# Meta-analysis of the risk of subsequent mood episodes in bipolar disorder

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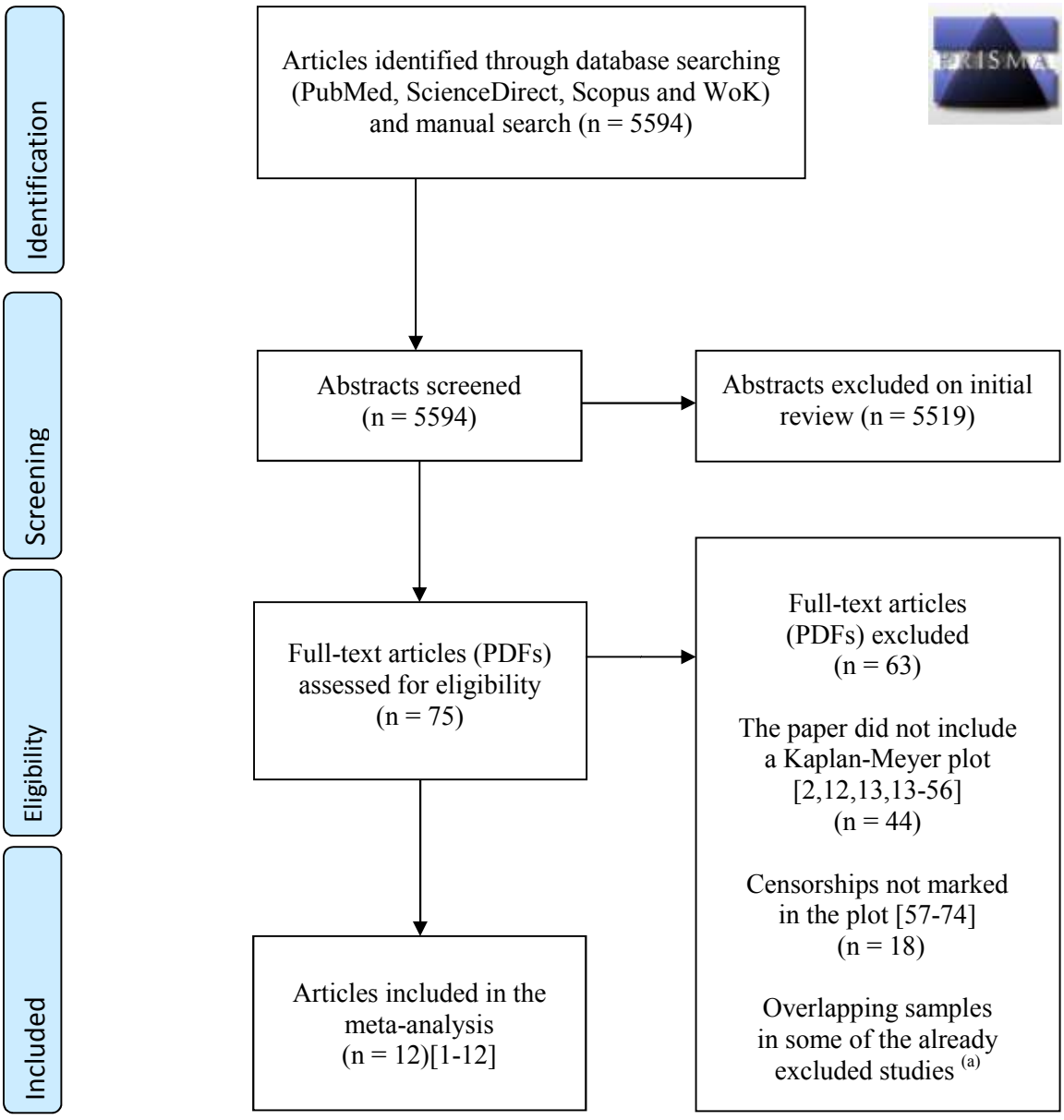
## SUPPLEMENTARY MATERIAL

**Supplementary Figure 1:** PRISMA flow chart




(a) Some of the excluded studies had in addition overlapping samples with the included studies.

**Supplementary Table 1**. Datasets included in the meta-analysis.

| | Funding | Individual data collection | N | Age (mean±SD) | Women | Type of BD | Starting status | Duration of follow-up [(a)] | Index episode [(b)] | Subsyndromal symptoms |
|---|---|---|---|---|---|---|---|---|---|---|
| *Adults recruited during an index episode* | | | | | | | | | | |
| Goetz *et al.*, 2007 (EMBLEM study) [1] [(c)] | Eli Lilly and Company | Raw data provided | 3459 | 45±13 | 55% | BD I | Onset | 3 years | 76% manic<br>24% mixed | - |
| Judd *et al.*, 2008 [2] | Roehr Fund of the University of California, San Diego | Data estimated with RMSE[(d)] ~6% / ~1% for patients with / without subsyndromal symptoms | 223 | 37±13 (only group statistics) | 57% (only group statistics) | 61% BD I<br>39% BD II<br>(only group statistics) | Recovery | 19 years | ≤ 17% manic<br>≤ 56% mixed<br>27% depressive<br>≤ 73% other / unknown<br>(only group statistics) | 27% yes<br>73% no |
| Simhandl *et al.*, 2014 [3] | Österreichische Forschungsförderungsgesellschaft mbH (FFG)<br>Instituto de Salud Carlos Miguel Servet | Raw data provided | 299 | 45±13 | 72% | 56% BD I<br>44% BD II | Admission | 4 years | 16% manic<br>14% mixed<br>59% depressive<br>11% other / unknown | - |
| Strakowski *et al.*, 2007 [4] | US NIMH and The National Science Council, Taiwan | Data estimated with RMSE[(d)] ~0% | 103 | 25±7 (only group statistics) | 26-64% (only group statistics) | BD I | Admission | 1 year | 67-98% manic<br>2-33% mixed<br>(only group statistics) | - |
| Tohen *et al.*, 1990 [5] | NIMH (partial funding) | Data estimated with RMSE[(d)] ~1% | 75 | 31±11 (only group statistics) | 51% (only group statistics) | BD I | Recovery | 4 years | 100% manic | - |
| Subtotal | | | 4159 | 44±14 | 56-57% | 95% BD I<br>5% BD II | 83% onset<br>10% admission<br>7% recovery | 19 years | 68-70% manic<br>21-24% mixed<br>6% depressive<br>1-5% other / unknown | - |
| *Adolescents recruited during an index episode* | | | | | | | | | | |
| Geller *et al.*, 2008 [6] | US National Institutes of Health | Raw data provided | 101 | 12±3 | 36% | BD I | Recovery | 8 years | 48% manic<br>52% mixed | - |
| Strober *et al.*, 1995 [7] | Source of funding not reported | Data estimated with RMSE[(d)] ~0% | 52 | 16±1 (only group statistics) | 50-54% (only group statistics) | BD I | Admission | 5 years | 37% manic<br>19% mixed<br>25% depressive<br>19% other / unknown | - |
| Subtotal | | | 153 | 13±3 | 41-42% | 100% BD I | 34% admission<br>66% recovery | 8 years | 44% manic<br>41% mixed<br>8% depressive<br>7% other / unknown | - |
| *Adults recruited during euthymia (or as outpatients)* | | | | | | | | | | |
| De Dios *et al.*, 2012 [8] | Source of funding not reported | Data estimated with RMSE[(d)] ~7% / ~2% for patients with / without subsyndromal symptoms | 225 | 49±13 (only group statistics) | 52% (only group statistics) | 75% BD I<br>25% BD II<br>(only group statistics) | - | 5 years | - | 28% yes<br>72% no |
| Gonzalez-Pinto *et al*. 2011 [9] | Health Research Funds from the Spanish Government, European Regional Development Funds (FEDER), Stanley Research Foundation | Raw data provided | 120 | 46±16 | 60% | BD I | - | 10 years | 60-63% manic<br>4-7% mixed<br>33-36% depressive<br>≤ 3% other / unknown | - |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Kraemer *et al.*, 2013 [10] | Eli Lilly and Company | Raw data provided | 642 | 48±13 | 57% | ≥ 62% BD I<br>≤ 38% BD-II | - | 2 years | 13-33% manic<br>13-33% mixed<br>46-66% depressive<br>9-29% other | - |
| Montoya *et al.*, 2010 [11] | Eli Lilly and Company | Data estimated with RMSE[(d)] ~5% / ~1% for patients with / without normal functioning | 398 | 46±14 (only group statistics) | 56% (only group statistics) | BD I | - | 2 years | 50% manic<br>5% mixed<br>45% depressive<br>(only group statistics) | 12% yes<br>88% no |
| Tundo *et al.*, 2013 [12] | Fondazione dell'Istituto di Psicopatologia Onlus, Rome, Italy | Raw data provided | 140 | 39±13 | 58% | 55% BD I<br>45% BD II | - | 8 years | 14% manic<br>10% mixed<br>71% depressive<br>5% other | 14% yes<br>86% no |
| Subtotal | | | 1525 | 47±15 | 56% | 76-92% BD I<br>8-24% BD II | - | 10 years | 25-48% manic<br>8-31% mixed<br>40-64% depressive<br>4-28% other | - |
| *Total* | | | 5837 | 44±14 | 56% | 90-94% BD I<br>6-10% BD II | - | 19 years | 56-63% manic<br>18-27% mixed<br>15-21% depressive<br>2-11% other | - |

Data only available as group statistics are gray-colored.
(a) 'Duration of follow up' refers to the maximum duration, i.e. not considering the participants who became ill or dropped out earlier
(b) 'Other index episodes' include hypomania and dysthymia
(c) The EMBLEM study comprised 530 investigators across 14 European countries
(d) RMSE: root mean square error

**Supplementary Table 2.** Median time to a subsequent mood episode (SME) and risk of SME in patients with BD.

| | | Studies | N | Age (mean±SD) | Women | Starting status | Duration of follow-up | Drop out rate (1st year of follow-up) | | Median time to an SME (95% CI) | Rates of SMEs (95% CI) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | 1st year of the follow-up | 2nd year of follow-up | 3rd year of follow-up |
| Adults recruited during an index episode | Overall | Goetz *et al.*; Judd *et al.*; Simhandl *et al.*; Strakowski *et al.*; Tohen *et al.* [1-4] | 4159 | 44±14 | 56-57% | 83% onset<br>10% admission<br>7% recovery | < 19 years | 53.9% | | 1.44 years (1.32-1.78) | 43.9% (42.0-45.7%) | 18.5% (15.4-21.5%) | 20.7% (15.0-26.0%) |
| | Age | Goetz *et al.*; Simhandl *et al.* [1,3] | 3746 | 45±13 | 55-58% | 92% onset<br>8% admission | ≤ 4 years | 55.9% | | 1.45 years (1.32-1.78) | 43.5% (41.5-45.4%) | 20.0% (16.2-23.6%) | 20.3% (11.7-28.0%) |
| | Sex | Goetz *et al.*; Simhandl *et al.* [1,3] | 3693 | ~45±13 | 57% | 92% onset<br>8% admission | ≤ 4 years | 55.8% | Males | 1.75 years (1.34-1.89) | 41.0% (37.9-44.0%) | 23.8% (17.3-29.8%) | 23.6% (4.5-38.9%) |
| | | | | | | | | | Females | 1.35 years (1.26-1.78) | 45.4% (42.7-48.0%) | 16.7% (12.1-21.1%) | 19.5% (9.7-28.2%) |
| | Type of disorder | Goetz *et al.*; Simhandl *et al.*; Strakowski *et al.*; Tohen *et al.* [1,3-5] | 3936 | ~44±13 | 56-57% | 88% onset<br>10% admission<br>2% recovery | ≤ 4 years | 55.4% | BD-I | 1.63 years (1.32-1.87) | 43.2% (41.2-45.2%) | 17.4% (13.9-20.8%) | 17.2% (9.3-24.4%) |
| | | | | | | | | | BD-II | 0.81 years (0.60-1.38) | 54.7% (45.0-62.7) | 31.6% (17.5-43.3%) | 34.3% (15.5-48.9%) |
| | Polarity of index episode | Goetz *et al.*; Simhandl *et al.*; Tohen *et al.*[1,3,5] | 3800 | ~44±13 | 57% | 91% onset<br>7% admission<br>2% recovery | ≤ 4 years | 55.5% | Manic | 1.80 years (1.38-2.28) | 42.0% (39.6-44.3%) | 17.8% (13.4-21.9%) | 17.9% (6.3-28.0%) |
| | | | | | | | | | Mixed | 1.28 years (0.93-3.49) | 46.5% (42.2-50.6%) | 14.7% (7.6-21.3%) | 5.3% (0.0-14.8%) |
| | | | | | | | | | Depressive | 0.96 years (0.71-1.50) | 51.2% (43.1-58.2%) | 28.1% (17.1-37.7%) | 30.6% (16.4-42.5%) |
| | Polarity of relapse episode | Goetz *et al.*; Simhandl *et al.*[1,3] | 3758 | 45±13 | 57% | 92% onset<br>8% admission | ≤ 4 years | 55.9% | Manic | (>follow-up) | 18.0% (16.3-19.6%) | 1.5% (0.2-2.7%) | 3.2% (0.0-7.5%) |
| | | | | | | | | | Mixed | (>follow-up) | 8.8% (7.5-10.1%) | 1.0% (0.0-1.9%) | ~0% |
| | | | | | | | | | Depressive (BD-I) | (>follow-up) | 14.2% (12.6-15.8%) | 1.3% (0.3-2.3%) | 5.4% (0.0-11.3%) |
| | | | | | | | | | Depressive (BD-II) | 1.28 years (0.71-2.05) | 46.4% (36.6-54.8%) | 24.9% (11.6-36.3%) | 22.9% (6.3-36.6%) |
| Adolescents | | Geller *et al.*; Strober *et al.* [6,7] | 153 | 13±3 | 41-42% | 34% admission<br>66% recovery | ≤ 8 years | 0.0% | | 3.01 years (2.07-4.04) | 20.9% (14.2-27.1%) | 24.1% (16.0-31.3%) | 14.8% (7.0-21.8%) |
| Adults recruited during euthymia (or as outpatients) | | De Dios *et al.*; Gonzalez-Pinto *et al.*; Kraemer *et al.*; Montoya *et al.*; Tundo *et al.* [8-12] | 1525 | 47±15 | 56% | 100% euthymia | ≤ 10 years | 33.5% | | 2.76 years (2.42-3.26) | 29.9% (27.4-32.2%) | 15.4% (11.4-19.3%) | 21.0% (13.9-27.5%) |
| Subsyndromal symptoms | | De Dios *et al.*; Judd *et al.*; Montoya *et al.*; Tundo *et al.* [2,8,11,12] | 986 | 44±14 | 56% | 23% recovery<br>77% euthymia | < 19 years | 27.2% | Yes | 0.75 years (0.52-1.03) | 57.0% (49.0-63.8%) | 28.9% (14.4-41.0%) | 21.8% (2.8-37.1%) |
| | | | | | | | | | No | 2.30 years (2.07-2.75) | 30.8% (27.4-34.0%) | 19.1% (14.3-23.6%) | 22.5% (16.0-28.4%) |

**Supplementary Methods: Procedure used to recreate individual patient SMEs**

First, Kaplan-Meier plots are digitalized so that each curve angle or censor mark is associated to a pixel coordinate. Second, coordinates are scaled in order that the width of the plot corresponds to the maximum follow-up time, and the height of the plot to 100% individuals. Finally, the script recreates the survival plot starting from time zero and 100% individuals.

The scripts understand every censor mark as a patient being lost from follow-up at that time, and every curve descent as one or more patients having an SME at that time. Note that the magnitude of each descent depends on the number of patients experiencing an SME at that time. When the link between the magnitude of the descent and the number of patients having an SME is inexact (e.g., we understood that 2.2-2.8 could correspond to either 2 or 3 SMEs), the number of patients is randomly rounded up or down, and the recreation process is repeated many times (5000) in order to find the best recreation according to the root mean square error (RMSE) criterion. This approach is similar to that proposed by Messori *et al* [75] which already showed an excellent recreation of the data without accounting for censor marks (correlations ranged between r=0.989 and 1). We required the plots to have the censors marked in order to ensure the accuracy of the recreations.

To allow other researchers use this procedure, we include the script in R in the following page.

```
library(survival);

#####################################################################
# Curve must be digitalized in a text file with the following       #
# columns:                                                          #
# - x and y: pixel coordinates                                      #
# - type: "time0" and "time1" (coordinates of X axis) and           #
#   "curve" or "censor".                                            #
#####################################################################

curve2ipd = function (file, samplesize, followup) {
    randomizations = 5000;
    curve = read.table(file, head = TRUE);
    x0 = curve$x[curve$type == 'time0'];
    x1 = curve$x[curve$type == 'time1'];
    y0 = curve$y[curve$type == 'time0'];
    curve = subset(curve, type == 'curve' | type == 'censor');
    curve$time = round(followup * (curve$x - x0) / (x1 - x0));
    curve$surv = (y0 - curve$y) / (y0 - min(curve$y));
    times = unique(sort(curve$time[curve$time > 0]));
    ep = c();
    for (time in times) {
        ep = c(ep, min(curve$surv[curve$time == time]));
    }
    best.ipd = NA;
    best.survfit = NA;
    best.swsd = Inf;
    for (randomization in 1:randomizations) {
        ipd = data.frame(time = c(), status = c());
        n.risk = samplesize;
        for (time in times) {
            n.censor = sum(curve$time == time &
                    curve$type == 'censor');
            n.risk = n.risk - n.censor;
            surv = curve$surv[curve$time == time];
            n.event = (1 - min(surv) / max(surv)) * n.risk;
            if (abs(round(n.event) - n.event) < 0.2) {
                n.event = round(n.event);
            } else if (runif(1) < 0.5) {
                n.event = floor(n.event);
            } else {
                n.event = ceiling(n.event);
            }
            if (n.event < 0) {
                n.event = 0;
            } else if (n.event > n.risk) {
                n.event = n.risk;
            }
            n.risk = n.risk - n.event;
            ipd = rbind(ipd, data.frame(
                time = rep(time, n.event + n.censor),
                status = c(rep(1, n.event), rep(0, n.censor))
            ));
        }
        if (n.risk > 0) {
```

```
            ipd = rbind(ipd, data.frame(
                time = rep(time, n.risk),
                status = rep(0, n.risk)));
        }
        survfit = survfit(Surv(ipd$time, ipd$status) ~ 1);
        swsd = 0
        for (i in 1:length(times)) {
            dtime = survfit$time - times[i]
            dtime[dtime > 0] = NA
            surv = survfit$surv[order(dtime, decreasing = T)[1]]
            swsd_i = (ep[i] - surv)^2 / ep[i]^2;
            if (!is.na(swsd_i)) {
                swsd = swsd + swsd_i;
            }
        }
        if (swsd < best.swsd) {
            best.ipd = ipd;
            best.survfit = survfit;
            best.swsd = swsd;
        }
        if (!randomization %% 100) {
            cat(file, ': SWSD(', randomization, ') = ',
                    round(swsd, 4), '; best SWSD = ',
                    round(best.swsd, 4), '\n', sep = '');
        }
    }
    cat('Final survival  = ',
            best.survfit$surv[length(best.survfit$surv)],
            ' (observed: ', ep[length(ep)], ')\n');
    cat('RMSE = ', sqrt(best.swsd / length(times)) * 100, '%\n',
            sep = '');
    plot(best.survfit);
    best.ipd;
}
```

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