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Cohort Profile

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

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Why was the cohort set up?

The Heinz C. Prechter Longitudinal Study of Bipolar Disorder (PrBP), launched in 2005, is an open cohort study at the University of Michigan, Ann Arbor, USA. The study is specifically designed to identify and characterize the mechanisms underlying bipolar disorder (BP) and to develop methods to predict clinical outcomes of the disorder. The aims of the study are listed in Box 1.

Bipolar disorders are a chronic, heterogeneous and complex spectrum of conditions that typically are first identified in late adolescence and consist of pathological mood swings that include varying intensities of mania and depression.[1] A comprehensive description of the phenotype should include characterization of the longitudinal course of the disease, such as onset, symptom severity patterns, cognitive functioning and comorbidities. Outcomes include impaired social, vocational and personal functioning that often results in disability. Suicide and suicidal behaviours are common in BP and 4% of individuals with BP attempt suicide annually;[2] individuals with BP die by suicide at a 15-fold greater rate than that of the general population.[3]

There is no established aetiology of BP. Ongoing and future studies in this cohort target mechanisms related to aetiology of this illness. High heritability has been observed for the past century,[4] and an overlapping risk is observed with other mood disorders.[5,6] The search for BP susceptibility genes has identified approximately 12 genetic loci,[7] each with an odds ratio (OR) for the risk allele in the range of 1.1–1.5, suggesting the contribution of many genes each with small effects. There is evidence at the epigenetic[8] and interpersonal[9] levels for the interactive influence of genes and environment in the manifestation of BP.

The causal and modifying elements are numerous and therefore require a pluralistic approach to studying causality in BP (like many human diseases) (Figure 1). The origins of causal pluralism approaches in psychiatry began with Adolf Meyer[10] who viewed each person as an individual experiment of nature. Acknowledging Meyer's

Box 1 Information about the Heinz C. Prechter Longitudinal Study of Bipolar Disorder

Aims

1. To identify and characterize the mechanisms underlying bipolar disorder and to develop methods to predict clinical outcomes of the disorder
2. To compare the natural history of bipolar disorder over multiple phenotypic classes compared with healthy controls and other mood disorders
3. To determine social, psychological, medical, biological, and genetic determinants of course of bipolar disorder
4. To train and validate prediction models that can enhance clinical practice
5. To provide an infrastructure for additional basic and translational research

Inclusion criteria:

Cases: diagnosis of treated BP
Controls: no personal or family psychiatric history
English speaking
Age 18 or older

Exclusion criteria:

Mental retardation
Active substance dependence
Head injury
Medical illness causing BP

Data access:

Data are available on request, from the Heinz C. Prechter Bipolar Research Program website [http://www.prechterfund.org/about/contact/]

Dissemination of information and results:

Research projects (opportunities for participation in new studies) are listed at [http://www.prechterfund.org/bipolar-research/projects/]

Publications are listed (with links) and updated monthly at [http://www.prechterfund.org/bipolar-research/publications/]

influence, the *Perspectives of Psychiatry*[11] identifies four perspectives through which one may approach psychiatric disorders. The pluralistic approach provides the opportunity to integrate diverse information[12] free from dichotomous constraints and also offers a pragmatic approach to causality[13] and an open mind to discovery. Nevertheless, a framework is needed to organize classes of phenotypes within the broad domain of human disease in order to test effects of a proposed class on the clinical manifestation of the disease.

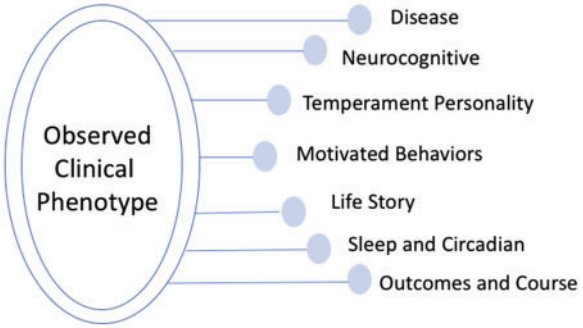

Figure 1. Seven Phenotypic classes of the Observed Phenotype. The manifestation of human disease is the result of multiple etiological elements from the individual, the environment and the interaction between the two. Causality is pluralistic with contributions from several phenotypic classes that vary over time.

Seven phenotypic classes (Figure 1) are the focus of this study and include the four perspectives of McHugh and Slavney.[11] The rationale for evaluation of a broad range of phenotypes is the need for a comprehensive assessment of the BP patient in the most efficient manner possible. All have been the focus of academic enquiry in BP and integrated into textbook discussions,[1] but are rarely studied using the comprehensive approach of the current study. The 'Disease' class is considered to be the driving biological mechanism. 'Motivated behaviours' describes a class of phenotypes that drive what the individual does; behaviours behind substance use have the capacity to cause or modify phenotypic expression. 'Dimensions of temperament or personality' compose a class of characteristics that interact with and frequently dominate clinical manifestations and are vital to the study of aetiology and causality. The class of 'Life experiences' includes social and environmental influences spanning a range of human experiences which impact the individual with the capacity to significantly modulate disease manifestation. The class of 'Neurocognitive functions' measures memory, executive functioning and other cognitive features to relate functioning to disease expression. 'Circadian and sleep' patterns are a phenotypic class that influences the nature and course of the illness. Finally, the 'Clinical outcome' patterns vary among people with BP and define classes of patients according to treatment response or functional capacity. This phenotypic class-based approach predated the Research Domain Criteria (RDoC) project of the National Institutes of Mental Health (NIMH),[14] a project that advocates a quantitative approach to clinical and biological phenomena rather than diagnostic categories. Both use

dimensional measures of phenomenology, biology and outcomes. The phenotypic class-based approach described herein has the advantage that most measures were selected to have direct clinical utility, and use practical dimensional data easily integrated with research.

Who is in the cohort?

The PrBP consists of an open cohort of individuals ascertained non-systematically to have BP, and healthy controls who agree to be followed longitudinally. Our goal is to study participants over their lifetime; at this time, the institutional review board (IRB) allows only 10-year renewal time periods. The participants are generally from southeast Michigan. The primary clinical source of participants was from admissions to the University of Michigan (UM) Health System psychiatric outpatient and inpatient clinical services. Inclusion criteria for BP I are based on DSM IV[15] criteria and on initial screening by telephone. Participants are required to have a history of treatment for a manic episode, whereas BP II individuals are required to have recurrent depression in addition to hypomania. All diagnoses are confirmed by a best-estimate diagnostic process with a review of all available research as well as clinical and medical data. The BP diagnostic group was allowed to have additional psychiatric comorbidities. All affective diagnoses are included and entered into the study as the participant qualified in pre-screening; this includes BP Not Otherwise Specified (NOS), Schizoaffective BP type, Major Depressive Disorder (MDD) and recurrent and other affective disorders (e.g. BP II single episode, MDD single episode, Schizoaffective Depressive type, Depression NOS and Dysthymia). Only one affective diagnosis is assigned to each participant. Non-affective disorders (e.g. substance use disorders, anxiety disorders, eating disorders and attention-deficit/hyperactivity disorder) were assigned when diagnosed, and were comorbid with the affective diagnosis. Controls were required to have no personal history of any psychiatric condition as well as a negative family history for psychiatric disorder. Control individuals who developed a psychiatric condition subsequent to ascertainment were continued in the study, caveated with their diagnostic category (e.g. major depression). It is recognized that the PrBP cohort is biased towards classic bipolar individuals from the community who are willing to commit to long-term follow-up. The inclusion and exclusion criteria are outlined in Box 1.

The sample currently includes 1111 participants: 731 individuals with any type of BP diagnosis, 23 with MDD, 34 with other mood disorders, 46 with non-mood/non-affective psychiatric illness and 277 healthy controls. Of those 731 with BP, 498 have BP I, 136 have BP II, 73 have BP NOS and 24 were diagnosed with schizoaffective disorder, bipolar type. The retention rate is 75% since the inception of the study. There are two main reasons behind not limiting the sample to the individuals with BP and controls. First, individuals in the cohort may move in and out of a diagnosis over the 10-year follow-up period (e.g. controls developing a psychiatric condition subsequent to ascertainment). If an individual's diagnosis changes, we do not exclude—instead, we follow the individual with their new diagnosis (e.g. depression). Second, the National Institute of Mental Health's RDoC discourages conducting studies within narrowly defined and categorically-based DSM/ICD diagnoses. Instead, RDoC encourages modelling of trajectories that cut across categorical diagnoses and in a wide range of study domains. In this manner, this study's methods may prove exemplary as the psychiatric research community integrates the DSM/ICD to a RDoC dimensional-oriented approach.[16] Every effort is made to followup these individuals, and every 2 years the National Death Index (NDI)[17] is searched for information on individuals who have not been in contact nor responded to enquiries for 2 years.

The demographic, socioeconomic and clinical characteristics of the sample are included in Table 1. Most participants were White (79%) and female (66%), with a mean age of 38.6 years at study entry. Average age of onset of illness (age of first depression or first mania) among individuals with BP was 17.3, with an average number of 7.2 mania episodes. Participants with BP had a high frequency of comorbid psychiatric conditions. Table 2 presents descriptive measures of depression, mania and health-related quality of life (HRQoL) at baseline (study entry). Symptoms of depression and mania were higher and HRQoL scores were worse for individuals with BP compared with controls (Table 2).

Supplementary Tables 1 and 2 (available as Supplementary data at *IJE* online) describe the distribution of psychiatric disorders and chronic medical conditions in the pooled sample as well as based on diagnosis category. Supplementary Table 3 (available as Supplementary data at *IJE* online) describes the distribution of follow-up status and reasons for withdrawal from the cohort. Of the 1111 participants who were enrolled, 960 (86%) had longitudinal data defined as two or more observations at different time points over the follow-up period.

How often have they been followed up?

The measures and the assessment frequency for this study are described in Table 3. Individuals are followed up on a bi-monthly basis with self-report measures of severity of mood symptoms using the 9-item Patient Health

Table 1. Descriptive statistics of the Prechter cohort at entry into the study

	Total cohort	Any mood disorder	All bipolar (BP)	BP I disorder	BP II	BP NOS	SAD-BP	MDD	Other affective disorders	Non-affective only	Controls (no diagnosis)
n	1111	788	731	498	136	73	24	23	34	46	277
Demographics											
Age at enrolment, mean (STD)	38.64 (14.25)	39.83 (13.60)	39.63 (13.49)	40.03 (13.30)	41.28 (14.59)	37.90 (13.73)	38.08 (12.68)	43.17 (12.72)	40.71 (15.43)	41.24 (14.29)	35.46 (15.45)
Women	729 (66%)	536 (68%)	481 (66%)	316 (63%)	100 (74%)	51 (69%)	14 (58%)	12 (52%)	24 (65%)	19 (41%)	174 (62%)
Socioeconomics											
Education, Mean (STD)	15.53 (2.47)	15.41 (2.51)	15.49 (2.52)	15.37 (2.70)	15.81 (2.19)	14.89 (2.58)	14.58 (2.41)	14.48 (2.69)	14.73 (2.50)	15.39 (2.28)	15.91(2.43)
Unemployed	193 (17%)	146 (19%)	131 (18%)	84 (17%)	21 (15%)	21 (28%)	5 (21%)	7 (33%)	8 (22%)	12 5(26%)	35 (13%)
Marital status[a]											
Married	356 (32%)	261 (33%)	246 (34%)	177 (36%)	52 (38%)	12 (16%)	5 (21%)	6 (26%)	9 (26%)	13 (28%)	82 (30%)
Separated	30 (3%)	25 (3%)	23 (3%)	15 (3%)	5 (4%)	3 (4%)	0 (0%)	2 (9%)	0 (0%)	1 (2%)	4 (1%)
Divorced	185 (17%)	152 (19%)	136 (19%)	89 (18%)	25 (18%)	17 (23%)	5 (21%)	4 (17%)	12 (35%)	8 (17%)	25 (9%)
Widowed	16 (1%)	10 (1%)	10 (1%)	5 (1%)	3 (2%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (2%)
Never married	523 (47%)	339 (43%)	315 (43%)	211 (42%)	51 (38%)	39 (53%)	14 (58%)	11 (48%)	13 (38%)	24 (52%)	160 (58%)
Race[b]											
White	894 (80%)	662 (84%)	620 (85%)	424 (85%)	117 (86%)	61 (84%)	18 (75%)	17 (74%)	25 (74%)	31 (67%)	201 (73%)
Black or African-American	103 (9%)	64 (8%)	53 (7%)	35 (7%)	8 (6%)	6 (8%)	4 (17%)	3 (13%)	8 (24%)	3 (7%)	36 (13%)
Asian	39 (4%)	9 (1%)	8 (1%)	6 (1%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	1 (3%)	6 (13%)	24 (9%)
Native Hawaiian or other Pacific Islander	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
American Indian/ Alaskan native	4 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	2 (1%)
	47	33	30	19	5	5	1	3	0	4	10

(continued)

Table 1. Continued

	Total cohort	Any mood disorder	All bipolar (BP)	BP I disorder	BP II	BP NOS	SAD-BP	MDD	Other affective disorders	Non-affective only	Controls (no diagnosis)
n	1111	788	731	498	136	73	24	23	34	46	277
More than one race	(4%)	(4%)	(4%)	(4%)	(4%)	(7%)	(4%)	(13%)	(0%)	(9%)	(4%)
Unknown	12 (1%)	10 (1%)	10 (1%)	6 (1%)	4 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	1 (0.4%)
Baseline clinical factors[c]											
Age at onset, mean (STD)	11.88 (10.62)	16.04 (9.24)	17.27 (7.87)	17.51 (8.12)	15.90 (6.66)	16.61 (6.34)	19.13 (9.29)	21.00 (10.29)	5.94 (14.05)	3.69 (10.38)	0(0)
Number of mania episodes, mean (STD)	4.52 (15.71)	6.37 (18.34)	7.20 (19.33)	9.50 (19.38)	0 (0)	1.26 (7.48)	15.38 (49.33)	0 (0)	1.79 (10.46)	0 (0)	0 (0)
Number of depression episodes, mean (STD)	14.72 (35.93)	21.34 (41.60)	23.89 (43.27)	22.96 (43.75)	31.16 (46.20)	16.85 (26.41)	12.90 (22.90)	20.22 (53.08)	3.93 (11.60)	0.11 (0.53)	0 (0)
Number of hypomania episodes, mean (STD)	15.83 (47.24)	23.61 (56.08)	27.04 (59.28)	25.26 (59.45)	32.29 (58.80)	21.93 (48.03)	49.84 (82.34)	0 (0)	0.52 (2.69)	0 (0)	0 (0)
Heart disease	24 (2%)	22 (3%)	20 (3%)	13 (3%)	5 (4%)	1 (1%)	1 (4%)	1 (4%)	1 (4%)	0 (0%)	2 (1%)
Migraine	293 (26%)	261 (33%)	253 (35%)	161 (32%)	60 (44%)	24 (33%)	8 (33%)	2 (9%)	6 (25%)	2 (4%)	30 (11%)

Bipolar (BP) participants were diagnosed according to the DSM IV criteria.

BP NOS, BP not otherwise specified; SAD-BP, schizoaffective bipolar type; MDD, major depressive disorder.

[a]One missing data point among BP1.

[b]Missing data for seven BP1, one BP II, one SAD-BP and two controls.

[c]Assessment for post-traumatic stress disorder began in 2010 after half of the sample was ascertained.

Table 2. Baseline symptoms and survey results based on condition; all values are mean (standard deviation)

	All	All mood	BP	BP1	BP II	BP NOS	SAD-BP	MDD	Other affective disorders	Non-affective only	Controls
Mood symptoms											
Depression (PHQ 9)	9.02	6.86	9.65	8.93	10.96	11.66	11.33	9.00	4.69	2.11	1.39
	(6.86)	(6.83)	(6.73)	(6.72)	(6.30)	(6.52)	(7.87)	(8.12)	(5.74)	(2.82)	(2.22)
Depression (HAM-D)	10.37	13.48	14.49	13.73	16.52	15.20	16.25	13.06	5.30	2.85	1.19
	(11.38)	(11.56)	(11.57)	(11.53)	(11.40)	(11.68)	(12.15)	(11.53)	(6.23)	(4.55)	(2.15)
Mania (ASRM)	4.03	3.69	4.11	3.87	4.49	4.96	4.47	3.41	4.42	2.97	2.89
	(3.68)	(3.71)	(3.69)	(3.63)	(3.53)	(4.04)	(4.40)	(3.48)	(4.12)	(3.84)	(3.48)
Mania (YMRS)	2.53	3.30	3.58	3.31	3.84	3.99	6.72	1.94	0.71	1.00	0.16
	(4.35)	(4.75)	(4.86)	(4.81)	(4.66)	(4.80)	(6.25)	(3.17)	(1.52)	(3.56)	(0.81)
Function and quality of life											
HRQoL(SF-36; PCS)	49.88 (9.36)	48.27 (10.31)	48.22 (10.35)	48.35 (10.22)	47.83 (10.54)	48.03 (10.82)	48.49 (11.63)	45.25 (12.55)	51.00 (7.77)	50.38 (9.24)	53.59 (4.94)
HRQoL(SF-36; MCS)	41.63 (8.85)	38.59 (8.94)	38.21 (8.84)	38.98 (8.95)	37.65 (8.32)	35.28 (8.64)	32.76 (7.14)	39.5 (11.73)	46.28 (5.28)	47.72 (4.62)	47.77 (4.36)
Function(LFQ)	213	21.90	22.27	21.37	22.78	24.24	28.00	21.17	20.33	17.24	15.31
	(7.99)	(8.31)	(8.39)	(8.52)	(7.58)	(7.83)	(9.92)	(8.03)	(9.71)	(5.06)	(4.28)
Medical conditions (count)	2.95	3.52	3.58	3.53	3.73	3.41	4.33	2.96	2.53	1.78	1.52
	(2.44)	(2.49)	(2.49)	(2.51)	(2.35)	(2.26)	(3.28)	(2.36)	(2.42)	(1.92)	(1.58)
Personality											
Neuroticism	56.96	62.83	63.54	62.27	66.14	70.63	65.33	61.81	49.57	47.90	43.52
	(15.63)	(14.08)	(13.86)	(13.85)	(14.13)	(13.92)	(12.08)	(11.65)	(13.42)	(10.98)	(10.03)
Extraversion	49.26	48.27	48.06	48.90	44.89	43.63	49.58	49.56	51.71	51.05	51.50
	(11.59)	(12.33)	(12.36)	(12.44)	(12.29)	(15.31)	(9.78)	(15.14)	(9.43)	(12.25)	(8.91)
Openness	56.92	57.99	58.22	58.69	57.43	60.69	55.78	53.25	56.07	53.44	54.80
	(11.91)	(12.29)	(12.40)	(12.56)	(12.27)	(10.68)	(11.91)	(10.01)	(10.69)	(8.36)	(11.05)
Agreeableness	49.66	49.29	49.16	50	47.31	53.19	45.78	49.5	51.57	47	51.06
	(12.26)	(12.82)	(12.94)	(12.49)	(14.01)	(13.19)	(13.09)	(11.82)	(11.02)	(10.72)	(10.87)
Conscientiousness	46.04	44.17	43.75	43.13	47.09	43.88	41.69	47.44	50.54	49.31	50.24
	(13.16)	(13.75)	(13.60)	(13.62)	(13.83)	(13.53)	(12.29)	(12.66)	(15.73)	(11.33)	(10.64)

PHQ-9, Patient Health Questionnaire-9 item; ASRM, Altman Self-Rating Mania Scale: HRQoL, Health Related Quality of Life; LFQ, Life Functioning Questionnaire; YMRS, Young Mania Rating Scale; HAM-D, Hamilton Depression Rating Scale: SF-36, Short Form Survey- 36-Item.

Table 3. Measures and their timing across study domains

Phenotypic Class	Measure/Process	Items	Format	Construct/Subdomains	Timing in the Cohort
Disease	*Diagnostic* Interview for Genetic Studies (*DIGS*)[30]	[a]	Interviewer	Categorical Disorders/Psychiatric Disorder(s)	Baseline
	Longitudinal Interval Follow up Evaluation[29]	[a]	Interviewer	Categorical Disorders/Psychiatric Disorder(s)	Bi-annual
Temperament - Personality	Revised *NEO Personality* Inventory (*NEO* PI-*R*))[31]	240	Self-rated	Personality: Extraversion, Agreeableness, Neuroticism, Openness to Experience, Conscientiousness,	Baseline, 1 Year, 5 Year, 10 Year
	BIS-11: Barratt Impulsiveness Scale[35]	30	Self-rated	Impulsivity	Baseline
	Buss-Durkee Hostility Inventory[33]	75	Self-rated	Hostility	Baseline
	Brown-Goodwin Aggression History[34]	11	Self-rated	Aggression	Baseline
Motivated Behavior	Fagerstrom Test for Nicotine Dependence (FTND)[26]	6	Self-rated	Substance use: Nicotine Dependence	Every 6 months
	Alcohol Use Disorders Identification Test – Revised (AUDIT-R)[25]	10	Self-rated	Substance use: Alcohol Dependence	Every 6 months
Life Experiences	*Life Events Occurrence* Survey (*LEOS*)[28]	38	Self-rated	Life Events	Every 6 months
	Life Events Checklist (*LEC*)[38]	38	Self-rated	Life Events	Annually
	Family Adaptability and Cohesion Evaluation Scale (*FACES) II*[88]	30	Self-rated	Social Relations	Annually
	Childhood Trauma Questionnaire (CTQ)[40]	28	Self-rated	Childhood Trauma	Baseline
	Life Functioning Questionnaire (LFQ)[89]	14	Self-rated	Functionality	Every 2 Months
	Experiences in Close Relationships Revised[39]	36	Self-rated	Close Relationships	Baseline
	Working Alliance Inventory[90]	12	Self-rated	Functionaliy	Baseline
Neuro-cognitive Function	Wechsler Abbreviated Scale of Intelligence[91]	[a]	Technician administered	Intellectual Functioning	Baseline
	California Verbal Learning Test[92]	[a]	Technician administered	Verbal Learning and Memory	Baseline, years 1, 5, 10
	Rey-Osterrieth Complex Figure Test[93,94]	[a]	Technician administered	Visual Learning and Memory	Baseline, years 1, 5, 10
	Facial Emotion Perception Test[95]	[a]	Technician administered	Emotion Processing	Baseline, years 1, 5, 10
	Emotion Processing Test[96]	[a]	Technician Administered	Emotion Processing	Baseline, years 1, 5, 10
	Purdue Pegboard Test[97]	[a]	Technician administered	Fine Motor Functioning	Baseline, years 1, 5, 10
	Parametric Go/No Go Test[98]	[a]	Technician administered	Attention and Response Control	Baseline, years 1, 5, 10
	Stroop Color Word Test[99]	[a]	Technician administered	Executive Functioning	Baseline, years 1, 5, 10
	Trail Making Test[100]	[a]	Technician administered	Executive Functioning	Baseline, years 1, 5, 10
	Wisconsin Card Sort Test[101]	[a]	Technician administered	Executive Functioning	Baseline, years 1, 5, 10
	Synonym Knowledge Test[102]	[a]	Technician administered	Premorbid verbal skills	Baseline, years 1, 5
	Test of Memory Malingering[103]	[a]	Technician administered	Effort / Dissimulation	Baseline, years 1, 5, 10
Circadian and sleep patterns	Epworth Sleepiness Scale[46]	8	Self-rated	Subjective sleep quality, Sleep latency, Sleep duration, Habitual sleep *Efficiency*	Annually

(continued)

Table 3. Continued

Phenotypic Class	Measure/Process	Items	Format	Construct/Subdomains	Timing in the Cohort
	Pittsburgh Sleep Quality Index[27]	11	Self-rated	Subjective sleep quality, Sleep latency, Sleep duration Habitual sleep *Efficiency*	Every Six Months
	Munich Chronotype Questionnaire (MCTQ)[47]	37	Self-rated	Chronotype: Morning or Evening person	Annually
	Seasonal Pattern Assessment *Questionnaire* (*SPAQ*)[22]	29	Self-rated	Seasonality of Circadian and Sleep	Baseline
Clinical	Patient Health Questionnaire (PHQ)[18]	9	Self-rated	Depression	Every 2 Months
Outcomes	Hamilton Depression Rating Scale (*HAM-D*)[48]	21	Interviewer	Depression	Annually
	Young Mania Rating Scale (YMRS)[49]	11	Interviewer	Mania	Annually
	Altman Self-Rating Mania Scale (ASRM)[19]	5	Self-rated	Mania	Every 2 Months
	General Anxiety Disorder (GAD)[21]	7	Self-rated	Anxiety	Every 2 Months
	Columbia Suicide Severity Rating Scale (C-SSRS)[23]	[a]	Self-rated	Suicidality	Annually
	Short Form Health Survey 12-Item (*SF-12*)[20]	12	Self-rated	Quality of Life	Every 2 Months
	Short Form Health Survey 36-Item (*SF-36*)[24]	36	Self-rated	Quality of Life	Every 6 months

[a]The number of items in the test varies with the patient response.

Questionnaire (PHQ-9)[18] and Altman Self-Rating Mania Scale (ASRM).[19] Individuals also filled out the Short Form 12 (SF12).[20] Since 2012, we have also added the Generalized Anxiety Disorder 7-item (GAD-7),[21] Seasonal Pattern Assessment Questionnaire (SPAQ)[22] and Columbia Suicide Severity Rating Scale (C-SSRS)[23] scales to our battery. At 6 months, all participants completed the Short Form 36 (SF36),[24] Alcohol Use Disorders Identification Test (AUDIT),[25] Fagerstrom Test for Nicotine Dependence (FTND),[26] Pittsburgh Sleep Quality Index (PSQI)[27] and Life Events and Occurrences Scale (LEOS).[28] Annual measures included measures of clinical severity, life functioning and environmental assessments (see Table 3). Neurocognitive assessments were performed at baseline, year 1, year 5 and year 10. The Longitudinal Interval Follow-up Evaluation (LIFE)[29] was administered by clinicians every 2 years. A best estimate diagnostic review process was performed after the initial evaluation and was reviewed by two doctoral level clinicians with consideration of the available medical records and other relevant historical records such as pharmaceutical records. When the diagnosis is suspected to have changed following a clinically relevant event such as an admission or a LIFE interview, a best-estimate process is triggered to re-review the diagnosis. When the diagnosis changes, the individual continues to be followed but is no longer considered to be a member of the initial diagnostic category.

What has been measured?

Bipolar disorder was deconstructed into seven phenotypic classes as outlined in Figure 1 (phenoclasses), each of which contains relevant measures that describe elements that map to the specific class.

Disease class

The standard categorical diagnoses of disease were gathered using the Diagnostic Interview for Genetic Studies (DIGS),[30] a detailed clinical assessment that applies operational criteria to determine the lifetime diagnoses. The LIFE,[29] a clinical assessment selected to estimate the episode frequency over the preceding time period, was administered on average every 2 years.

Neurocognitive class

Neurocognitive measures of auditory and visual memory, emotion processing, motor control and excecutive functioning, which includes inhibitory control, conceptual reasoning and set shifting, are listed in Table 3. The goal of assessing this phenotypic class was to measure neurocognitive functioning in individuals with BP compared with controls, in order to evaluate the relationship between

neurocognitive functioning and BP. Measures were repeated to evaluate the effect of variable mood states and time course on cognitive states.

Psychological dimensions class

Personality and temperament are dimensional features measured with the NEO-Personality Inventory Revised (NEO PI-R),[31] a 240-item self-report scale based on the five-factor model of personality.[32] Additional temperamental and psychological measures include the Buss-Durkee Hostility Inventory (BDHI) which measures an attitudinal component of hostility (Resentment and Suspicion) and a motor component (Assault, Indirect Hostility, Irritability and Verbal Hostility),[33] Brown-Goodwin Life History of Aggression (BGLHA)[34] and Barratt Impulsiveness Scale (BIS-11).[35] The goal of these measures was to determine the psychological manifestation of disease.

Motivated behaviour class

The most common motivated behaviours among individuals with BP include substance use disorders such as alcohol abuse and use of illicit drugs and tobacco, which are frequently abused by individuals with BP. Lifetime data are gathered (DIGS interview)[30] and ongoing use patterns are assessed bi-annually using the AUDIT scale.[25] Smoking is assessed using the Fagerstrom Test for Nicotine Dependence (FTND).[26] The onset, nature and frequency of substance use relative to BP is of aetiological interest as it remains unclear as to whether BP can be caused or exacerbated by substance abuse[36] or if substance abuse occurs consequentially to BP disorder and influences the course of illness.[37]

Life story class

The life story class records data on life events,[28,38] experiences in intimate relationships,[39] childhood trauma[40] and the familial environment.[41,42] Personal experiences throughout life vary considerably, as does the personal perception of these experiences.[43] The data are self-report and often retrospective, selected to measure and compare the influence of life experiences in the context of BP disorder.

Circadian pattern and sleep class

BP disorder has been proposed to be an illness of circadian rhythms.[44] Associations have been reported with clock genes known to affect circadian patterns.[45] To determine the effect of this phenotypic class, we gathered data on circadian and sleep patterns using standard scales measuring sleep quality,[27] daytime sleepiness[46] and circadian patterns.[47]

Outcomes and severity class

Bipolar disorders are defined by DSM IV criteria[15] but are characterized by their trajectory, the severity of symptoms, the number of episodes, response to medications and the ability of the individual to engage in social, personal and vocational activities. In this study, regular measures of depression and mania symptoms were recorded using clinician-rated instruments[48,49] and self-rated instruments.[18–20] Included in this class are responses to medication and other interventional strategies to manage BP.

Other data

At the time of enrolment in the study, a blood sample was procured to obtain a DNA sample. Lymphoblastic cell lines were initially established but this was discontinued in 2012. All individuals currently undergo genotyping use the Infinium Human Core Exome v1–0 genomic panel from Illumina. A subset of the cohort has undergone an average of 9X whole genome sequencing. The genomic sequence has been imputed for the remainder.

What has been found? Key findings and publications

Comorbidities

Medical and psychiatric disorders are comorbid with BP in the PrBP cohort, which is consistent with previous studies.[50] Migraine headaches were found to be more frequent among BP compared with controls (31% vs 6%; odds ratio (OR) = 3.5, 95% confidence interval (CI): 2.1–5.8), with greater risks associated with female sex, increases in measures of severity (earlier onset and greater frequency of mood episodes) and a history abuse or neglect.[51] Eating disorders (ED), anxiety disorders and alcohol use disorders were also more common among individuals with BP compared with controls.[52] The age at onset of BP was earlier with comorbid ED (15.1 vs 18.4 years, $P = 0.002$); if anxiety onset preceded ED (13 vs 15.1 years, $P < 0.05$); and if the onset of alcohol use disorders occurred after a comorbid diagnosis of both BP and ED.[52] Comorbid alcohol use disorder and BP affected several measures of cognitive functioning.[53] In addition, metabolic syndrome is common among participants in the PrBP cohort.[54]

Trauma and life history

Life events and experiences shape the individual. A history of childhood trauma was common among the BP individuals compared with the controls, and in general is associated with a detrimental effect on inhibitory control and

attention accuracy as measured in Parametric Go/NoGo trials (NoGo $P = 0.013$; Go $P < 0.001$).[55] Reaction times were also associated with age of onset and illness duration. Depressive symptoms at the time of assessment were not associated with outcome.[55] A history of trauma increased the risk of ED.[52]

Diet, metabolites, microbiome and health outcome

Detailed dietary assessments identified lower intake of polyunsaturated fats and higher level of saturated fats in individuals with BP ($P = 0.021$), suggesting that lifestyle and dietary changes were warranted from a metabolic perspective.[56] Arachadonic acid levels were lower among those with a history of suicide attempts compared with non-attempters ($P = 0.026$).[57] Lower levels of linoleic acid predicted worse outcomes of mood burden ($P = 0.03$).[58] An association between the ratios of plasma ω-3 and ω-6 lipids with burden of disease measures was found in individuals with BP.[59] Taxonomical characterization of the microbiome in BP found a relative decrease in *Faecalibacterium*, a gut bacterium that is associated broadly with human disease states and is associated with increased measures of depressive symptoms and sleep disturbances among those with BP.[60] Antipsychotic medication has an effect on the microbiome by decreasing species diversity, specifically among females with BP ($P = 0.015$).[61]

Sex and gender differences in the course and risk factors of BP

In women, but not men, poor sleep quality at baseline predicted increased severity and frequency of episodes of depression ($P < 0.001$), and poor sleep quality was a stronger predictor than baseline depression.[62] Poor sleep quality at baseline was a predictor of the severity and variability of mania as well as frequency of mixed episodes.[63] In men, however, baseline depression was a stronger predictor of mood outcome compared with poor sleep quality.[62] Sex differences are identified in many studies of the PrBP cohort, from microbiome,[61] and comorbidities[51,52] to cognitive functioning.[64]

Personality traits and course of illness

Over 2 years of follow-up of patients with BP, personality trait—particularly neuroticism—was found to influence severity of the illness, measured by average depressive and mania symptoms.[62] Neuroticism was a stronger predictor of mood outcome in men than women. In men, neuroticism was also a stronger predictor of course than sleep quality.[62]

Neurocognitive function at baseline, over time, and genetic correlates

At study entry, neurocognitive function was poorer in BP than controls in several measures of memory, executive functioning and motor abilities;[65,66] however, changes in executive functioning from baseline to 5-year follow-up were similar across diagnostic groups.[67] Older age at baseline was associated with worse initial performance in executive functioning and with greater decline in processing speed with interference resolution as well as verbal fluency with processing speed. There is likely to be a combined effect of age and BP on cognitive functioning.[68] Higher education was marginally associated with a smaller declining slope for processing speed with interference resolution.[67] The phase of illness (elevated mood vs depressed mood) affected the cognitive scores, with the hypomanic/mixed affective state being more sensitive ($P = 0.0001$).[66] Overall, cognitive and emotional reactivity appears to be dysregulated in BP individuals.[69]

Cognitive ability is affected by treatment with second-generation antipsychotics (SGAs), with measurable influence from genetic variation; BP individuals with the *COMT* rs5993883 GG-genotype treated with SGAs had lower verbal learning and memory scores, and lower scores on a cognitive control task.[70] An interaction was found between SGA-*COMT* and GG-genotype on verbal learning, verbal memory and control.[70]

Genetics and cellular modelling

Data from the PrBP cohort have been included in genome-wide association (GWAS) studies[71,72] that have confirmed susceptibility genes *CACNA1C* and *ANK3* for BP. Offspring at risk of BP from this cohort[73] show an increase in the polygenic risk score (PRS) among those developing affective phenotypes.[74] Categorization according to internalizing (e.g. anxiety) disorders and externalizing (substance abuse) disorders clearly demonstrated familial aggregation.[75]

Cellular models of BP using neurons derived from induced pluripotent stem cells (iPSC) from fibroblasts sampled from the PrBP cohort found evidence of hyper-excitability of BP-derived neurons compared with control neurons. The hyper-excitability could be returned to control levels when the neurons were cultured overnight with a therapeutic concentration of lithium.[76,77] There was also evidence of disrupted neural patterning, consistent with a developmental aetiology driving BP.[78] Microarray analysis of these neurons has identified a panel of misregulated microRNAs[79] and alterations in astrocyte behaviour and function.[80]

Computational modelling

The clinical course and longitudinal pattern from the LIFE interview was the basis for Bayesian nonparametric

hierarchical modelling using latent class and patient-specific models. Three subtypes were justified using the course of subsyndromal patterns, and differed in the rates of attempted suicide, disability status and chronicity of affective symptoms.[81] Modelling of acoustic patterns of speech passively captured from conversations on a smartphone identified acoustic features associated with depressive and manic states, with acceptable accuracy for each state [area under the curve (AUC) 0.74 and 0.70, respectively.[82] Latent growth modelling of executive functioning in BP found an effect of age and baseline functioning. Individuals with BP had poorer executive functioning, but the linear slope of the decline over 5 years was the same as in the control group.[67]

What are the main strengths and weaknesses?

The major strength of the PrBP cohort is the detail and depth of clinical and biological data obtained about the participants. A core of dedicated participant collaborators continues to demonstrate a shared passion and vision for research dedicated to solutions for BP disorder. The study has investigators from psychiatry, engineering, mathematics, cell and developmental biology, among other disciplines, all of whom have contributed to the multidisciplinary nature of the cohort data. The project was designed to gather extensive amounts of data from the phenotype classes. There are extensive follow-up data on all individuals, with symptom severity measures gathered every 2 months, a semi-annual assessment of behaviours, an annual assessment of disease symptoms and environmental influences, and evaluation of cognitive functions at baseline and years 1, 5 and 10. A baseline biological measure, a genotype fingerprint consisting of 340 000 SNPs (single nucleotide polymorphisms), was routinely collected on these participants for analytical purposes and identity confirmation. A considerable amount of self-report data has been gathered on the participants; this is a strength from the perspective of consistency because the data are directly reported by the participant. A potential drawback of self-reported data is that there will be variability based on personal self-assessments, 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 and community in Southeast Michigan, reflected in the demographics (the majority of the cohort is White and college educated). This is an important consideration, given the potential link between social class and BP.[83,84] A related limitation includes its modest cohort size (particularly for minorities, the very young and elderly) of cases and controls, which is due in part 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 well-educated and committed group of participants who willing to participate in long-term studies and may not reflect the bipolar population with severe chronic illness in an underserved inner city community. The diagnostic categories remain in the DSM IV definitions and have yet to be updated to DSM 5. There are no substantive changes for the lifetime diagnosis of BP between DSM IV and DSM 5, as the DIGS 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 PI-R, a dimensional instrument based on the 5-factor model of personality;[31] no attempts were made to collect categorical personality information based on the DSM criteria. Similar to other cohorts such as STEP-BD,[85] LITMUS[86] and the Stanley Bipolar Study,[87] the average age of intake into the Prechter study is 38.6. Despite a mean age at first episode of 17.6 years, individuals with BP appear less likely to engage in the study at earlier phases of their illness.

The PrBP aspires to maintain active participation of individuals for their lifetime and to strengthen the engagement of minorities, younger people with BP, and those at risk for the illness. The Heinz C. Prechter Bipolar Genetic Repository provides access to these unique clinical and biological data. The availability of the data and the biological samples (DNA and cell lines), as well as continued commitment of the participants, will provide a solid base for ongoing research into mechanistic and preventative research programmes in bipolar and related mood disorders.

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

All data and samples are available through the Heinz C. Prechter Genetic Repository, distributed by the University of Michigan Central Biorepository (CBR). Enquiries: [http://www.prechterprogram.org/data]. Initial evaluation, DNA and genotype data are available for independent analyses. Longitudinal and outcomes data are available subject to review of the proposed analyses. Updated publications are referenced: [http://www.prechterfund.org/bipolar-research/publications/].

Supplementary Data

Supplementary data are available at *IJE* online.

Profile in a nutshell

- This open longitudinal cohort of bipolar disorder was set up to identify biological and psychological mechanisms, and clinical predictors of disease and outcomes. It advances a multi-modal approach for computational analyses using the unique features of the breadth and depth of data from seven phenotypic classes.
- Data for the PrBP cohort were collected in SE Michigan from 2005 to 2017; there are 1111 participants in the baseline sample described herein, and ascertainment and follow-up continues. The study population reflects the local population, 80% Caucasian and 20% minorities; the average age at entry is 39 (range 18 – 65).
- Bi-monthly follow-up takes place after an extensive baseline evaluation. Participants currently active: 850; aggregate attrition rate: 75%; 960 (86%) participants have at least two follow-up points.
- Seven phenotypic classes include categorical or dimensional assessments:(i) disease (DSM); (ii) neurocognitive; (iii) psychological/temperament; (iv) motivated behaviours; (v) life story; (vi) circadian patterns; and (vii) outcomes and severity.

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