Predictors of functional impairment in Bipolar Disorder: Results from the Global Bipolar Cohort collaborative network

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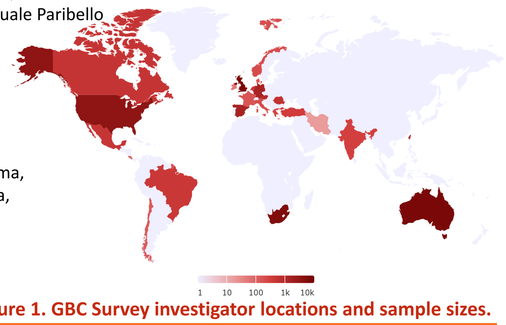

Figure 1. GBC Survey investigator locations and sample sizes.

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Background and Objectives

Persistent functional impairment is common in bipolar disorder (BD).[1] Functional outcome is influenced by several clinical and cognitive features, and socio-demographic factors that may be regionally specific. This project sought to unite the clinical research community to examine the influence of key factors on functional outcomes in well-characterized BD cohorts from around the world.

Methods

Over the years, several BD cohorts had been established internationally, which could be combined into a powerful global cohort that encompasses diversity within this heterogeneous psychiatric condition. The Global Bipolar Cohort consortium was established in 2019 to facilitate global collaborations, and expedite, leverage and optimize resources for powerful research that encompasses diversity within BD. Expanding on an initial study of 5,882 participants from 13 cohorts across 7 countries by Burdick *et al*,[2] an inventory of additional studies available globally was undertaken.

Global survey of bipolar studies

The GBC survey was designed to collect information on clinical and demographic features as well as availability of biological samples to maximize the use of existing data. The survey was created in mailchimp and distributed via direct email (n=691 contacts) or indirectly via consortium coordinators to their private email lists and/or via twitter. Survey respondents who indicated that they had functional outcome measures were invited to participate in the present study.

Defining good vs. bad functioning

Instructions for analysis to examine functional outcomes in bipolar disorder were provided to each participating group. Groups were asked to identify a single functional outcome measure from data collected at their site, with preference for the measure with : 1) the most complete data, 2) the most detailed assessment (e.g. FAST instead of GAF), and 3) the most overlap with other contributing sites. Measures were dichotomized into 'good' and 'bad' outcomes using: 1) *a priori* cutoff, or 2) mean z-scores [coding: good=0, and bad=1]. For marital and employment status, the demographics of cohort would determine the coding of widowed and retired status [i.e. coded as missing or (formerly) married/employed; noting that typical marital and retirement age varies from country to country].

Sample characteristics were completed to assist in the selection of variables for regression analysis. All available measures were considered, as appropriate to availability, reliability and sample size, ensuring a minimum of 10 subjects per variable ratio for regression analysis. Specific variables that were considered 'core' (see * in Table 2) were prioritized over other variables.

The design was intentionally inclusive, allowing sites to contribute results regardless of the specific measures used to assess mood, functional outcome, and other illness features. As such, data was not combined across cohorts, but each site conducted analysis of their own data, using a distributed data analyses framework.

Logistic regression to predict good vs. bad functioning

Investigators were instructed to run logistic regression using the "enter" method, including selected LEVEL ONE, TWO &/or THREE measures as independent variables (in the order of Table 2). The dependent variable was the functional outcome measure. The possible independent variables were: age, sex, race, education, BD subtype, psychosis history, current depression, current mania, # prior manias, # prior depressions, age onset depression, age onset mania, comorbid substance use disorder, comorbid anxiety disorder, general cognitive ability (*g*), premorbid IQ, medication (by class), total medication load. All model-level and predictor-level results were reported.

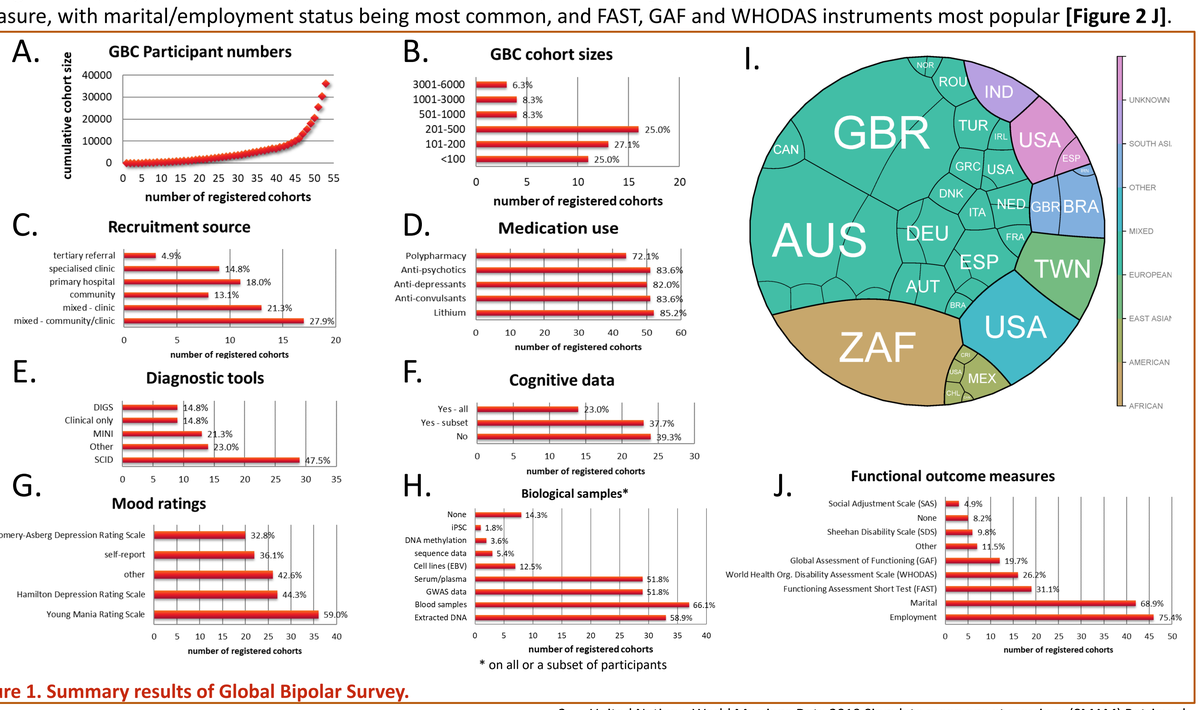
General cognitive ability: '*g*'

Sites that had cognitive data derived '*g*' using an unrotated principal component analysis (PCA) with up to two representative measures per cognitive domain (maintaining a minimum of 10 subjects per variable included). A global measure (e.g. IQ) could be substituted, but premorbid estimates of IQ were not included when calculating *g*.

Results

Global survey of bipolar studies

The GBC survey identified 51 cohorts to date, with a range of sizes (<100 to several thousand) that tallied to 36,300 participants **[Figure 1, Figure 2 A-B]**. Around 60% of the cohorts were clinic or hospital-based samples, and almost all had medication use data **[Figure 2 C-D]**. Most studies employed the SCID for diagnosis, and 60% had cognitive data on some or all of their cohort **[Figure 2 E-F]**. The Young Mania and Hamilton Rating Scales (YMRS, HDRS) were the most popular mood rating tools **[Figure 2 G]**. Only 14% had no biological samples, and 65% of study participants were of European origin **[Figure 2 I]**. Most cohorts (91.8%) had a functional outcome measure, with marital/employment status being most common, and FAST, GAF and WHODAS instruments most popular **[Figure 2 J]**.



* on all or a subset of participants

Figure 1. Summary results of Global Bipolar Survey.

Results (cont'd)

Functional study cohorts

A total of 24 investigator groups from 13 countries returned data for this study, including ~11,200 participants from Australia (n=4,265), North America (n=1,777), Europe (7 countries; n=3,508), Africa (n=615), and South Asia (n=1,025) **[Table 1]**.

For regression analysis, the cohorts used Global Assessment of Function (GAF; n=10), Functioning Assessment Short Test (FAST; n=4), marital (n=4) or employment status (n=5) as outcome **[Figure 3 A]**. All sites using marital status as outcome had age quartiles 2-3 above the country-specific mean marital age.[2] The cohort with oldest population was DOBi (m±SD=66.0±7.6) and youngest was UTHealth (30.9±14.7). Most cohorts had a predominance of female patients **[Figure 3 B]**, with an overall 62% female (n=7,136).

Overall, 43.8% of participants (n=5,637) were defined as having a 'bad' functional outcome. Logistic regression omnibus tests for the majority of sites were significant **[Table 1]**.

Table 1. Description of participating cohorts and overall regression model statistics.

Cohort	Region	Country	n total	% bad function	Variable: case ratio	Omnibus χ^2	Omnibus df	Omnibus Sig.
UTHealth	N.America	USA	326	64.1%	17.16	55.41	19	2.013E-05
GAIN	N.America	USA	1451	44.2%	111.62	195.80	13	9.935E-35
BDRN	Europe	UK	2042	45.5%	120.12	420.06	17	1.176E-78
BIPLONG	Europe	Austria	223	53.4%	11.15	38.81	20	0.00705
FOR2107	Europe	Germany	142	47.9%	10.14	48.71	14	1.003E-05
ATLADIS	Europe	Greece	275	56.7%	14.47	53.85	19	3.481E-05
DDBC	Europe	Netherlands	73	35.6%	9.13	38.99	11	5.318E-05
DOBi	Europe	Netherlands	106	40.6%	13.25	11.57	8	0.17140
Cagliari	Europe	Italy	266	50.0%	15.65	67.90	17	4.935E-08
SANTPAU	Europe	Spain	60	53.3%	10.00	11.61	6	0.07128
BIPOGENET-IPM	Europe	Spain	68	29.4%	11.33	9.42	6	0.15150
MadManic	Europe	Spain	124	27.4%	13.78	60.45	15	2.109E-07
FIDMAG	Europe	Spain	129	55.8%	12.90	111.00	10	3.353E-19
NIMHANS	Asia	India	390	61.5%	26.00	296.14	15	3.537E-54
GREAT	Asia	Taiwan	501	33.3%	55.66	30.19	13	0.0044
SelcukU	Asia	Turkey	134	35.1%	11.17	94.16	12	7.707E-15
NeuroGAP	Africa	South Africa	615	76.9%	87.86	107.46	7	3.088E-20
COFAMS	Oceania	Australia	70	52.9%	10.00	7.81	7	0.34955
COGSBD	Oceania	Australia	96	42.7%	10.67	32.24	9	0.00018
FUP	Oceania	Australia	1972	35.0%	123.25	135.42	16	5.651E-21
AGBD	Oceania	Australia	1598	61.4%	84.11	189.28	19	4.557E-30
UNSW	Oceania	Australia	235	40.4%	14.69	57.55	16	1.346E-06
IGP	Oceania	Australia	74	37.8%	10.57	29.28	7	0.00013
BCOS	Oceania	Australia	220	-	-	-	-	-

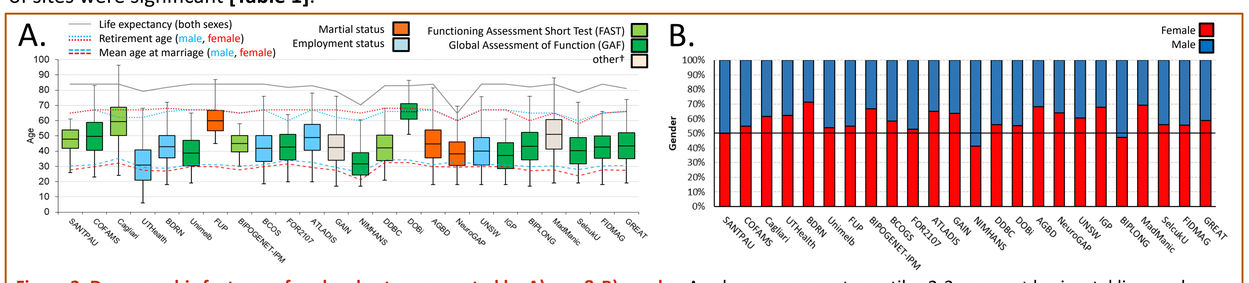


Figure 3. Demographic features of each cohort, represented by A) age & B) gender. Age boxes represent quartiles 2-3, mean at horizontal line, and whiskers indicating range. Boxes are colour coded by outcome measure. Country-specific age at marriage,[3] retirement and life expectancy[4] are shown. †, World Health Organisation Disability Assessment Scale (WHODAS v2.0) & a General impact of illness on life functioning (5-point scale).

Table 2. Summary of significant and top associations across cohorts

	# cohorts with measure	Sig Assoc P<0.05 N (%)	Top Assoc RANK=1 N (%)	Top Assoc RANK=1-3 N (%)
LEVEL ONE MEASURES	---	---	---	---
*Age	23	11 (47.8%)	6 (26.1%)	10 (43.5%)
*Sex	23	3 (13.0%)	1 (4.3%)	3 (13.0%)
*Race ‡	12	0 (0%)	0 (0%)	2 (16.7%)
*Education level	17	7 (41.2%)	2 (11.8%)	8 (47.1%)
LEVEL TWO MEASURES	---	---	---	---
*BD subtype	14	0 (0%)	0 (0%)	2 (14.3%)
*Psychosis History	21	0 (0%)	1 (4.8%)	3 (15.0%)
*Current depression	17	**13 (76.5%)**	**10 (58.8%)**	**12 (70.6%)**
*Current Mania	15	5 (33.3%)	0 (0%)	5 (33.3%)
Age at onset depression	5	0 (0%)	0 (0%)	1 (20.0%)
Age at onset mania	8	2 (25.0%)	1 (12.5%)	3 (37.5%)
# prior manias	1	0 (0%)	0 (0%)	0 (0%)
#prior depressions	1	0 (0%)	0 (0%)	0 (0%)
*# total episodes	12	3 (25.0%)	0 (0%)	3 (25.0%)
#hospitalizations	10	3 (3.0%)	0 (0%)	2 (20.0%)
#suicide attempts	9	2 (22.2%)	0 (0%)	2 (22.2%)
Comorbid substance disorder	10	4 (40.0%)	0 (0%)	2 (20.0%)
Comorbid anxiety disorder	9	1 (11.1%)	0 (0%)	0 (0%)
LEVEL THREE MEASURES	---	---	---	---
Global cognition (g)	4	1 (25.0%)	0 (0%)	2 (50.0%)
Premorbid IQ	4	0 (0%)	0 (0%)	1 (25.0%)
MEDICATIONS	---	---	---	---
None	8	2 (25.0%)	0 (0%)	1 (12.5%)
Lithium	14	5 (35.7%)	0 (0%)	3 (21.4%)
Anticonvulsants	12	2 (16.7%)	1 (8.3%)	1 (8.3%)
Antidepressants	10	4 (40.%)	1 (10.%)	4 (40.0%)
Antipsychotics	12	3 (25.0%)	0 (0%)	0 (0%)
Total # psychotropic medicines	11	1 (9.1%)	0 (0%)	1 (9.1%)

Note: * variables considered 'core' were prioritized over other variables. ‡ 11 of 12 cohorts with race variability were mostly European (EUR; 86.8%, n=8712), with non-EUR predominant in NeuroGAP (AFR 55%, other 37%). Cohorts that excluded race from regression were >95% EUR (n=7), SAS (NIMHANS), SEA (GREAT) or unknown.

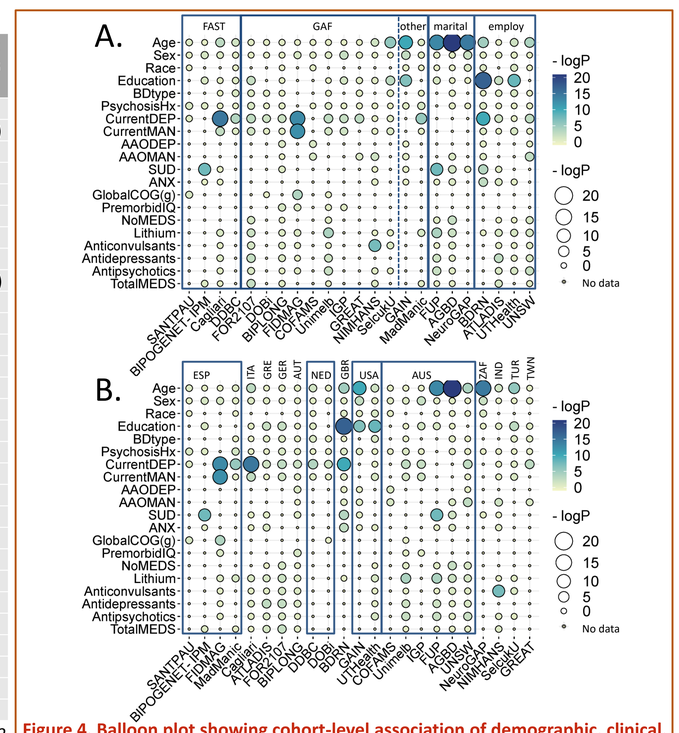


Figure 4. Balloon plot showing cohort-level association of demographic, clinical, cognitive and medication effects on functional outcomes. Panels show cohorts grouped by A) outcome measure, and B) geographic region. Significance of p-value ($-\log_{10}$P) is represented by circle size and colour. Variables with no data are indicated.

Depression is the strongest predictor of poor outcome

Of the 17 cohorts that had current depression measures, 13 (76.5%) showed significant association (p<0.05) with 'bad' outcome and 10 (58.8%) had this as their #1 top ranked association, by p-value **[Table 2].** The strongest effects with current depression were with outcome measures that reflected more current status (i.e. FAST, GAF and employment), whereas no relationship between current depression and long-term social outcomes (i.e. marital status) was observed **[Figure 4]**. This association is consistent with our earlier study,[2] where 10 of 12 independent cohorts (83.33%) showed significant association (p<0.05) between current depression and poor outcome, and 9 (75%) had depression as their #1 top ranked association, by p-value. Combining data across the 36 cohorts, 22 of 29 cohorts with this measure (75.86%) found association (p<0.05) and 19 (65.52%) had this as their #1 top ranked association, by p-value.

Conclusions

Poor functional outcomes are common in people with BD,[1] and also those with a family history of BD.[5] Persistent depressive symptoms appear to contribute to outcomes in BD, though some measures and outcomes may be conflated, and require further disentangling. A coordinated effort by the research community to increase representation of diverse persons may improve our understanding of BD, and help address treatment disparities globally.[6] Importantly, we hope this work will generate collaborations amongst participating groups.

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