

Research in the Heinz C. Prechter Bipolar Longitudinal Study of Bipolar Disorder has evolved in two main complementary directions: (i) the long-term outcomes patterns, including lifetime effects of the temperament, behaviours, sleep, life story, outcomes, and disease determinants of BD; and (ii) a focus on the functional, physical, emotional, molecular and neurocognitive aspects of the disorder. New research areas focus on longitudinal time-series studies emphasizing the high variability of symptoms and outcomes within BD. Bimonthly self-report assessment of symptom severity offers data-driven methods to categorize and stratify individuals according to the nature and intensity of symptoms and outcome variability.

At the beginning of the COVID-19 pandemic, the effects of the pandemic and related social, health and occupational changes on the cohort of participants were studied. The ongoing longitudinal design is well suited to studying the impact of the COVID-19 pandemic based on frequently collected

Table 1. The Heinz C. Prechter Longitudinal Study of Bipolar Disorder cohort descriptives as of 31 December 2022

| Characteristic	Bipolar 1 (*n* = 660)	Bipolar 2 with recurrent depression (*n* = 187)	Bipolar NOS (*n* = 81)	Healthy/control (*n* = 288)	Major depression recurrent (*n* = 36)	Non-affective diagnosis (*n* = 56)	Other affective diagnosis (*n* = 51)	Schizoaffective bipolar (*n* = 34)	Total (*n* = 1393)
Age at enrolment (years)									
Mean (SD)	39.9 (13.5)	40.9 (15.1)	37.3 (14.0)	35.8 (15.3)	38.9 (13.1)	41.4 (15.9)	38.8 (15.9)	36.4 (12.0)	38.9 (14.4)
Median [min, max]	38.0 [18.0, 85.0]	40.0 [18.0, 84.0]	36.0 [19.0, 72.0]	30.0 [18.0, 77.0]	38.0 [19.0, 67.0]	42.0 [19.0, 80.0]	33.0 [19.0, 73.0]	36.0 [20.0, 64.0]	36.0 [18.0, 85.0]
Duration enrolled (years)									
Mean (SD)	7.66 (5.07)	7.97 (4.58)	6.60 (4.41)	8.79 (4.71)	8.86 (4.95)	7.91 (4.47)	9.57 (4.78)	8.91 (4.71)	8.02 (4.88)
Median [min, max]	8.00 [0, 17.0]	8.00 [0, 17.0]	7.00 [0, 15.0]	10.0 [0, 17.0]	10.0 [0, 16.0]	7.50 [0, 16.0]	10.0 [0, 17.0]	10.0 [0, 16.0]	8.00 [0, 17.0]
Sex									
Female	421 (63.8%)	137 (73.3%)	51 (63.0%)	179 (62.2%)	22 (61.1%)	29 (51.8%)	32 (62.7%)	20 (58.8%)	891 (64.0%)
Male	237 (35.9%)	48 (25.7%)	29 (35.8%)	109 (37.8%)	14 (38.9%)	27 (48.2%)	19 (37.3%)	13 (38.2%)	496 (35.6%)
Other	<5 (<0.8%)	<5 (<2.7%)	<5 (<6.2%)	0	0	0	0	<5 (<14.7%)	6 (0.4%)
Ethnicity									
Hispanic or Latino	34 (5.2%)	10 (5.3%)	7 (8.6%)	21 (7.3%)	<5 (<13.9%)	7 (12.5%)	<5 (<9.8%)	<5 (<14.7%)	85 (6.1%)
Not Hispanic or Latino	625 (94.7%)	175 (93.6%)	74 (91.4%)	267 (92.7%)	33 (91.7%)	49 (87.5%)	47 (92.2%)	33 (97.1%)	1303 (93.5%)
Unknown	<5 (<0.8%)	<5 (<2.7%)	0	0	<5 (<13.9%)	0	0	0	5 (0.4%)
Race									
Caucasian	570 (86.4%)	159 (85.0%)	62 (76.5%)	200 (69.4%)	23 (63.9%)	38 (67.9%)	38 (74.5%)	25 (73.5%)	1115 (80.0%)
Non-Caucasian	90 (13.6%)	28 (15.0%)	19 (23.5%)	88 (30.6%)	13 (36.1%)	18 (32.1%)	13 (25.5%)	9 (26.5%)	278 (20.0%)
Status									
Alive	624 (94.5%)	179 (95.7%)	69 (85.2%)	286 (99.3%)	35 (97.2%)	54 (96.4%)	50 (98.0%)	32 (94.1%)	1329 (95.4%)
Deceased	36 (5.5%)	8 (4.3%)	12 (14.8%)	<5 (<1.7%)	<5 (<13.9%)	<5 (<8.9%)	<5 (<9.8%)	<5 (<14.7%)	64 (4.6%)
Discontinuing									
No	535 (81.1%)	157 (84.0%)	70 (86.4%)	246 (85.4%)	28 (77.8%)	32 (57.1%)	42 (82.4%)	29 (85.3%)	1139 (81.8%)
Yes	125 (18.9%)	30 (16.0%)	11 (13.6%)	42 (14.6%)	8 (22.2%)	24 (42.9%)	9 (17.6%)	5 (14.7%)	254 (18.2%)
Non-responders									
No	572 (86.7%)	167 (89.3%)	63 (77.8%)	255 (88.5%)	32 (88.9%)	52 (92.9%)	46 (90.2%)	30 (88.2%)	1217 (87.4%)
Yes	88 (13.3%)	20 (10.7%)	18 (22.2%)	33 (11.5%)	<5 (<13.9%)	<5 (<8.9%)	5 (9.8%)	<5 (<14.7%)	176 (12.6%)
Currently active									
No	249 (37.7%)	58 (31.0%)	41 (50.6%)	77 (26.7%)	13 (36.1%)	30 (53.6%)	15 (29.4%)	11 (32.4%)	494 (35.5%)
Yes	411 (62.3%)	129 (69.0%)	40 (49.4%)	211 (73.3%)	23 (63.9%)	26 (46.4%)	36 (70.6%)	23 (67.6%)	899 (64.5%)

NOS, not otherwise specified.
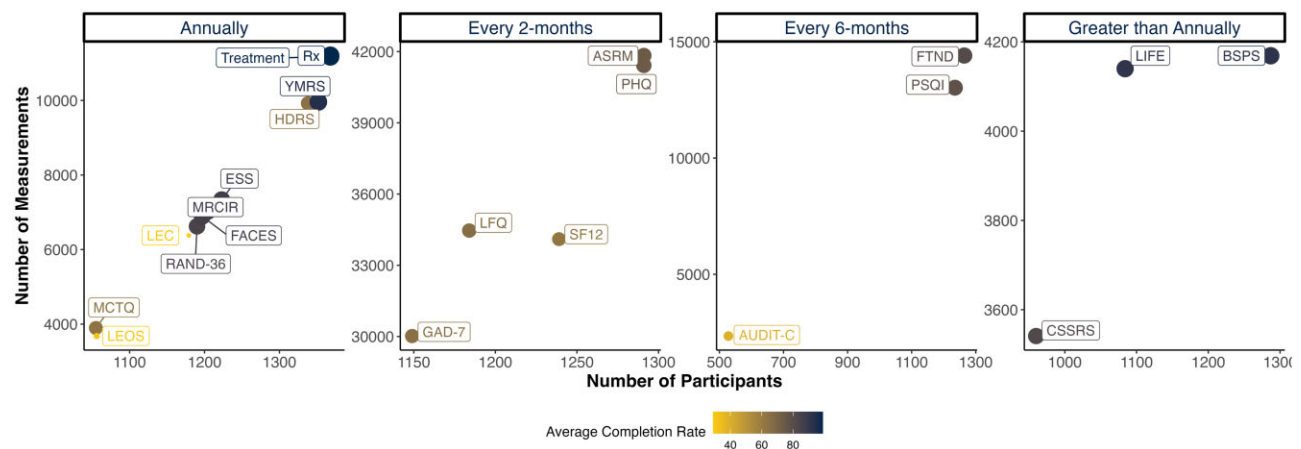
Figure 1. Survey completion. Number of measurements, number of participants and average percent completion of each measure stratified by the frequency of measure collection (a, b, c, d, e). Brief Social Phobia Scale (BSPS), Columbia Suicide Severity Rating Scale (CSSRS) and Longitudinal Interval Follow-up Evaluation (LIFE) are captured every 2 years and the neuropsychology battery consisting of 16 tests and 8 cognition domains is captured at baseline, Year 1, Year 5 and Year 10. Altman Self-Rating Mania Scale (ASRM), Alcohol Use Disorders Identification Test (AUDIT), Buss-Durkee Hostility Inventory (BDHI), Brown-Goodwin Lifetime History of Aggressive Behavior (BGAH), Behavior Inhibition System (BIS), BSPS, COVID-19 Impact Scale (CIS), CSSRS, Childhood Trauma Questionnaire (CTQ), Diagnostic Interview for Genetic Studies (DIGS), Experiences in Close Relationships (ECRQ), Epworth Sleepiness Scale (ESS), Family Adaptability and Cohesion Evaluation Scale (FACES II), Fagerstrom Test for Nicotine Dependence (FTND), Generalized Anxiety Disorder Scale (GAD-7), Hamilton Rating Scale for Depression (HDRS), Life Events Checklist (LEC), Life Events Occurrence Survey (LEOS), Life Functioning Questionnaire (LFQ), LIFE, Munich Chronotype Questionnaire (MCTQ), Measures Related to Close Interpersonal Relationships (MRCIR), Patient Health Questionnaire-9 (PHQ-9), Pittsburgh Sleep Quality Index (PSQI), Rand 36 Item SF Health Survey (RAND-36), Health Survey Short Form-12 (SF-12), Structured Interview Guide for Hamilton Depression Rating Scale (SIGH-D), Seasonal Pattern Assessment Questionnaire (SPAQ), Young Mania Rating Scale (YMRS).

measures before, during and after as the pandemic waxes and wanes. An initial investigation, specifically studying the effects of a mandatory state-wide stay-at-home order, showed that the effects of the mandatory isolation were notable on all individuals in the study. However, those with BD were affected more, experienced more significant difficulty and did not recover as quickly as the unaffected controls.[7] The COVID-19 Impact Scale is now integrated into the study and completed bimonthly.[8] The newly captured data collected through this instrument will be used to monitor the immediate short-term influence of the pandemic as well as the functional outcome effects of the pandemic longitudinally.

Participating, capturing and analysing data through mobile technologies is a fresh direction of the cohort and study. This includes expansion of the LifeGoals[5] app to engage and monitor participants beyond our geographical area. Recruitment in LifeGoals and PRIORI are by invitation within our existing longitudinal member participants. The PRIORI app[6] is expanded to include monitoring of the ambient audio environment and calls of the individual in a secure manner designed to not compromise privacy. There is no attempt made nor is there opportunity to identify anyone outside of the individual participant, as audio data are asynchronously encrypted and immediately deleted from the smartphone. Data are decrypted and processed within our controlled server; all programming and data structures have been rigorously reviewed by our information assurance and cybersecurity teams, and the outcomes of processing are computational and descriptive in nature.

Biological mechanisms underlying BD will continue to be studied utilizing the high-throughput omics data in combination with cell and developmental biology approaches. Several cohort participants have provided fibroblasts ($n = 30$) and other biological materials to our biobank repository, including blood ($n = 770$) and saliva ($n = 60$) for genomics. Using the provided fibroblasts, 23 induced pluripotent stem cell lines (iPSCs) have been developed and altered using CRISPR

genomic editing technologies. These iPSC cell lines have been differentiated into different neuronal cell types and organoids. Immunohistochemical localization of lineage-restricted proteins was carried out in both cells and histological sections of organoids. At several time points during development, these cell lines and the organoids derived from them have been used to generate bulk single cell- and single nuclei-RNA sequencing to study the relational time-course developmental gene-expression differences between those with BD and controls. Proteomics and phospho-proteomics have also been completed in a developmental time-course manner to understand signalling differences during the development of different cell types and between those with BD and controls.

Who is in the cohort?

The Heinz C. Prechter Longitudinal Study of Bipolar Disorder is an open cohort of individuals with BD and other psychiatric illnesses and controls who agree to participate. Follow-up and enrolment are continuous and the original inclusion and exclusion criteria are unchanged.[3] Currently, there are 1393 participants (mean age at enrolment is 38.9 years; 64% female). The cohort includes 962 individuals with any type of BD diagnosis (i.e. within the 'bipolar spectrum' that includes schizoaffective, manic type), 36 with major depressive disorder (MDD), 51 with other mood disorders, 56 with non-mood/non-affective psychiatric illness and 288 controls (Table 1). The median time for which participants have been in the study is 8 years with a range of 0–17 years and there is an overall retention rate of 65%. As of 31 January 2023, 64 participants had died during the study and an additional 254 have elected to not continue, although most (94%) still approve of using previously obtained data. The majority (92%) of participants consented to be re-contacted for additional research or clinical trial studies. An annual participant satisfaction survey was implemented in 2018 and averages a 55% response rate each year. Much of

Table 2. Listing of survey instruments with the number of participants, distinct measurements, average percent complete, commencement year and collection frequency

Instrument	Number of participants	Number of measurements	Mean percentage complete	Year commenced	Collection frequency
Altman Self-Rating Mania Scale (ASRM)	1291	41 834	74	2006	Every 2 months
Alcohol Use Disorders Identification Test (AUDIT)	528	2345	39	2006	Every 6 months
Buss-Durkee Hostility Inventory (BDHI)	875	875	100	2010	Baseline
Brown-Goodwin Lifetime History of Aggressive Behavior (BGAH)	853	853	100	2010	Baseline
Behavior Inhibition System (BIS)	820	820	100	2009	Baseline
Brief Social Phobia Scale (BSPS)	1287	4169	92	2006	Greater than annually
COVID-19 Impact Scale (CIS)	818	8051		2020	Every 2 months
Columbia Suicide Severity Rating Scale (CSSRS)	976	3597	82	2012	Greater than annually
Childhood Trauma Questionnaire (CTQ)	1137	1137	100	2006	Baseline
Diagnostic Interview for Genetic Studies (DIGS)	1392	1392	100	2006	Baseline
Experiences in Close Relationships (ECRQ)	870	870	100	2011	Baseline
Epworth Sleepiness Scale (ESS)	1223	7337	87	2006	Annually
Family Adaptability and Cohesion Evaluation Scale (FACES II)	1197	6891	86	2006	Annually
Fagerstrom Test for Nicotine Dependence (FTND)	1264	14 408	81	2006	Every 6 months
Generalized Anxiety Disorder Scale (GAD-7)	1149	30 020	65	2012	Every 2 months
Hamilton Rating Scale for Depression (HDRS)	1338	9924	64	2006	Annually
Life Events Checklist (LEC)	1179	6378	29	2006	Annually
Life Events Occurrence Survey (LEOS)	1056	3680	30	2006	Annually
Life Functioning Questionnaire (LFQ)	1184	34 462	66	2011	Every 2 months
Longitudinal Interval Follow-up Evaluation (LIFE)	1084	4140	91	2008	Greater than annually
Munich Chronotype Questionnaire (MCTQ)	1055	3897	63	2006	Annually
Measures Related to Close Interpersonal Relationships (MRCIR)	1204	7020	86	2006	Annually
Neuropsych.BL	1324	1324	100	2006	Greater than annually
Neuropsych.yr1	947	947	100	2006	Greater than annually
Neuropsych.yr5	428	428	100	2006	Greater than annually
Neuropsych.yr10	120	120	100	2006	Greater than annually
Patient Health Questionnaire-9 (PHQ-9)	1291	41 419	74	2006	Every 2 months
Pittsburgh Sleep Quality Index (PSQI)	1235	13 025	78	2006	Every 6 months
Rand 36 Item SF Health Survey (RAND-36)	1190	6624	84	2006	Annually
Health Survey Short Form-12 (SF-12)	1239	34 102	62	2006	Every 2 months
Seasonal Pattern Assessment Questionnaire (SPAQ)	850	850	100	2012	Baseline
Young Mania Rating Scale (YMRS)	1352	9961	94	2006	Annually

the feedback is in a free text format monitored by the study team continuously and there are also categorical questions. For example, in 2020, 79% of the reporting participants indicated that their participation in the research study was 'Mostly Positive' and 91% of the participants with BD indicated that the study captures the critical elements of their illness, how they manage it and how it impacts their life.

What has been measured?

An update on the descriptive statistics and all measures collected in this cohort is provided in Tables 2 and 3 and shown graphically in Figure 1. A new category of measure is the COVID-19-related outcomes measure, which has been administered 8051 times across 818 participants since early 2020. Another new category of measure relates to predictive outcomes measuring and is based on the subset of the cohort that is now part of PRIORI, a sub-study that analyzes speech. The PRIORI data set includes a total of ∼5586 call hours representing 75 203 distinct calls from 99 individuals, of which 49 702 speech audio segments are annotated for emotion with 27 105 annotated segments transcribed. Finally, new biological material is being collected and generated, including

fibroblasts (*n* = 30 patient cell lines), iPSCs (*n* = 23 cell lines), brain organoids (*n* = 36 lines), hair (*n* = 15), astrocytes, neurons, glial cell types and saliva samples (*n* = 73). From these materials (except for hair), considerable omics data have been newly generated, in addition to the previously and continuously obtained genetic single nucleotide polymorphism (SNP) array data. Specifically, for the iPSC samples there is now bulk- and, single cell-RNA sequencing, proteomics and phosphoproteomics data.

What has it found? Key findings and publications

The Heinz C. Prechter Bipolar Longitudinal Study of Bipolar Disorder continues to collect and expand upon a wide range of phenotype data with the opportunity to integrate and analyse features at the intersection of multiple categorical and dimensional elements relevant to the disorder. Key among the findings is the ongoing commitment and engagement among the participants living with BD and the multidisciplinary engagement of the scientific community in BD-focused research.

Sleep and circadian rhythms affect outcomes among those living with BD. Typically, those with late chronotypes

Table 3. (a) Medical health and medication information with the number of participants and distinct measurements, average percent complete, commencement year and collection frequency; (b) the number of participants and collection frequency of different types of biological samples; and (c) the audio sample types including the number of participants, year commenced, call hours, distinct number of calls, distinct number of recordings, segments annotated and segments transcribed.

(a) Medical health information including medications

Clinical treatment information	Number of participants	Number of measurements	Mean percentage complete	Year commenced	Collection frequency
Medical health	1368	11 176	99	2006	Annually
Medication information	1368	11 205	99	2006	Annually

(b) Biological samples

Biological samples	Number of participants	Collection frequency
Whole-blood DNA	802	Baseline and opportunistically
Human hair samples	15	Baseline and opportunistically
Human plasma samples	723	Baseline and opportunistically
Whole-blood samples	117	Baseline and opportunistically

(c) Predicting Individual Outcomes for Rapid Intervention (PRIORI) study data

Audio samples	PRIORI Voice	PRIORI Ambient
Number of participants	99	12
Year commenced	2012	2022
Call hours	5586	N/A
Distinct calls	75 203	N/A
Distinct recordings	N/A	22 110
Segments annotated	49 702	49 054
Segments transcribed	27 105	0

PRIORI Voice and PRIORI Ambient are the two iterations of the PRIORI project. DNA, deoxyribonucleic acid.

experience more frequent depressive symptoms over time.[9] Poor sleep is a predictor of poor outcomes including neurocognitive functioning.[10] Neurocognitive and personality traits appear to be relatively stable over time.[11] Those living with BD show, on average, lower cognitive performance but the age-related rates of decline are similar to those of the unaffected controls.[12] There were differences in personality attributes: those with BD usually have higher Neuroticism scores and lower Conscientiousness and Extroversion scores compared with controls. Occupational capacity is lower overall among BD patients as cognitive flexibility and depressive scores consistently compromised work capacity.[11]

The outcome of the COVID-19 pandemic and associated health, occupational and social guidelines is of major interest in the cohort. Evaluations are ongoing and an initial report that focused on a lockdown period in the state of Michigan found those with BD experienced a greater impact from the disruptions in routines, income/employment, social support and pandemic-related stress. Further, those with BD recovered slower than those without BD and women were more affected. Older individuals were less affected overall.[7]

The study and characterization of the biological mechanisms underlying BD remain a major thrust of the Heinz C. Prechter Bipolar Longitudinal Study of Bipolar Disorder. There is strong evidence that synaptic activity differs significantly between BD and control groups, and this activity is influenced by the cargo of astrocyte-derived exosomes that reduce synaptic density, neurite outgrowth and calcium signalling.[13] Comparison of calcium transients from those with BD and controls regarding excitatory (glutamatergic) neurons has identified deficiencies in the BD group that may be amendable to small molecule targeting. GABAergic, gamma-aminobutyric acid, interneurons and astrocytes appear to

excite cycles earlier than controls producing fewer inhibitory neurons. Neuronal differentiation has been significantly improved by adding polyunsaturated fatty acids (PUFAs) (chronically lacking in the diet of individuals with BD) to the culture medium and has resulted in increased measures of synaptic density and activity. Focused animal models have targeted the *ANK3* variants and demonstrated that mice exhibit a reduction, suggestive of a loss of function, in forebrain GABAergic synapses with widespread disruptions in neuronal integrity.[14,15] Similarly to the addition of PUFAs to neuronal cultures (above), metabolic pathway analyses are consistent with persistent dysregulation in the PUFA and inflammatory mechanisms with evidence of a complex relationship between medications, diet, the environment of the gut and the brain.[16]

Electrophysiology and neuroimaging sub-studies of the cohort have focused on the capacity for processing facial expressions and emotions along with eye gaze and point to trait sensitivity to negative facial and emotional expression in BD that is reduced in the manic phase.[17,18] These works and others emphasize social cognition traits in BD and suggest that these elements may become targeted interventions. A history of childhood trauma has a significant effect on the course and outcome pattern.[19–21]

Predictive modelling of outcome patterns based on longitudinal patterns suggest an affective instability model wherein mood states do not follow a rhythmic process; rather, BD episodes arise in the context of persistent instability with a delayed and dysregulated return to normal states once perturbed.[22] Mobile monitoring of outcomes is currently a focus and determining the long-term efficacy of mobile monitoring strategies is a priority of the Prechter Program.

The research programme maintains and regularly updates a website with the year-by-year publications that are based on

the cohort. The link is: https://medicine.umich.edu/dept/prechter-program/bipolar-research/publications-our-researchers.

What are the main strengths and weaknesses?

The major strength of the Heinz C. Prechter Longitudinal Study of Bipolar Disorder is the detailed breadth and depth of the clinical and biological data obtained, including data on medical and mental health comorbidities. This is a result of having multidisciplinary investigators from psychiatry, engineering, mathematics, neuroscience, and cell and developmental biology. Further, a core of dedicated participant collaborators continues with a shared vision for participating in research dedicated to solutions and innovations for the prevention, treatment and management of BD. A considerable amount of self-report data has been gathered on the participants digitally; this is a strength from the perspective of consistency because the participant directly reports the data and, as an undesigned benefit, the group was able to continue regular data collection in the post-pandemic remote environment.

A potential drawback of self-reported data is that there will be variability based on personal self-assessments (e.g. self-awareness) but this is mitigated in most questionnaires by providing descriptive statements associated with the numerical values. Additional weaknesses include the limited geographical ascertainment from a college town (Ann Arbor, MI) and surrounding community in south-east Michigan, reflected in the demographics (80% of the cohort is Caucasian and college-educated). This is an important consideration given the potential link between socio-economic status and BD. A related limitation includes its modest cohort size (particularly for minorities, the very young and the elderly) of people with BD and controls, partly due to the labour-intensive nature of clinical research and the commitment required from participants for longitudinal follow-up. This may skew the sample towards a group of participants (with potentially higher functioning and with more resources) who are able to participate in long-term studies and may not reflect the general population with severe chronic BD illness. As most elements of the study are now administered remotely, we plan to extend the geographical boundaries of our cohort and move into communities that will increase the diversity of our sample. To improve the diversity of this cohort, the research programme has created a Diversity Action Committee to engage with surrounding communities on diversity, equity and inclusion. We strive to make this cohort and workplace more diverse, equitable and inclusive while actively identifying and shifting focus to recruitment from populations not well represented in the cohort or in research on BD in general. The impact of this initiative is starting to show results: 31% of the 74 newly recruited participants since 2020 are under-represented racial minorities.

Another weakness is that the diagnostic categories remain in the DSM-IV definitions and have yet to be updated to DSM-5. However, there are no substantive changes for the lifetime diagnosis of BD between DSM-IV and DSM-5, as our diagnostic interview uses the most severe episode of depression and mania to establish the initial study entry diagnosis. Data on temperament and personality were collected with standardized assessment tools such as the NEO Personality Inventory-Revised as such and no attempts were made to collect categorical personality information based on the DSM criteria. Similarly to other cohorts such as STEP-BD,[23]

LiTMUS[24] and the Stanley Bipolar Study,[25] the average age of intake into the Heinz C. Prechter Longitudinal Study of Bipolar Disorder is 38.6 years. Despite a mean age at first episode of 17.6 years, individuals with BD appear less likely to engage in the study at earlier phases of their illness. As such, the early impacts of the illness may be under-represented in our sample, which speaks directly to the challenges of understanding longitudinal changes. Moreover, risk of death (suicide, overdose, other accidental) is substantially elevated in BD and the late mean age of enrolment will miss more severe cases who are deceased. The Heinz C. Prechter Longitudinal Study of Bipolar Disorder aspires to maintain active participation of individuals for their lifetime and to strengthen our engagement with minorities, those with greater levels of occupational/residential impacts, younger people with BD and those at risk for the illness via heritable identification.

Can I get hold of the data? Where can I find out more?

All clinical, longitudinal, biological and deoxyribonucleic acid samples are available through the Heinz C. Prechter Genetic Repository, distributed by the University of Michigan Central Biorepository. Initial diagnostic evaluation, omics data and longitudinal measures and outcome data, including coded subsets of the PRIORI speech data set, are available via request at prechter-data-request@med.umich.edu conditional on data-use agreement. Data can be shared in an itemized flat file format or a data analyst may be available for collaboration who can provide aggregate summaries as demonstrated in other global collaborations.[26] An ongoing updated publication listing is provided at http://www.prechterfund.org/bipolar-research/publications/. For specific enquiries and further information, please contact Melvin McInnis, MD at the following e-mail address: mmcinnis@umich.edu.

Ethics approval

The Heinz C. Prechter Longitudinal Study of Bipolar Disorder is reviewed annually and approved by the University of Michigan Institutional Review Board, IRBMED, HUM0000606. All participants provided written informed consent prior to enrolment in the study. Consent is reviewed with the participant annually for continuation in the study.

Data availability

See 'Can I get hold of the data?' above.

Author contributions

Conflict of interest

M.G.M. has consulted for Janssen and Otsuka Pharmaceuticals and received research support from Janssen. M.G.M. and E.M.P. are identified as inventors on US Patents No. 9 730 649 and 11 545 173, both held by the Regents of the University of Michigan and related to the technology behind the PRIORI app. H.J.B. serves on the scientific advisory board for Natrol, LLC and Moving Mindz, Pty Ltd. All other authors report no conflicts related to this work.

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