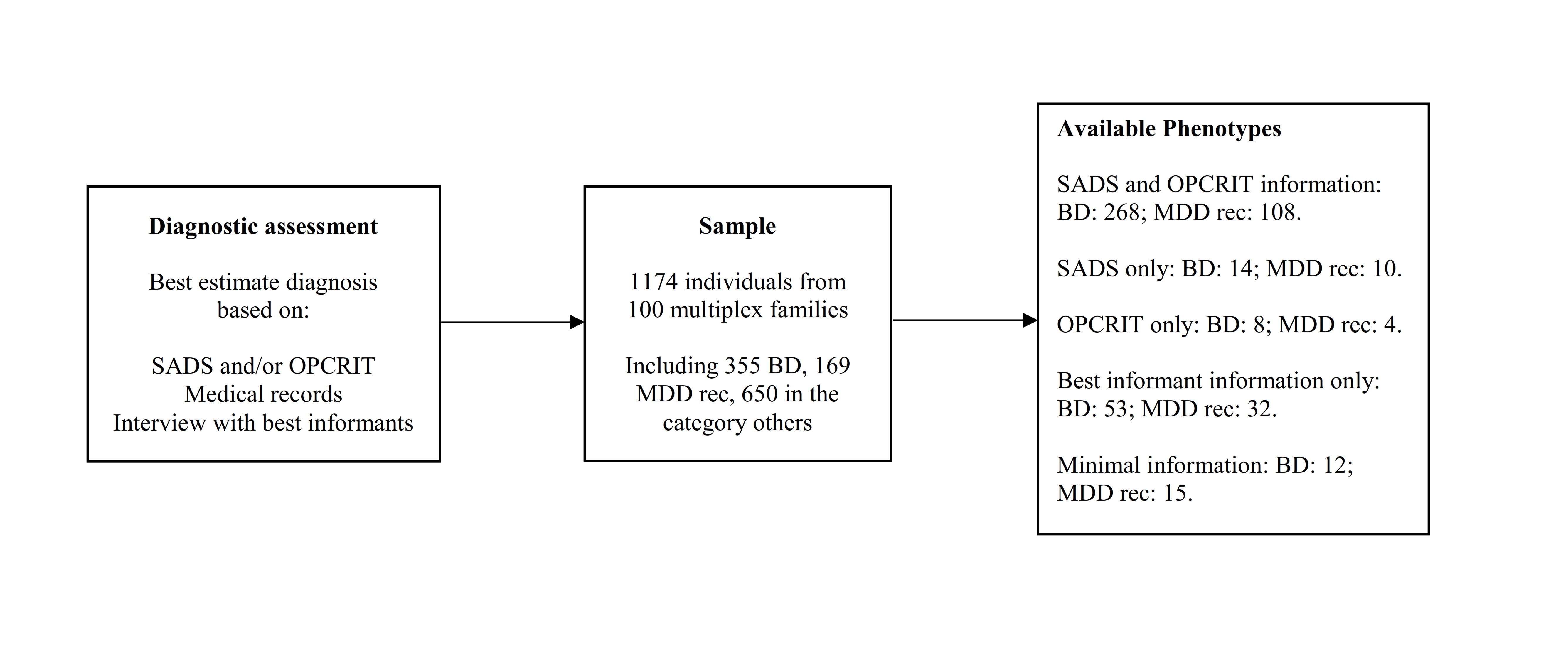
**Supplementary Figure 1:** Recruitment procedure for BD and MDD rec patients in the 100 multiplex-families



\* BD = Bipolar Disorder category: Bipolar Disorder I (N = 258), Bipolar Disorder II (N = 78), Bipolar Disorder not otherwise specified (N = 18), Schizoaffective Disorder Bipolar Type (N = 1); MDD rec = Major Depressive Disorder recurrent; Others category: Major Depressive Disorder single episode (N = 35), Depressive Disorder not otherwise specified (N = 12), Drug or Alcohol Abuse or Dependence (N = 31), Schizophrenia (N = 2), Agoraphobia (N = 1), and Healthy (N = 569).

**Supplementary Table 1:** Differences in clinical and treatment characteristics between BD (BD-I, BD-II, BP-NOS, SCA-B) and MDD rec patients from the original cohort.

|  |  |  |  |
| --- | --- | --- | --- |
| Clinical and treatment characteristics | BD  Ntotal=355  M (SD) | MDD rec  Ntotal=169  M (SD) | T student  or  Mann Whitney/*p* |
| **Lifetime**  Age of first treatment (N=362)  Age of first hospitalization (N=140)  Number of suicide attempts (N=93)  **Depressive episodes**  Age of first episode (N=462) | 27.07 (11.1)  30.16 (12.0)  1.88 (1.4)  24.71 (11.7) | 34.64 (13.6)  28.60 (11.0)  1.46 (1.1)  29.17 (15.3) | -4.78/<.001  -0.17/.862  -1.37/.171  -2.91/.004 |
| Clinical and treatment characteristics | Bipolar  N (%) | MDD  N (%) | Chi Square/p |
| **Lifetime**  Previous continuous treatment (N=484)  Hospitalization (N=524)  Total duration of hospitalization > 3months (N=144)  Alcohol abuse (N=524)  Drug abuse (N=524)  Cyclothymic personality (N=524)  Attempted suicide (N=524)  Unable to work for >= 6 months within last 5 years due to psychological problems (N= 500) | 243 (73.2)  149 (42.1)  65 (47.4)  34 (9.6)  22 (6.2)  34 (9.6)  80 (22.6)  109 (32.0) | 83 (54.6)  9 (5.3)  2 (28.6)  8 (4.7)  6 (3.5)  13 (7.6)  13 (7.5)  34 (21.4) | 16.38/<.001  73.83/<.001  0.95/.329  3.74/.053  1.64/.201  0.54/.463  17.59/<.001  46.20/<.001 |
| **Depressive episodes**  >4 episodes (N=519)  Longest episode(>3 months) (N=502)  Hospitalization (N=508)  Medication (N=510)  ECT (N=507)  Attempted suicide (N=506)  Hallucinations (N=508)  Delusions (N=508) | 268 (76.1)  314 (93.5)  52 (15.3)  306 (90.0)  10 (3.0)  66 (19.5)  28 (8.3)  37 (10.9) | 122 (72.6)  145 (87.3)  8 (4.7)  149 (87.6)  5 (3.0)  14 (8.3)  8 (4.7)  6 (3.6) | 0.75/.386  5.28/.022  12.18/<.001  0.65/.419  0/1  10.56/ .001  2.13/.145  7.89/.005 |
| **Manic episodes**  >4 episodes (N=351)  Longest episode(>1 month) (N=267)  Hospitalization (N=267)  Medication (N=267)  Attempted suicide (N=265)  Hallucinations (N=266)  Delusions (N=267) | 172 (48.7)  135 (40.6)  123 (46.1)  242 (90.6)  14 (5.3)  18 (6.8)  208 (77.9) |  |  |

Note. BD: Bipolar Disorder; MDD rec: Major Depressive Disorder recurrent; M: Mean; SD: Standard Deviation; ECT: Electro-Convulsive Therapy.

**Supplementary Table 2:** Total number of pedigrees and number of BD (BD-I, BD-II, BP-NOS, SCA-B) and MDD rec patients and MDD rec patients per pedigree

|  |  |  |
| --- | --- | --- |
| Number of pedigrees per geographical  province | No. of individuals | No. of affected individuals |
| 29 families from Málaga | 54 | 27 |
| 37 | 18 |
| 34 | 15 |
| 24 | 6 |
| 22 | 17 |
| 17 | 9 |
| 16 | 9 |
| 15 | 9 |
| 15 | 9 |
| 14 | 5 |
| 14 | 4 |
| 13 | 8 |
| 13 | 5 |
| 13 | 4 |
| 12 | 5 |
| 11 | 4 |
| 10 | 7 |
| 10 | 5 |
| 10 | 5 |
| 10 | 5 |
| 9 | 6 |
| 8 | 5 |
| 8 | 5 |
| 8 | 4 |
| 8 | 2 |
| 6 | 3 |
| 5 | 4 |
| 5 | 4 |
| 4 | 2 |
| 15 families from Granada | 22 | 12 |
| 21 | 10 |
| 20 | 7 |
| 18 | 7 |
| 15 | 6 |
| 14 | 6 |
| 14 | 5 |
| 10 | 7 |
| 10 | 4 |
| 10 | 4 |
| 9 | 4 |
| 8 | 4 |
| 7 | 5 |
| 7 | 2 |
| 5 | 4 |
| 29 families from Córdoba | 23 | 6 |
| 17 | 9 |
| 17 | 8 |
| 16 | 7 |
| 15 | 7 |
| 15 | 7 |
| 14 | 5 |
| 14 | 5 |
| 11 | 5 |
| 11 | 4 |
| 11 | 4 |
| 11 | 2 |
| 10 | 6 |
| 10 | 4 |
| 9 | 5 |
| 9 | 4 |
| 9 | 3 |
| 8 | 4 |
| 8 | 3 |
| 8 | 2 |
| 8 | 2 |
| 7 | 5 |
| 7 | 3 |
| 6 | 2 |
| 6 | 2 |
| 6 | 2 |
| 5 | 2 |
| 3 | 2 |
| 3 | 1 |
| 18 families from Jaén | 30 | 11 |
| 18 | 9 |
| 15 | 7 |
| 13 | 4 |
| 12 | 4 |
| 11 | 5 |
| 11 | 5 |
| 11 | 4 |
| 11 | 3 |
| 11 | 2 |
| 11 | 2 |
| 10 | 4 |
| 10 | 4 |
| 10 | 3 |
| 9 | 4 |
| 9 | 2 |
| 8 | 1 |
| 7 | 2 |
| 9 families from Cádiz | 12 | 7 |
| 10 | 4 |
| 8 | 5 |
| 3 | 3 |
| 3 | 2 |
| 3 | 2 |
| 2 | 2 |
| 2 | 2 |
| 2 | 2 |

**Supplementary Information:**

**Analysis of the clinical symptom dimensions Mania/Excitement, Depression, Disorganization, Positive symptoms, and Negative Symptoms in subjects from the Original Cohort**

The five symptom dimensions Mania/Excitement, Depression, Disorganization, Positive symptoms, and Negative Symptoms were derived from the Operational Criteria Checklist for Psychotic Illness (OPCRIT)1. These five symptom dimensions were selected as they are the most frequently reported dimensions in the literature2-10. For each symptom dimension, OPCRIT items for which factor loadings of > 0.30 in more than 50% of the preformed factorials analyses had been reported were selected. The selected OPCRIT items per dimension are shown in the Supplementary Table 3. All OPCRIT items were dichotomized and summed up separately for each dimension. Missing items were imputed by assuming that > 50% of subjects with the same diagnosis would display the item. Results did not vary significantly between imputed and original data. The sum score per dimension was then multiplied by 1011. The results are shown in Supplementary Table 3.

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**Supplementary Table 3:** Mean differences in selected OPCRIT dimensions between BD (BD-I, BD-II, BP-NOS, SCA-B), and MDD rec patients

|  |  |  |  |
| --- | --- | --- | --- |
| Lifetime symptoms (OPCRIT) | BD  (Ntotal=276)  M (SD) | MDD rec  (Ntotal=112)  M (SD) | Mann Whitney/*p* |
| Excitement/Mania | 8.555 (1.378) | 0.089 (0.834) | -16.12/<.001 |
| Excessive activity | 0.899 (0.302) | 0.009 (0.945) | -16.54/<.001 |
| Reckless activity | 0.221 (0.417) | 0 | -5.41/<.001 |
| Distractibility | 0.898 (0.302) | 0.009 (0.094) | -16.54/<.001 |
| Reduced need for sleep | 0.942 (0.234) | 0.018 (0.133) | -17.59/<.001 |
| Pressured speech | 0.971 (0.168) | 0.009 (0.094) | -18.56/<.001 |
| Thoughts racing | 0.942 (0.235) | 0.009 (0.094) | -17.72/<.001 |
| Elevated mood | 0.978 (0.146) | 0.009 (0.094) | -18.89/<.001 |
| Increased self-esteem | 0.993 (0.085) | 0.009 (0.094) | -19.27/<.001 |
| Depression | 8.967 (1.902) | 8.199 (1.004) | -8.824/<.001 |
| Dysphoria | 0.956 (0.204) | 0.964 (0.186) | -0.348/.728 |
| Suicidal ideation | 0.818 (0.385) | 0.714 (0.454) | -2.283/.022 |
| Loss of energy | 0.960 (0.196) | 1 (0) | -2.141/.032 |
| Loss of pleasure | 0.942 (0.234) | 0.982 (0.133) | -1.700/.089 |
| Poor concentration | 0.927 (0.260) | 0.964 (0.186) | -1.136/.174 |
| Excessive self-reproach | 0.822 (0.382) | 0.741 (0.440) | -2.279/.070 |
| Dismissed libido | 0.942 (0.234) | 0.929 (0.259) | 0.498/.618 |
| Slowed activity | 0.956 (0.204) | 1(0) | -2.339/.025 |
| Diurnal mood variation | 0.692 (0.462) | 0.661 (0.476) | -0.600/.549 |
| Initial insomnia | 0.935 (0.247) | 0.982 (0.133) | -1.909/.056 |
| Early morning wakening | 0.906 (0.293) | 0.018 (0.133) | -16.589/<.001 |
| Poor appetite | 0.902 (0.298) | 0.884 (0.322) | -0.535/.593 |
| Positive Symptoms | 0.356 (0.873) | 0.089 (0.414) | -3.106/.002 |
| Persecutory delusions | 0.098 (0.298) | 0.036 (0.186) | -2.042/.041 |
| Third person auditory hallucinations | 0.025 (0.157) | 0 | -1.669/.089 |
| Thought insertion | 0 | 0 |  |
| Delusion of influence | 0.054 (0.227) | 0.009 (0.094) | -2.036/.042 |
| Delusion of passivity | 0 | 0 |  |
| Disorganization | 0.027 (0.300) | 0 (0) | -1.106/.269 |
| Speech difficult to understand | 0.007 (0.085) | 0 | -0.902/.367 |
| Positive formal thought disorder | 0.004 (0.060) | 0 | -0.637/.524 |
| Inappropriate affect | 0 | 0 |  |
| Bizarre behavior | 0 | 0 |  |
| Negative Symptoms | 0.023 (0.072) | 0.002 (0.033) | -2.548/.011 |
| Negative formal thought disorder | 0 | 0 |  |
| Restricted affect | 0.091 (0.287) | 0.018 (0.133) | -2.548/.011 |
| Blunted affect | 0 | 0 |  |

Note. BD: Bipolar Disorder; MDD rec: Major Depressive Disorder recurrent; OPCRIT: The Operational Criteria Checklist for Psychotic Illness; M: Mean; SD: Standard Deviation. The range of scores is 0-10.