

# Suicide, Hospital-Presenting Suicide Attempts, and Criminality in Bipolar Disorder: Examination of Risk for Multiple Adverse Outcomes

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## ABSTRACT

**Objective:** To compare risks for suicidality and criminality in a national cohort of people diagnosed with bipolar disorder, and to assess how risk factor profiles differ between these outcomes.

**Method:** We conducted 2 case-cohort studies using interlinked Swedish national registers. Primarily, using *International Classification of Diseases (ICD)* coding, we identified 15,337 people diagnosed with bipolar disorder, 1973–2009, matched by age and gender to 20 individuals per case sampled randomly from the general population. We estimated risks of suicide and hospital-presenting attempted suicide, and violent and nonviolent criminal offending. We separately assessed these risks among 14,677 unaffected siblings matched to a second general population sample.

**Results:** 22.2% of bipolar disorder cohort members engaged in suicidal or criminal acts after diagnosis. They were at greatly elevated risk for completed suicide (risk ratio = 18.8; 95% CI, 16.0–22.2), attempted suicide (risk ratio = 14.3; 95% CI, 13.5–15.2), violent crime (risk ratio = 5.0; 95% CI, 4.6–5.4), and nonviolent crime (risk ratio = 2.9; 95% CI, 2.8–3.1) compared with the general population. Elevations in risk were far less marked among the unaffected siblings than in the bipolar disorder cohort. Three factors independently predicted raised risk of all 4 adverse outcomes: if the first 2 patient episodes for bipolar disorder required admission, a history of attempted suicide, and a history of diagnosed alcohol/drug disorder. Criminal offending before bipolar diagnosis was an especially strong independent predictor of criminality after diagnosis.

**Conclusions:** The combined risk of suicidality or criminality is substantially elevated in both relative and absolute terms. Clinical prediction rules focusing on multiple vulnerabilities following onset of bipolar disorder, especially when there is history of attempted suicide, substance misuse disorders, or criminal offending, may improve risk management.

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People diagnosed with bipolar disorder more frequently die prematurely versus the general population,<sup>1–3</sup> and this mortality gap may have widened in recent decades.<sup>4</sup> They have a markedly elevated suicide risk, even when compared to people with other serious mental illnesses. An estimated 10%–15% of people with bipolar disorder may die by suicide,<sup>5–7</sup> although more recent work has reported a lower cumulative incidence.<sup>8</sup> Risk for nonfatal suicidality is also raised.<sup>6,9,10</sup> Higher risk of perpetrated interpersonal violence has been reported,<sup>11–15</sup> levels of aggression may be especially raised with bipolar disorder in comparison with other types of psychopathology,<sup>16</sup> and elevated criminality risk per se has also been shown.<sup>17–19</sup> Research has attempted to explain why these 2 adverse outcome domains—suicidality and criminality—may share common causal mechanisms in serious mental illness. Emotional dysregulation,<sup>20</sup> aggressive impulsivity,<sup>21</sup> and alcohol misuse<sup>22</sup> are among the mechanisms proposed. Clinicians require a greater understanding of pathways to and effective interventions for tackling multiple self-destructive behaviors.<sup>23,24</sup>

Developing effective ways of identifying and modifying these risks is a clinical priority but is hampered by our limited understanding of their causes in bipolar disorder. Systematic reviews have highlighted small sample sizes and imprecise and heterogeneous effect estimates.<sup>6,15</sup> Little is known about the determinants of elevated risk, the role of familial factors, and the extent to which they are distinct or shared across outcomes. The latter is important, as it may allow for targeted early interventions addressing the shared risk factors and more tailored treatment for individuals at heightened risk of one particular outcome. To our knowledge, no previously published studies have examined risk for multiple adverse outcomes within the same bipolar disorder study cohort.

This article reports estimated risks of completed and attempted suicide, and of violent and nonviolent criminality, in a national bipolar disorder cohort. We aimed to estimate relative risks for this cohort against the general population and, secondly, to replicate these analyses using unaffected siblings as a comparison. The latter enabled us to assess the impact of unmeasured genetic and early environmental familial confounders. Finally, within the bipolar disorder cohort only, we compared risk factors across multiple outcomes, using a generic set of explanatory variables measuring demographic and criminological factors, clinical history, and parental factors. The study cohort was an extension of a previously reported bipolar disorder cohort,<sup>15</sup> which was based on 3,743 individuals followed up until 2004 assessing violent crime as the sole outcome. With an extra 5 years of case ascertainment and follow-up, and the inclusion of outpatient episodes since 2001, the current sample was over 4 times larger, and we now report risks for multiple outcomes and also information on individual and familial risk factors.

- Assessment of multiple risks is important for all patients diagnosed with bipolar disorder.
- The identification of high-risk groups, including bipolar patients who have already harmed themselves or who have committed crimes, can be improved by using risk factor information.
- Early effective treatment for alcohol or drug comorbidity is likely to be important in bipolar patients.
- Developing treatments that focus on likely mediators of multiple risks, such as impulsivity and disinhibition, may provide benefits for patients with bipolar disorder across a range of adverse outcomes.

## METHOD

### National Registers

We utilized the following registers:

- Patient Register, Cause of Death Register (National Board of Health and Welfare) (<http://www.socialstyrelsen.se/english>);
- National Crime Register (National Council for Crime Prevention) (<http://www.bra.se/bra/bra-in-english/home.html>);
- Total Population Register, Multi-Generation Register, Migration Register (Statistics Sweden) (<http://www.scb.se/en/>).

The data custodians are the Swedish national government agencies listed above. Access to the registry data for conducting research can be sought by making formal applications directly to these agencies, with a Swedish academic institution. The registers were interlinked with almost total completeness using unique civil registration numbers assigned to each Swedish birth and immigrant. Since the 1970s, the Patient Register has recorded hospital treatment for both somatic and psychiatric illnesses, including forensic units and the few private health care providers, with almost 100% of these episodes captured since 1987.<sup>25</sup> Only 1% of all hospital discharges have missing civil registration numbers.<sup>26</sup> The Patient Register contains historical information regarding inpatient psychiatric treatment, and, by using civil registration numbers and the Multi-Generation Register, we could achieve near-complete linkage between bipolar disorder cohort members and their first-degree relatives. However, these sources lacked measures for some of the candidate-shared causal traits, such as emotional dysregulation and impulsivity. In relation to suicidality, we could not examine key clinical factors such as extent of depressive symptoms, hopelessness, noncompliance with treatment, rapid cycling, and bipolar I versus II disorder.<sup>6</sup> A limitation of studying administrative registers is that important explanatory variables are unavailable because they have not been

routinely collected.<sup>27</sup> However, the large cohort sizes and reliability of examined risk factors enables precision to bear on important uncertainties.

### Bipolar Disorder Cohort

We identified all 15,337 individuals aged 15 years and older with 2 or more outpatient or inpatient episodes with a bipolar disorder diagnosis during January 1, 1973, to December 31, 2009. This approach maximized diagnostic specificity and sensitivity and is consistent with a recent validation study<sup>28</sup> conducted in the Patient Register. That study<sup>28</sup> reported a positive predictive value of 0.92 compared to clinical diagnoses based on medical records, although it excluded suicides and other deaths soon after first bipolar disorder diagnosis. We applied the following *International Classification of Diseases (ICD)* codes: *ICD-8* (1973–1986) 296.00, 296.1, 296.2, 296.3, 296.88, and 296.99 (296.20 excluded)<sup>29</sup>; *ICD-9* (1987–1996) 296.0, 296.2, 296.3, 296.4, 296.8, and 296.9<sup>30</sup>; and *ICD-10* (since 1997) F30–31.<sup>31</sup> We applied the same criteria as the previous validation study<sup>28</sup>; ie, excluding *ICD-8* 296.20 and *ICD-9* 296.1, thereby omitting cases of major depressive disorder. Having the first 2 hospital episodes for bipolar disorder as an inpatient, as opposed to 1 or both as an outpatient, was examined as a potential proxy for disease severity, as used by a Danish register-based study.<sup>32</sup> Each cohort member was matched by age and gender to 20 individuals without bipolar disorder randomly sampled from the general population (N = 306,740). We matched parsimoniously to avoid the exposed and unexposed cohorts being too similar to one another through overmatching, and also to preclude unnecessary power loss.<sup>33</sup>

The bipolar disorder cohort and their matched comparison subjects were followed up from first diagnosis date (index date) until death, emigration, or end of follow-up (December 31, 2009). In examining nonfatal outcomes (attempted suicide and violent/nonviolent crime), follow-up ended when the first outcome event occurred after index date.

### Unaffected Sibling Cohort

Using the Multi-Generation Register,<sup>34</sup> we identified a comparative cohort of all full siblings of the bipolar disorder cohort who were unaffected by the disorder (N = 14,677), although these individuals may have had other psychiatric diagnoses. The unaffected sibling cohort was matched by age and gender to 295,198 people randomly selected from the general population. Equivalent follow-up procedures were applied to the sibling cohort as to the bipolar disorder cohort. The index date for commencing follow-up was the date when the unaffected sibling was the same exact age as his or her affected sibling was when first diagnosed. The following groups of unaffected siblings were excluded, as they provided no follow-up information: (1) those who died or emigrated (without returning to live in Sweden) before their index date and (2) those with an index date later than December 31, 2009.

### Multiple Adverse Outcomes

Suicides were ascertained from the Cause of Death Register. To reduce false-negative misclassification,<sup>35</sup> and to be consistent with recent Swedish studies,<sup>36,37</sup> we included cases of undetermined intent: E950–959, E980–989 (*ICD-8* and *ICD-9*); and X60–84, Y10–34 (*ICD-10*). This coding range identified more than 99% of all Swedish suicides.<sup>38</sup> The same codes were used to identify hospital-presenting attempted suicides that occurred after first bipolar disorder diagnosis. This group included cases treated in emergency departments as well as those admitted as inpatients. Hospital-presenting cases provide a marker of severity. They also place a heavy burden on health service costs, and secondary care is an ideal setting for delivering interventions to prevent repetition and suicide. All convictions since 1973 for violent and nonviolent criminal offending at age 15 and older were obtained from the National Crime Register. Violent crime included homicide, attempted homicide, assault, robbery, arson, threat or intimidation, and all sexual offenses (including rape, sexual coercion/harassment, and child molestation).

### Measurement of Risk Factors

Explanatory variables were grouped into demographic, criminological, clinical history, and parental factors. *Unmarried* was defined as being single, separated, divorced or widowed—a time-fixed variable measured at first bipolar disorder diagnosis. *Low-income family* was defined as those in the lowest tertile nationally. Family income is a powerful way of adjusting for socioeconomic status, more so than individual-level data because many bipolar disorder patients are not employed. Being a first- or second-generation immigrant meant that the cohort member, or at least 1 of his or her parents, was born abroad. Attempted suicide, alcohol/drug disorder diagnoses (to cohort members or to their parents), and any psychiatric diagnosis (to parents) were extracted from the Patient Register. As with completed suicides, the following codes were used to identify hospital-presenting suicide attempts: *ICD-8* and *ICD-9* E950–959, E980–989; and *ICD-10* X60–84, Y10–34. This variable was therefore examined as both an explanatory and an outcome variable.

### Statistical Analyses

Analyses were performed using Stata version 12 (StataCorp). Using conditional fixed-effects Poisson regression,<sup>39</sup> we estimated risk ratios for adverse outcome in the bipolar disorder and unaffected sibling cohorts versus the respective age- and gender-matched general population comparison groups. For the unaffected sibling analyses, standard errors were corrected for familial clustering among multiple siblings.<sup>40</sup> In the second analytic phase, we fitted Cox proportional hazards regression models to identify determinants of the 4 adverse outcomes among the bipolar cohort by applying time at risk from first diagnosis to the adverse event date. We omitted all periods spent living abroad before returning to live in Sweden from these survival-time counts. These models were fitted separately

from any other explanatory variables except for age at first diagnosis. We generated multivariable models of mutually adjusted risk factors. For example, the association between previous attempted suicide and death by suicide was adjusted for age, gender, first 2 treatment episodes as an inpatient, and alcohol/drug disorders, and so forth.

## RESULTS

### Relative Risks: Bipolar Disorder Cohort Versus the General Population

Over a fifth (22.2%) of cohort members engaged in suicidal or criminal acts after bipolar disorder diagnosis, with considerably higher risks compared with the general population (Table 1). The effect sizes were strongest for suicide, followed by attempted suicide, violent crime, and nonviolent crime. Adjustment for alcohol/drug disorder attenuated the effects, although a significant and marked independent risk elevation persisted across all 4 outcomes. Additional adjustment for family income level, being an immigrant, and marital status attenuated the estimates minimally. We fitted gender interaction terms to these models, and for each one, the relative risk versus the gender-specific general population sample was significantly greater among women than men with bipolar disorder ( $P < .001$ ). Although the female excess risks were consistently higher, the absolute risks were greater in men (see eTable 1 for gender-specific analyses). We estimated risk ratios separately for “suicidality only” and “criminality only.” These results indicate that the elevated risks for the 2 outcomes did not strongly confound one another, although a greater proportion of the heightened risk for criminality was explained by suicidality versus the equivalent proportion of the increased suicidality risk explained by criminality.

We also calculated the ratio of the number of individuals who attempted suicide versus those who died by suicide and the ratio of the number of individuals who committed nonviolent versus violent crimes. We formally compared these ratios for the bipolar disorder cohort against the general population. They indicated that, in bipolar disorder, suicidality was more likely to be lethal and criminality more likely to be violent: (1) for attempted to completed suicide, ratio = 6.97 (1,897/272) in bipolar disorder and ratio = 9.19 (2,655/289) in general population ( $\chi^2 = 9.5$ ,  $P = .002$ ); (2) for nonviolent to violent criminal offending, ratio = 2.58 (1,638/635) in bipolar disorder and ratio = 4.40 (11,176/2,542) in general population ( $\chi^2 = 108.4$ ,  $P < .001$ ).

The great majority of suicides and first violent crimes after diagnosis occurred within a 5-year time frame, with a median of 3.4 years for suicide and 2.4 years for first violent crime (for time distribution to outcomes, see eTable 2).

### Relative Risks: Unaffected Sibling Cohort Versus the General Population

As indicated by the 95% CIs not overlapping with the point estimates, unaffected siblings had significantly higher risk for each adverse outcome than the general population (Table 1). The risks elevations were, however, considerably

**Table 1. Risk Ratios for Adverse Outcomes in the Bipolar Disorder and Unaffected Sibling Cohorts Versus the General Population**

| Adverse Outcome            | Bipolar Disorder Cohort |      | General Population <sup>a</sup> |      | Risk Ratio <sup>b</sup> | 95% CI      | Adjusted Risk Ratio <sup>c</sup> | 95% CI      |
|----------------------------|-------------------------|------|---------------------------------|------|-------------------------|-------------|----------------------------------|-------------|
|                            | n                       | %    | n                               | %    |                         |             |                                  |             |
| Suicidality or criminality | 3,406                   | 22.2 | 14,226                          | 4.6  | 4.79                    | 4.61–4.97   | 3.03                             | 2.91–3.16   |
| Suicide                    | 272                     | 1.8  | 289                             | 0.09 | 18.82                   | 15.95–22.21 | 14.59                            | 12.12–17.56 |
| Attempted suicide          | 1,897                   | 12.4 | 2,655                           | 0.9  | 14.29                   | 13.47–15.16 | 8.74                             | 8.16–9.36   |
| Suicidality only           | 1,573                   | 10.3 | 2,101                           | 0.7  | 14.97                   | 14.03–15.99 | 10.18                            | 9.47–10.94  |
| Violent crime              | 635                     | 4.1  | 2,542                           | 0.8  | 5.00                    | 4.58–5.45   | 2.81                             | 2.54–3.11   |
| Nonviolent crime           | 1,638                   | 10.7 | 11,176                          | 3.6  | 2.93                    | 2.78–3.09   | 1.77                             | 1.67–1.87   |
| Criminality only           | 1,334                   | 8.7  | 11,342                          | 3.7  | 2.35                    | 2.22–2.49   | 1.55                             | 1.46–1.65   |
|                            | Unaffected Siblings     |      | General Population              |      |                         |             |                                  |             |
| Suicidality or criminality | 1,513                   | 10.3 | 22,201                          | 7.5  | 1.37                    | 1.30–1.44   | 1.24                             | 1.18–1.30   |
| Suicide                    | 70                      | 0.5  | 507                             | 0.2  | 2.79                    | 2.15–3.61   | 2.51                             | 1.88–3.34   |
| Attempted suicide          | 356                     | 2.4  | 3,543                           | 1.2  | 2.02                    | 1.81–2.26   | 1.80                             | 1.60–2.03   |
| Suicidality only           | 275                     | 1.9  | 2,773                           | 0.9  | 2.00                    | 1.76–2.26   | 1.84                             | 1.61–2.10   |
| Violent crime              | 317                     | 2.2  | 4,402                           | 1.5  | 1.45                    | 1.29–1.63   | 1.22                             | 1.09–1.37   |
| Nonviolent crime           | 1,140                   | 7.8  | 17,866                          | 6.1  | 1.28                    | 1.21–1.36   | 1.16                             | 1.10–1.23   |
| Criminality only           | 1,103                   | 7.5  | 18,247                          | 6.2  | 1.21                    | 1.14–1.29   | 1.12                             | 1.05–1.18   |

<sup>a</sup>The adverse outcome risks for the general population samples, as presented above, were somewhat higher for the unaffected sibling analyses than for the bipolar disorder cohort analyses. This difference in risk occurred by design due to the gender matching in the general population samples—there was a marked preponderance of female subjects in the bipolar disorder cohort, whereas the gender split was almost 50:50 among the unaffected siblings.

<sup>b</sup>Risk ratio estimated by conditional fixed-effects Poisson regression and adjusted inherently for age and gender in the matched design.

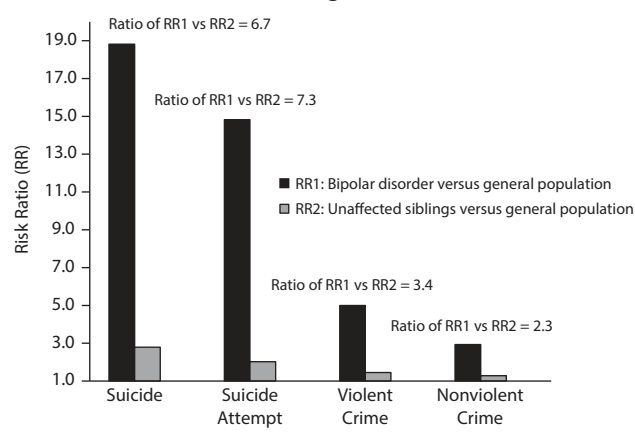
<sup>c</sup>Risk ratio additionally adjusted for an alcohol/drug disorder diagnosis before or after bipolar disorder diagnosis, family income level, being an immigrant, and marital status.

smaller compared with the bipolar disorder cohort effect sizes. Figure 1 compares risk ratios for the bipolar disorder and unaffected sibling cohorts. The ratios of the 2 risk ratios (ie, bipolar cohort vs unaffected siblings) were substantially greater for suicidality than for criminality.

### Risk Factors Within the Bipolar Disorder Cohort

Risk factors for suicidality are presented in Table 2. Among the demographic factors, being male predicted higher suicide risk and lower attempted suicide risk, and being unmarried was protective against suicide. Being from a low income family was a weak predictor of attempted suicide. Having the first 2 patient episodes for bipolar disorder as an inpatient carried a raised risk of both suicide and attempted suicide. The following clinical factors, all occurring before first bipolar diagnosis, predicted future risk of fatal and nonfatal suicidality: attempted suicide, alcohol/drug disorder diagnosis, and nonviolent crime. History of violent crime predicted attempted suicide, but was nonsignificant for suicide. None of the parental factors examined were close to reaching significance in predicting suicide. For attempted suicide, however, there were weakly significant associations with the following parental factors: suicide, alcohol/drug disorder diagnosis, and violent and nonviolent crime.

Risk factors were similar between the 2 forms of criminality (Table 3). Being male, from a low-income family, or an immigrant all predicted higher risk of both types of criminal offending. The effect sizes for male gender were especially strong. First 2 patient episodes for bipolar disorder as an inpatient, clinical histories of attempted suicide, alcohol/drug disorder diagnosis, and violent and nonviolent crime all predicted higher risk of subsequent violent and

**Figure 1. Comparison of Risk Ratios Between the Bipolar Disorder and Unaffected Sibling Cohorts**

nonviolent criminality after diagnosis. Parental suicide and alcohol/drug disorder diagnosis predicted higher risk of violent and nonviolent crime. Additionally, parental violent and nonviolent crime predicted higher risk for nonviolent crime after diagnosis.

Finally, we generated multiple regression models (Table 4). The following 3 risk factors independently predicted all 4 outcomes: first 2 patient episodes for bipolar disorder as an inpatient, history of attempted suicide, and history of alcohol/drug disorder diagnosis.

## DISCUSSION

### Summary of Main Findings

We examined risks of suicidality and criminality in bipolar disorder in absolute terms and also relative to

**Table 2. Hazard Ratios for Patient and Parental Risk Factors for Suicide and Attempted Suicide in the Bipolar Disorder Cohort<sup>a</sup>**

| Explanatory Variable                                   | Suicide |                |              |                  | Attempted Suicide |                |              |                  |
|--|---------|----------------|--------------|------------------|-------------------|----------------|--------------|------------------|
|  | n       | Rate per 1,000 | Hazard Ratio | 95% CI           | n                 | Rate per 1,000 | Hazard Ratio | 95% CI           |
| Patients' demographic and criminological factors       |         |                |              |                  |                   |                |              |                  |
| Male gender  | 149     | 4.0            | <b>1.70</b>  | <b>1.34–2.17</b> | 577               | 17.1           | <b>0.64</b>  | <b>0.58–0.70</b> |
| Unmarried  | 117     | 2.4            | <b>0.55</b>  | <b>0.43–0.70</b> | 1,146             | 26.6           | 1.00         | 0.91–1.10        |
| Low-income family                                      | 90      | 2.9            | 1.02         | 0.78–1.32        | 609               | 22.9           | <b>1.10</b>  | <b>1.00–1.22</b> |
| First- or second-generation immigrant                  | 50      | 2.7            | 0.82         | 0.61–1.12        | 419               | 25.3           | 0.99         | 0.89–1.10        |
| Violent crime  | 27      | 4.4            | 1.40         | 0.94–2.09        | 201               | 37.7           | <b>1.55</b>  | <b>1.34–1.80</b> |
| Nonviolent crime                                       | 83      | 4.3            | <b>1.53</b>  | <b>1.18–1.99</b> | 547               | 33.0           | <b>1.47</b>  | <b>1.33–1.63</b> |
| Patients' clinical history                             |         |                |              |                  |                   |                |              |                  |
| First 2 bipolar disorder treatment episodes: inpatient | 179     | 3.7            | <b>2.46</b>  | <b>1.84–3.27</b> | 834               | 20.7           | <b>1.38</b>  | <b>1.25–1.53</b> |
| Attempted suicide                                      | 87      | 6.8            | <b>2.66</b>  | <b>2.06–3.45</b> | 747               | 77.6           | <b>3.92</b>  | <b>3.57–4.31</b> |
| Alcohol/drug disorder diagnosis                        | 48      | 6.5            | <b>2.21</b>  | <b>1.61–3.05</b> | 460               | 79.9           | <b>3.19</b>  | <b>2.86–3.55</b> |
| Parental factors                                       |         |                |              |                  |                   |                |              |                  |
| Suicide  | 12      | 4.1            | 1.31         | 0.73–2.33        | 81                | 33.9           | <b>1.35</b>  | <b>1.08–1.69</b> |
| Any psychiatric diagnosis                              | 24      | 2.5            | 0.79         | 0.52–1.20        | 243               | 29.3           | 1.11         | 0.97–1.27        |
| Alcohol/drug disorder diagnosis                        | 12      | 4.1            | 1.26         | 0.70–2.25        | 102               | 40.4           | <b>1.41</b>  | <b>1.16–1.73</b> |
| Violent crime  | 7       | 2.8            | 0.90         | 0.42–1.90        | 77                | 35.5           | <b>1.27</b>  | <b>1.01–1.59</b> |
| Nonviolent crime                                       | 26      | 2.5            | 0.80         | 0.53–1.20        | 270               | 30.0           | <b>1.14</b>  | <b>1.00–1.30</b> |

<sup>a</sup>All of the Cox proportional hazards regression models presented in the table were adjusted for age at first discharge with a bipolar disorder diagnosis; statistically significant effects ( $P < .05$ ) are highlighted in bold text.

**Table 3. Hazard Ratios for Patient and Parental Risk Factors for Violent and Nonviolent Crime in the Bipolar Disorder Cohort<sup>a</sup>**

| Explanatory Variable                                   | Violent Crime |                |              |                  | Nonviolent Crime |                |              |                  |
|--|---------------|----------------|--------------|------------------|------------------|----------------|--------------|------------------|
|  | n             | Rate per 1,000 | Hazard Ratio | 95% CI           | n                | Rate per 1,000 | Hazard Ratio | 95% CI           |
| Patients' demographic and criminological factors       |               |                |              |                  |                  |                |              |                  |
| Male gender  | 459           | 13.7           | <b>4.02</b>  | <b>3.38–4.79</b> | 1,047            | 34.8           | <b>2.90</b>  | <b>2.62–3.21</b> |
| Unmarried  | 382           | 8.4            | 1.13         | 0.96–1.34        | 984              | 23.1           | 1.06         | 0.95–1.18        |
| Low-income family                                      | 267           | 9.4            | <b>1.58</b>  | <b>1.35–1.86</b> | 613              | 23.5           | <b>1.34</b>  | <b>1.20–1.48</b> |
| First- or second-generation immigrant                  | 172           | 9.9            | <b>1.37</b>  | <b>1.15–1.64</b> | 432              | 26.2           | <b>1.27</b>  | <b>1.14–1.42</b> |
| Violent crime  | 208           | 42.3           | <b>7.79</b>  | <b>6.57–9.23</b> | 378              | 88.9           | <b>4.65</b>  | <b>4.13–5.23</b> |
| Nonviolent crime                                       | 357           | 21.4           | <b>5.22</b>  | <b>4.45–6.13</b> | 893              | 64.2           | <b>5.10</b>  | <b>4.61–5.64</b> |
| Patients' clinical history                             |               |                |              |                  |                  |                |              |                  |
| First 2 bipolar disorder treatment episodes: inpatient | 380           | 8.6            | <b>2.11</b>  | <b>1.76–2.53</b> | 780              | 19.6           | <b>1.57</b>  | <b>1.40–1.75</b> |
| Attempted suicide                                      | 143           | 11.9           | <b>1.64</b>  | <b>1.36–1.98</b> | 352              | 31.7           | <b>1.46</b>  | <b>1.29–1.64</b> |
| Alcohol/drug disorder diagnosis                        | 144           | 21.8           | <b>3.17</b>  | <b>2.62–3.84</b> | 416              | 74.3           | <b>3.49</b>  | <b>3.11–3.92</b> |
| Parental factors                                       |               |                |              |                  |                  |                |              |                  |
| Suicide  | 31            | 11.5           | <b>1.54</b>  | <b>1.07–2.21</b> | 76               | 31.3           | <b>1.47</b>  | <b>1.16–1.85</b> |
| Any psychiatric diagnosis                              | 79            | 8.8            | 1.12         | 0.89–1.42        | 204              | 24.2           | 1.11         | 0.95–1.28        |
| Alcohol/drug disorder diagnosis                        | 33            | 11.7           | <b>1.45</b>  | <b>1.02–2.06</b> | 88               | 34.2           | <b>1.46</b>  | <b>1.18–1.81</b> |
| Violent crime  | 23            | 9.6            | 1.18         | 0.78–1.79        | 81               | 37.6           | <b>1.68</b>  | <b>1.34–2.11</b> |
| Nonviolent crime                                       | 86            | 8.9            | 1.14         | 0.91–1.44        | 230              | 25.9           | <b>1.19</b>  | <b>1.04–1.37</b> |

<sup>a</sup>All of the Cox proportional hazards regression models presented in the table were adjusted for age at first discharge with a bipolar disorder diagnosis; statistically significant effects ( $P < .05$ ) are highlighted in bold text.

**Table 4. Independent Risk Factors for Multiple Adverse Outcomes in the Bipolar Disorder Cohort<sup>a</sup>**

| Mutually Independent Risk Factor                  | Suicide      |           | Attempted Suicide |           | Violent Crime |           | Nonviolent Crime |           |
|---|--------------|-----------|-------------------|-----------|---------------|-----------|------------------|-----------|
|   | Hazard Ratio | 95% CI    | Hazard Ratio      | 95% CI    | Hazard Ratio  | 95% CI    | Hazard Ratio     | 95% CI    |
| Male  | 1.86         | 1.46–2.37 | 0.64              | 0.58–0.71 | 2.58          | 2.14–3.11 | 2.00             | 1.79–2.23 |
| Unmarried   | 0.54         | 0.42–0.69 | ...               | ...       | ...           | ...       | ...              | ...       |
| Low-income family                                 | ...          | ...       | ...               | ...       | 1.41          | 1.20–1.66 | 1.21             | 1.09–1.35 |
| First- or second-generation immigrant             | ...          | ...       | ...               | ...       | 1.28          | 1.07–1.53 | 1.22             | 1.09–1.37 |
| Violent crime                                     | ...          | ...       | ...               | ...       | 2.97          | 2.44–3.61 | 1.59             | 1.39–1.81 |
| Nonviolent crime                                  | ...          | ...       | 1.21              | 1.08–1.36 | 2.50          | 2.07–3.01 | 3.13             | 2.79–3.51 |
| First 2 bipolar disorder episodes as an inpatient | 2.13         | 1.59–2.85 | 1.48              | 1.34–1.64 | 1.76          | 1.47–2.11 | 1.39             | 1.25–1.55 |
| Attempted suicide                                 | 2.63         | 2.00–3.45 | 3.10              | 2.81–3.43 | 1.38          | 1.13–1.69 | 1.15             | 1.01–1.30 |
| Alcohol/drug disorder diagnosis                   | 1.65         | 1.17–2.31 | 2.17              | 1.93–2.44 | 1.60          | 1.30–1.98 | 2.12             | 1.87–2.41 |
| Parental suicide                                  | ...          | ...       | ...               | ...       | ...           | ...       | 1.27             | 1.00–1.60 |
| Parental violent crime                            | ...          | ...       | ...               | ...       | ...           | ...       | 1.35             | 1.08–1.69 |

<sup>a</sup>All of the Cox proportional hazards regression models presented in the table were adjusted for age at first discharge with a bipolar disorder diagnosis, and the hazard ratios were also mutually adjusted for all of the other explanatory variables listed under each of the 4 adverse outcomes. Symbol: ... = Variable was not included as a mutually independent predictor of risk in the final multivariable model for a given outcome.

the general population. Over a fifth of the study cohort engaged in suicidal or criminal acts following disease onset. Compared with the general population, individuals with bipolar disorder had greatly elevated risk for completed and attempted suicide. Relative risks for violent and nonviolent crime were also elevated, although to a lesser degree. Among people with suicidality outcomes, those diagnosed with bipolar disorder were more likely to die by suicide than the general population; among those who committed crimes, persons with bipolar disorder were more likely to offend violently. Second, we examined risk factors. This included comparing risks in unaffected siblings of the bipolar cohort with the general population to quantify unmeasured familial effects. We found increased risks in the unaffected siblings, although these risk elevations were substantially smaller than when comparing the bipolar disorder cohort with the general population. In our analysis of individual and parental risk factors for fatal and nonfatal suicidality and for violent and nonviolent criminality, although there was some evidence of shared determinants across the outcomes, a wider range of factors were associated with subsequent criminality than with suicidality. The observed lower suicide risk in unmarried individuals with bipolar disorder was a highly specific association.

### Comparison With Existing Evidence

A meta-analysis<sup>6</sup> of suicide in bipolar disorder found 2 main risk factors: hopelessness and, as in our study, previous suicide attempt. In line with our findings, substance misuse has been shown to be an important predictor of suicidality in bipolar disorder.<sup>41,42</sup> We found that being unmarried is inversely associated with suicide, in contrast to this being a general-population risk factor.<sup>43</sup> This finding is consistent with Danish studies of all hospital-treated psychiatric patients.<sup>44,45</sup> The reason for this counterintuitive association may be that married persons, and those better educated with rewarding jobs and higher incomes, experience a greater sense of loss or shame when they experience severe mental illness.<sup>44</sup> We did not find a significant association between parental history of suicide and elevated suicide risk in the bipolar disorder cohort, which was unexpected given previous reports.<sup>46</sup> This discrepancy may reflect an absence of selection biases in our population-based investigation.

Relative risk for violent criminal offending in people with bipolar disorder versus the general population has been systematically reviewed recently,<sup>15</sup> but risk factors for this outcome remain unclarified. The substantially higher risk in men, and also those with violent and nonviolent offending history, was expected, and the important role of substance abuse is consistent with previous research.<sup>14</sup> We have generated new findings showing higher violent crime risk in bipolar disorder for people from low-income families and immigrants. Our finding that history of attempted suicide predicts violent and nonviolent criminality is also novel. This reinforces evidence that these are highly correlated behaviors in certain diagnostic groups,<sup>23</sup> including bipolar disorder.

### Interpretation

The combined *absolute* risk for suicidality or criminality was high, and it is likely that we would have found a considerably greater risk for adverse outcome had our outcome measures captured less severe presentations. Thus, for suicidality, we included only fatalities and hospital-presenting attempts, and, for criminality, we included only convictions. Inclusion of less serious presentations may have attenuated the observed *relative* risk estimates versus the general population, had these measures been available. The raised risks for multiple adverse outcomes in bipolar disorder may be mediated by poor impulse control.<sup>17,47,48</sup> We did not measure impulsivity directly, but our findings clearly indicate a key role for substance misuse. High levels of disinhibition during manic or hypomanic phases of illness due to heavy alcohol or drug use may be an important underlying mechanism,<sup>49,50</sup> or increased risk of suicidality could be due to low mood induced or exacerbated by substance misuse during depressive illness phases.<sup>51</sup> Delusional thoughts may lead to suicidal ideation and acts in bipolar disorder,<sup>52</sup> and altered cognitive processing in relation to risk aversion<sup>53</sup> could be another common mechanism for these outcomes. Although we observed significant risk elevations in the unaffected sibling cohort, the ratios of effect sizes for the bipolar cohort versus those for the unaffected siblings were large, especially in relation to suicidality. This indicates that most of the raised risk is specific to bipolar disorder independent of the effects of unmeasured but shared genetic and environmental confounding.

### Strengths and Limitations

One of our study's key strengths, something that is rarely investigated, was the unaffected sibling comparison. Given that register-based studies are often prone to substantial residual confounding,<sup>27</sup> this enabled us to establish with greater certainty the likely magnitude of elevated risk with bipolar disorder. Other strengths included complete linkage between registers, statistical power and precision, measurement of explanatory variables prior to outcome, and complete ascertainment of multiple adverse outcomes in a single national cohort. Important limitations included a lack of measures for candidate clinical risk factors such as bipolar I versus II disorder,<sup>54</sup> rapid cycling,<sup>55</sup> and current illness phase.<sup>18,56</sup> We had no measure of actual disease onset, and initial experience of bipolar symptomatology may have been some years before first hospital treatment.<sup>57</sup> We did not consider other adverse outcomes, such as violent or sexual crime victimization<sup>58,59</sup> and serious or fatal accidental injury.<sup>60</sup> We did not assess potentially protective medication<sup>61,62</sup> and nonpharmacologic therapies.<sup>63</sup> Finally, we did not examine childhood adversity factors, although our unaffected sibling analyses provided a powerful means of adjusting for unmeasured early environmental and genetic factors.

### Conclusions

Our findings highlight the importance of comprehensive assessment of multiple outcomes in bipolar disorder. The development and testing of predictive models are urgently

required to determine whether they can improve risk management in these patients. Risk is particularly raised among patients who have already harmed themselves or committed crimes. Intervening early to treat high-risk patients, including those with alcohol/drug comorbidity, may be important, and further investigations are required to determine the most effective treatments. Psychosocial assessment reduces risk of repetition and suicide among people attending emergency departments following self-harm<sup>64</sup> and could be beneficial for bipolar disorder patients with such history. Finally, treatments that focus on likely mediators of multiple risks, such as impulsivity and disinhibition, may provide benefits across a range of adverse outcomes.

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**Authors' contributions:** Drs Webb and Fazel had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design were performed by Drs Webb, Lichtenstein, and Fazel; acquisition of data was performed by Drs Lichtenstein and Fazel; analysis and interpretation of data were performed by all authors; drafting of the manuscript was performed by Drs Webb and Fazel; critical revision of the manuscript for important intellectual content was performed by all authors; statistical analysis was performed by Dr Webb; funding was obtained by Drs Lichtenstein and Fazel; administrative, technical, or material support was performed by Drs Lichtenstein and Fazel; and study supervision was performed by Dr Fazel.

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**Supplementary material:** See accompanying pages.

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*Editor's Note:* We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Maria A. Oquendo, MD, at [moquendo@psychiatrist.com](mailto:moquendo@psychiatrist.com).

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Supplementary material follows this article.

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## **Supplementary Material**

**Article Title:** Suicide, Hospital-Presenting Suicide Attempts, and Criminality in Bipolar Disorder: Examination of Risk for Multiple Adverse Outcomes

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### **List of Supplementary Material for the article**

1. [eTable 1](#) Gender-specific risk ratios for adverse outcomes in the bipolar disorder (BD) cohort versus the general population
2. [eTable 2](#) Distribution of time in years to suicide or first violent crime in the bipolar disorder (BD) cohort after first diagnosis

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**eTable 1: Gender-specific risk ratios for adverse outcomes in the bipolar disorder (BD) cohort versus the general population**

| Adverse outcomes           | BD cohort |      | General population |      | Risk Ratio <sup>a</sup> (95% CI) |               | Adjusted Risk Ratio <sup>b</sup> (95% CI) |               |
|----------------------------|-----------|------|--------------------|------|----------------------------------|---------------|---|---------------|
|                            | n         | %    | n                  | %    |                                  |               |   |               |
| <b>Males:</b>              |           |      |                    |      |                                  |               |   |               |
| Suicidality or criminality | 1575      | 27.2 | 9726               | 8.4  | 3.24                             | (3.07-3.42)   | 2.11                                      | (2.00-2.24)   |
| Suicide                    | 149       | 2.6  | 198                | 0.2  | 15.05                            | (12.17-18.62) | 19.14                                     | (14.10-25.99) |
| Attempted suicide          | 577       | 10.0 | 1105               | 1.0  | 10.44                            | (9.44-11.55)  | 5.93                                      | (5.27-6.67)   |
| Suicidality <i>only</i>    | 407       | 7.0  | 758                | 0.7  | 10.74                            | (9.52-12.11)  | 7.94                                      | (6.97-9.04)   |
| Violent crime              | 459       | 7.9  | 2153               | 1.9  | 4.26                             | (3.86-4.72)   | 2.44                                      | (2.18-2.73)   |
| Nonviolent crime           | 1047      | 18.1 | 8211               | 7.1  | 2.55                             | (2.39-2.72)   | 1.59                                      | (1.48-1.71)   |
| Criminality <i>only</i>    | 894       | 15.4 | 8459               | 7.3  | 2.11                             | (1.97-2.26)   | 1.44                                      | (1.34-1.55)   |
| <b>Females:</b>            |           |      |                    |      |                                  |               |   |               |
| Suicidality or criminality | 1831      | 19.2 | 4500               | 2.4  | 8.14                             | (7.71-8.59)   | 4.92                                      | (4.62-5.24)   |
| Suicide                    | 123       | 1.3  | 91                 | 0.05 | 27.03                            | (20.62-35.45) | 12.24                                     | (9.66-15.51)  |
| Attempted suicide          | 1320      | 13.8 | 1550               | 0.8  | 17.03                            | (15.83-18.33) | 10.81                                     | (9.93-11.76)  |
| Suicidality <i>only</i>    | 1166      | 12.2 | 1343               | 0.7  | 17.36                            | (16.05-18.78) | 11.42                                     | (10.46-12.46) |
| Violent crime              | 176       | 1.8  | 389                | 0.2  | 9.05                             | (7.57-10.81)  | 5.03                                      | (4.03-6.28)   |
| Nonviolent crime           | 591       | 6.2  | 2965               | 1.6  | 3.99                             | (3.65-4.35)   | 2.19                                      | (1.97-2.42)   |
| Criminality <i>only</i>    | 440       | 4.6  | 2883               | 1.5  | 3.05                             | (2.76-3.37)   | 1.81                                      | (1.62-2.03)   |

<sup>a</sup> Risk ratio estimated by conditional fixed-effects Poisson regression, and adjusted inherently for age and gender in the matched design

<sup>b</sup> Risk ratio additionally adjusted for an alcohol/drug disorder diagnosis before or after bipolar disorder diagnosis, family income level, being an immigrant, and marital status

**eTable 2: Distribution of time in years to suicide or first violent crime in the bipolar disorder (BD) cohort after first diagnosis**

| <b>Adverse outcomes</b>       | <b>n</b> | <b>%</b> | <b>Median</b> | <b>(IQR)</b> |
|-------------------------------|----------|----------|---------------|--------------|
| <u>Suicide (n=272):</u>       |          |          |               |              |
| Within 5 years                | 171      | 62.9     | 3.44          | (1.31-7.12)  |
| 5-9 years                     | 55       | 18.7     |               |              |
| 10-14 years                   | 25       | 9.2      |               |              |
| 15 years or longer            | 25       | 9.2      |               |              |
| <u>Violent crime (n=635):</u> |          |          |               |              |
| Within 5 years                | 446      | 70.2     | 2.36          | (0.82-6.03)  |
| 5-9 years                     | 100      | 15.7     |               |              |
| 10-14 years                   | 39       | 6.1      |               |              |
| 15 years or longer            | 50       | 7.9      |               |              |