

Abstract: 221 words. Text: 2,637 words.  
4 Tables, 1 Figure, 3 Supplementary Tables

# **Incidence of Parkinson's disease, dementia, cerebrovascular disease and stroke in bipolar disorder compared to other psychiatric disorders: an electronic health records network study of 66 million people**

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**Key words:** bipolar disorder - dementia – electronic health records - Parkinson's disease – stroke – cerebrovascular disease

**Running head:** Neurodegenerative outcomes in bipolar disorder

## ABSTRACT

*Objectives:* Bipolar disorder has been associated with an increased risk for neurodegenerative diseases, but uncertainties remain. The risk relative to other psychiatric disorders is not established.

*Methods:* We used a federated electronic health records network of 66 million people including over 700,000 with bipolar disorder. We assessed incidence of a first diagnosis of Parkinson's disease, dementia, cerebrovascular disease, and stroke, in patients at least one year after diagnosis of bipolar disorder. Rates were compared to propensity score matched cohorts of subjects with mixed disorders, recurrent major depressive disorder (MDD), or schizophrenia.

*Results:* Parkinson's disease was commoner in bipolar disorder compared to all three cohorts (odds ratios [OR] ranging from 1.26 to 2.65). Dementia incidence was greater in bipolar disorder than in mixed disorders (OR=1.61) or MDD (OR=1.40), but not different from schizophrenia (OR=0.96). Cerebrovascular disease and stroke were commoner in bipolar disorder than in schizophrenia (OR=1.35) or mixed disorders (OR=1.20) and equivocally raised compared to MDD. Results were robust to a wide range of confounding demographic, diagnostic, and medication risk factors for neurodegenerative disorders.

*Conclusions:* Bipolar disorder confers an elevated risk for developing neurodegenerative disorders and cerebrovascular disease compared to other major adult psychiatric disorders. The results cannot be attributed to recognised confounders. The results are consistent with neuroprogressive views of bipolar disorder. The underlying mechanisms remain to be discovered.

## 1. INTRODUCTION

Bipolar disorder is conceptualised as a neurodevelopmental disorder,<sup>1-3</sup> yet also as a progressive one in which accelerated brain aging occurs.<sup>4-7</sup> The same dual view also pertains to the cognitive impairment which is a core feature of disorder.<sup>8</sup>

There is no evidence that bipolar disorder has a degenerative or vascular neuropathology,<sup>9</sup> but there is increasing evidence that it is associated with an elevated risk for neurodegenerative and cerebrovascular diseases. A recent meta-analysis including about 70,000 bipolar disorder patients found a 3.35-fold increased risk of Parkinson's disease compared to controls;<sup>10</sup> subgroup analyses suggested that this was only in small part attributable to parkinsonism resulting from antipsychotic or other medication. For dementia, extending earlier reports,<sup>11,12,13</sup> a recent meta-analysis comprising 6,859 bipolar disorder cases and 487,966 controls found an almost 3-fold increase in dementia in the bipolar group; dementia risk was also elevated compared to patients with major depressive disorder (MDD).<sup>14</sup> The risk of dementia was lower in bipolar disorder patients who had been treated with lithium, in line with other indications that the drug may have neuroprotective effects.<sup>15-17</sup> The higher rate of dementia in bipolar disorder than MDD is notable since depression itself has been associated with elevated dementia risk,<sup>11,18,19</sup> and affective disorders as whole confer an increased risk compared to various medical illnesses.<sup>20</sup> The incidence of cerebrovascular disease and stroke in bipolar disorder is not well established, although some data suggest both might be increased.<sup>21,22</sup>

Here we investigated the incidence of Parkinson's disease, dementia, and cerebrovascular disease and stroke, in bipolar disorder using a large electronic health records network. We compared patients with bipolar disorder to three other cohorts: one with a mixture of anxiety and affective diagnoses, one with recurrent MDD, and one with schizophrenia. All cohorts excluded patients who had any recorded neurodegenerative diagnosis prior to, or within a year after, their psychiatric diagnosis. We used propensity score matching for a range of factors to reduce confounding between cohorts. This strategy allowed us to examine whether bipolar disorder is associated with differential risk for neurodegenerative outcomes relative to other common adult psychiatric disorders.

## 2. METHODS

## 2.1 The TriNetX network

The TriNetX network ([www.trinetx.com](http://www.trinetx.com)) and its functionality have been described previously.<sup>23,24</sup> Briefly, it is comprised of federated electronic health records from a mixture of hospitals, primary care, and specialist providers. We performed our analyses using the TriNetX Analytics network to capture anonymised data from 54 health care organisations in the USA, totalling 66.8 million patients, including over 700,000 with bipolar disorder. TriNetX has a waiver from the Western Institutional Review Board since only aggregated counts and summaries of de-identified information are used. A wide range of data are available regarding demographics, diagnostics (using ICD-10 codes), prescriptions, and lab values. Most data were captured from 2007 onwards, and data are updated on average every 24 days. Via the web browser, cohorts can be created based on specified inclusion and exclusion criteria, and comparisons then made between pairs of cohorts for outcomes of interest over a specified time period. A built-in propensity score matching capability<sup>25,26</sup> allows control for variables which differ between cohorts and which might confound the comparison. Further details of the TriNetX network, its data sources and validations, and the propensity score matching methods, can be found in the Supplementary Materials.

## 2.2 Creation and matching of cohorts

We created a cohort of patients with bipolar disorder who, at the time of diagnosis and for at least one year thereafter, were free of Parkinson's disease, dementia, or cerebrovascular disease. We also excluded anyone with secondary parkinsonism or mild cognitive impairment since these can be prodromal to or mistaken for the outcomes of interest. The requirement to be free of any neurodegenerative outcome for at least a year after diagnosis of bipolar disorder was intended to reduce the chance of misdiagnosis.<sup>27</sup> A list of all ICD-10 codes used is given in Supplementary Table 1.

Three comparison cohorts were then created. First, patients with a range of anxiety and non-recurrent affective disorders (see Supplementary Table 1 and Table 1 for details), referred to here as 'mixed disorders'. Second, a cohort of patients with a diagnosis of recurrent MDD. Third, we compared bipolar disorder with schizophrenia, since this helps control for other confounders, notably antipsychotic use. For all three cohorts, the same exclusion criteria for neurodegeneration and cerebrovascular disease were applied as for the bipolar disorder cohort.

## 2.3 Outcomes and analyses

Using the propensity score matching function, our primary analyses were carried out having matched each pair of cohorts for age, sex and race, and for their most recent recorded blood pressure and body mass index. All these variables can affect risk of neurodegenerative disorders and stroke<sup>28-32</sup> and, without matching, the cohorts differed on one or more of these factors (data not shown). A standard difference of less than 0.1 indicates good matching.<sup>33</sup>

We conducted two sensitivity analyses. First, we excluded patients who had ever been treated with lithium, given its possible neuroprotective effects, and because the tremor sometimes observed with lithium treatment could be misdiagnosed as Parkinson's disease. Second, we further matched the cohorts for a range of additional diagnoses and medications that have been reportedly associated, whether causally or otherwise, with risk of developing Parkinson's disease, dementia or stroke. The additional diagnoses were: alcohol use disorder, cardiovascular disease (including hypertension and ischemic heart disease), head injury, diabetes mellitus, and nicotine dependence; the medications were antihypertensives, statins, platelet aggregation inhibitors, non-steroidal anti-inflammatories, biguanides and oestrogens. See Supplementary Table 1 for further information and codes for all variables.

The primary outcomes of interest were a diagnosis of Parkinson's disease, dementia, or cerebrovascular disease. We also examined major dementia subtypes and stroke separately, and determined the age at diagnosis of each outcome. Mortality was also compared between cohorts. Our outcome period was from one year after diagnosis of bipolar disorder onwards; the longest duration of follow up was 18 years. Results were expressed as odds ratios (OR) and 95% confidence intervals, calculated using standard methods implemented within the TriNetX network.

We followed the STROBE guidelines for observational studies.<sup>34</sup>

## 3. RESULTS

Using propensity score matching we created three pairs of cohorts: bipolar disorder vs. mixed disorders (N=604,430 in each cohort); bipolar disorder vs. MDD (N=559,401), and bipolar disorder vs. schizophrenia (N=131,795). Cohort demographic details are shown in Tables 1-3. All

cohorts are well matched for age, sex, race, blood pressure and body mass index. Additional information regarding comorbid diagnoses and medication usage is given in Supplementary Table 2.

### 3.1 Bipolar disorder vs. mixed disorders

Compared to the cohort of patients with mixed disorders (anxiety disorders and depressive episodes), bipolar disorder was associated with elevated risks of all neurodegenerative outcomes (Table 1 and Figure 1). The biggest difference was for Parkinson's disease (OR 2.65 [2.44-2.88]), with an OR of 1.61 [1.53-1.68] for dementia, and 1.20 [1.17-1.23] for cerebrovascular disease. Mortality rates did not differ between cohorts. Results were essentially unchanged if patients who had ever been treated with lithium were excluded, except that the increased risk for stroke was no longer observed (Table 1). Matching the cohorts for the additional diagnoses and medications that may be associated with risk of neurodegenerative disorders also did not markedly change the findings (Supplementary Table 3a). The age at diagnosis of neurodegenerative outcomes was lower in bipolar disorder (Table 4).

### 3.2 Bipolar disorder vs. major depressive disorder

The comparisons between bipolar disorder and MDD are shown in Table 2. Bipolar disorder is associated with a greater risk of Parkinson's disease (OR 2.15 [1.99-2.33]) and dementia (OR 1.40 [1.34-1.47]), with both occurring at an earlier age (Table 4). Cerebrovascular disease and stroke do not show marked nor consistent differences between bipolar disorder and MDD (Table 2). Mortality was higher in bipolar disorder than in MDD (OR 1.21 [1.18-1.24]). Following the more extensive propensity score matching, the higher rates of Parkinson's disease and dementia remained, and the incidence of cerebrovascular disease and stroke in bipolar disorder became significantly increased (Supplementary Table 3b).

### 3.3 Bipolar disorder vs schizophrenia

Compared to the mixed disorder and MDD cohorts, the cohorts for bipolar disorder and schizophrenia were smaller, older, and with a male predominance, but were again well matched (Table 3). The incidence of Parkinson's disease (OR 1.26 [1.12-1.42]) and cerebrovascular disease

(1.35 [1.29-1.42]) was higher in bipolar disorder than in schizophrenia, but the risk of dementia was similar (OR 0.96 [0.89-1.03]; Figure 1). These findings applied to lithium-free cohorts as well. Incidence of death was lower in bipolar disorder than schizophrenia (OR 0.77 [0.74-0.80]). No further matching was required for the additional diagnoses and treatments that might affect neurodegeneration risk because the cohorts were already matched for these factors. Age at diagnosis of Parkinson's disease and dementia were similar between groups, but the bipolar disorder patients were younger when diagnosed with cerebrovascular disease (Table 4).

## 4. DISCUSSION

A possible association between psychiatric disorders and risk for neurodegenerative conditions has long been considered, particularly for elevated rates of dementia in people with a history of schizophrenia<sup>35</sup> or depression.<sup>11,18,19</sup> More recently, bipolar disorder has come under scrutiny too, with meta-analyses suggesting increased rates of dementia,<sup>12-15</sup> Parkinson's disease<sup>10</sup> and cerebrovascular disease.<sup>21,22</sup> Our data support all these associations, and extend them in three main ways. First, our study is substantially larger than all previous studies and meta-analyses, adding robustness and precision to the risk estimates. Second, it shows differential risks between these outcomes, and higher risks for bipolar disorder compared to other common adult psychiatric disorders. Third, the extensive matching of cohorts allowed control over many potential confounders which have also been associated with risk of these outcomes, such as comorbid diagnoses (e.g. alcohol use disorder, diabetes), demographic factors (e.g. body mass index), and medications (e.g. anti-hypertensives, non-steroidal anti-inflammatories), allowing greater confidence in interpretation of the results.

### 4.1 Bipolar disorder and Parkinson's disease

An important confounder when assessing risk of Parkinson's disease in psychiatric disorders is antipsychotic medication and, to a lesser extent, lithium. Our finding of an increased risk in bipolar disorder cannot readily be explained by either factor since it was seen compared to the schizophrenia cohort (in which antipsychotic usage was greater), and was observed in the lithium-naïve cohorts. Similarly, use of beta-blockers and other anti-hypertensives can confound estimates of Parkinson's disease (<sup>36,37</sup> and our unpublished observations), but was matched between cohorts. Our results therefore support and extend prior reports of an association between bipolar disorder

and Parkinson's disease,<sup>10</sup> including an earlier age of onset.<sup>38</sup> The elevated risk compared to MDD is notable since depression itself is robustly associated with of Parkinson's disease.<sup>39,40</sup> As a possible mechanism, it has been proposed that there is a dopaminergic component to bipolar disorder pathogenesis<sup>41,42</sup> which renders patients at risk of Parkinson's disease.<sup>10</sup>

## 4.2 Bipolar disorder and dementia

The incidence of dementia was greater in bipolar disorder compared to mixed disorders and MDD, with no clear difference between clinically diagnosed subtypes of dementia. In contrast to some prior indications,<sup>14-17</sup> we did not see evidence that lithium treatment mitigated this risk, in that results were unchanged in the lithium-naïve cohorts. However, lithium use was low, in line with other recent findings,<sup>43,44</sup> with only 10% of patients having been prescribed it, and hence we were not well powered to investigate this question. We were able to control for many other factors that may affect dementia risk, such as a history of head injury, alcohol use disorder, hypertension, and a range of medications. In total, our results corroborate and extend the evidence for a relationship between bipolar disorder and dementia,<sup>11-15</sup> including the differential risk compared to MDD.<sup>14,15,19</sup> Cognitive impairment is a core feature of bipolar disorder but its basis, and whether it worsens with age, has been controversial.<sup>4,8,45</sup> Many studies have failed to find evidence of progression, consistent with the lack of any neurodegenerative pathology intrinsic to bipolar disorder.<sup>9</sup> The evidence of an increased risk of dementia suggests that any progressive cognitive decline which is observed is a reflection of this subgroup, rather than being a feature inherent to the disorder; however, available data do not allow these possibilities to be distinguished clearly.

The only outcome for which bipolar disorder was not associated with a higher incidence, nor an earlier age of onset, was for dementia relative to the schizophrenia cohort; if anything, the trend for risk was in the opposite direction. This may reflect the elevated dementia risk associated with schizophrenia.<sup>35</sup> In schizophrenia, the dementia is not attributable to Alzheimer's disease nor any other recognised neuropathological signature.<sup>46,47</sup> Given the many aetiological and pathophysiological overlaps between schizophrenia and bipolar disorder, one might speculate that dementia in bipolar disorder is similarly unexplained. We are not aware of substantive neuropathological data regarding this possibility, although Alzheimer's disease biomarkers are not observed in cerebrospinal fluid of cognitively impaired patients with bipolar disorder.<sup>48</sup> Instead, inflammatory markers are present,<sup>49</sup> which may give an indication as to the nature of the underlying process.



### 4.3 Bipolar disorder, cerebrovascular disease and stroke

The increased incidence of cerebrovascular disease in bipolar disorder is consistent with Correll and colleagues,<sup>22</sup> whilst the higher stroke risk extends preliminary evidence from a case-control comparison.<sup>21</sup> It is notable that the increases are seen not only relative to mixed disorders but also to schizophrenia, since the latter is itself associated with markedly higher rates of vascular disease.<sup>22</sup> It also makes residual confounding (e.g. by antipsychotic medication, or lifestyle) an unlikely explanation. Instead, it may be related to the reduced cerebrovascular reactivity observed in young patients with bipolar disorder, hypothesised to reflect an increased vulnerability to cerebrovascular disease.<sup>50</sup> The results for cerebrovascular disease and stroke in bipolar disorder compared to MDD were equivocal, perhaps reflecting the fact that depression is also linked to vascular disease<sup>51</sup> and stroke.<sup>52</sup>

### 4.4 Strengths and limitations

The main strengths of this study are the size of the cohorts, the extensive information available about demographics, diagnoses, and medications, and the use of propensity score matching to substantially reduce confounding. These factors together suggest that the results are relatively robust. Nevertheless, the study has several limitations. First, residual confounding can never be eliminated entirely.<sup>53,54</sup> In particular, there is a lack of information in the network about potentially relevant factors such as socioeconomic status, smoking (other than recorded nicotine dependence) and alcohol use (other than a diagnosis of alcohol use disorder). Second, we know the age at which a diagnosis was first recorded at a participating health care organisation, but the diagnosis could have been made previously elsewhere and the record not transferred. For the same reason, we do not know how long after onset of bipolar disorder the neurodegenerative outcome – or death – occurred (other than being at least one year later). Third, important psychiatric details are lacking, such as bipolar subtype (the majority are coded as unspecified [F31.9]), and the number of psychiatric admissions and mood episodes, which have been associated with a greater risk of Parkinson's disease<sup>38</sup> and dementia.<sup>55,56</sup> Fourth, the higher mortality in bipolar disorder than MDD, and the lower mortality compared to schizophrenia, whilst in keeping with other data,<sup>57</sup> complicates interpretation of the results. Finally, the electronic health records may be incomplete, whether due to gaps in the coding of information, or because patients have received additional health care from non-participating organisations.

## 4.5 Conclusions

Despite these caveats, the results show that bipolar disorder is associated with an increased risk of the major neurodegenerative outcomes compared to other common adult psychiatric disorders. Since the latter are themselves associated with increased rates of neurodegenerative disease compared to people without psychiatric disorders, and compared to those who have chronic medical disorders, the findings in bipolar disorder become more striking. The associations are not readily attributable to confounders, and suggest a particular pathophysiological relationship between bipolar disorder and vulnerability to neurodegeneration. The increased risks and earlier ages of onset are broadly supportive of the view that bipolar disorder predisposes to accelerated brain aging; however, the pathways and mechanisms remain to be determined.

**Acknowledgements:** PJH was granted unrestricted access to the TriNetX Analytics network for the purposes of research relevant to psychiatry, and with no constraints on the analyses performed nor the decision to publish. PJH is supported by the National Institute for Health Research (NIHR) Oxford Health Biomedical Research Centre (grant BRC-1215-20005). The views expressed are those of the authors and not necessarily those of the National Health Service, NIHR, or the United Kingdom Department of Health. We thank Max Taquet for helpful advice.

**Conflicts of Interest.** SL is an employee of TriNetX Inc.

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**Data availability:** Data are subject to third party restrictions. Data available from PJH with the permission of TriNetX Inc.

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**Table 1.** Bipolar disorder compared to mixed disorders: cohort characteristics and outcomes.

**Table 2.** Bipolar disorder compared to major depressive disorder: cohort characteristics and outcomes.

**Table 3.** Bipolar disorder compared to schizophrenia: cohort characteristics and outcomes.

**Table 4.** Age at diagnosis of outcomes.

**Figure 1.** Risks of developing Parkinson's disease, dementia, or cerebrovascular disease, in patients with bipolar disorder compared to those with mixed disorders, major depressive disorder or schizophrenia. Error bars are 95% confidence intervals.

**Table 1. Bipolar disorder compared to mixed disorders: cohort characteristics and outcomes**

|  | Full cohort                   |                              |                                  |  | Lithium-free cohort           |                              |                                  |
|--|-------------------------------|------------------------------|----------------------------------|--|-------------------------------|------------------------------|----------------------------------|
| <b>Baseline characteristics</b>          | Bipolar disorder              | Mixed disorders <sup>†</sup> | Standard difference <sup>‡</sup> |  | Bipolar disorder              | Mixed disorders              | Standard difference <sup>‡</sup> |
| Number                                   | 604,430                       | 604,430                      |                                  |  | 557,775                       | 557,775                      |                                  |
| Age at index (y, mean [SD])              | 38.5 [15.7]                   | 37.3 [18.7]                  | <0.07                            |  | 38.5 [15.7]                   | 38.7 [16.0]                  | <0.02                            |
| Sex (M:F)                                | 40%:60%                       | 39%:61%                      | <0.01                            |  | 40%:60%                       | 39%:61%                      | <0.02                            |
| Race <sup>§</sup>                        | 74% W, 13% AA, 13% O          | 74% W, 13% AA, 13% O         | <0.01                            |  | 72% W, 15% AA, 13% O          | 72% W, 15% AA, 13% O         | <0.01                            |
| Blood pressure <sup>¶</sup>              | 122/74                        | 123/75                       | <0.08                            |  | 122/74                        | 122/75                       | <0.08                            |
| Body mass index <sup>¶</sup> (mean [SD]) | 29.6 [8.4]                    | 29.8 [18.3]                  | <0.02                            |  | 29.6 [8.4]                    | 29.0 [8.1]                   | <0.08                            |
| <b>Outcomes</b>                          | Incidence in bipolar disorder | Incidence in mixed disorders | Odds ratio (95% CI)              |  | Incidence in bipolar disorder | Incidence in mixed disorders | Odds ratio (95% CI)              |
| Parkinson's disease                      | 2,089 (0.35%)                 | 789 (0.13%)                  | <b>2.65 (2.44-2.88)</b>          |  | 1,632 (0.29%)                 | 651 (0.12%)                  | <b>2.51 (2.29-2.75)</b>          |
| Dementia (any)                           | 4,431 (0.73%)                 | 2,766 (0.46%)                | <b>1.61 (1.53-1.68)</b>          |  | 3,752 (0.67%)                 | 2,144 (0.38%)                | <b>1.75 (1.66-1.85)</b>          |
| Alzheimer's disease                      | 747 (0.12%)                   | 644 (0.11%)                  | <b>1.16 (1.04-1.29)</b>          |  | 628 (0.11%)                   | 446 (0.08%)                  | <b>1.41 (1.25-1.59)</b>          |
| Vascular dementia                        | 829 (0.14%)                   | 494 (0.08%)                  | <b>1.68 (1.50-1.88)</b>          |  | 678 (0.12%)                   | 377 (0.07%)                  | <b>1.80 (1.59-2.04)</b>          |
| Unspecified dementia                     | 3,017 (0.50%)                 | 1,887 (0.31%)                | <b>1.60 (1.51-1.70)</b>          |  | 2,588 (0.46%)                 | 1,477 (0.26%)                | <b>1.76 (1.65-1.87)</b>          |
| Cerebrovascular disease                  | 13,171 (2.18%)                | 11,046 (1.83%)               | <b>1.20 (1.17-1.23)</b>          |  | 11,503 (2.06%)                | 10,165 (1.82%)               | <b>1.13 (1.10-1.16)</b>          |
| Stroke                                   | 6,059 (1.00%)                 | 5,162 (0.85%)                | <b>1.18 (1.13-1.22)</b>          |  | 5,184 (0.93%)                 | 5,041 (0.90%)                | 1.03 (0.99-1.07)                 |
| Death                                    | 14,462 (2.39%)                | 14,143 (2.34%)               | 1.02 (1.00-1.05)                 |  | 13,203 (2.37%)                | 12,857 (2.30%)               | 1.03 (1.00-1.05)                 |

<sup>†</sup>Comprising: anxiety disorders (60%); major depressive episode (45%); unspecified mental disorder (17%). phobia (16%); OCD (9%). Patients could have more than one of these diagnoses. For ICD-10 codes see Supplementary Table 1.

<sup>‡</sup>Values below 0.1 indicate matching between cohorts.

<sup>§</sup>W: Caucasian; AA: Black or African American; O: other or not known

<sup>¶</sup>Most recent value at cohort entry



**Table 2. Bipolar disorder compared to major depressive disorder: cohort characteristics and outcomes**

|                                 | Full cohorts                  |  |                         |  | Lithium-free cohorts          |  |                         |
|---------------------------------|-------------------------------|--|-------------------------|--|-------------------------------|--|-------------------------|
| <b>Baseline characteristics</b> | Bipolar disorder              | Major depressive disorder              | Standard difference†    |  | Bipolar disorder              | Major depressive disorder              | Standard difference†    |
| Number                          | 559,401                       | 559,401                                |                         |  | 523,327                       | 523,327                                |                         |
| Age at index (y; mean [SD])     | 39.0 [16.0]                   | 40.5 [16.4]                            | <0.10                   |  | 39.2 [15.8]                   | 39.0 [15.9]                            | <0.02                   |
| Sex (M:F)                       | 35%:65%                       | 36%:64%                                | <0.01                   |  | 37%:63%                       | 36%:64%                                | <0.02                   |
| Race‡                           | 75% W, 12% AA, 13% O          | 75% W, 12% AA, 13% O                   | <0.04                   |  | 74% W, 13% AA, 13% O          | 74% W, 13% AA, 13% O                   | <0.04                   |
| Blood pressure§                 | 122/74                        | 122/75                                 | <0.09                   |  | 122/74                        | 122/75                                 | <0.07                   |
| Body mass index§ (mean [SD])    | 29.6 [8.4]                    | 29.9 [8.3]                             | <0.03                   |  | 29.7 [8.4]                    | 29.7 [8.4]                             | <0.01                   |
| <b>Outcomes</b>                 | Incidence in bipolar disorder | Incidence in major depressive disorder | Odds ratio (95% CI)     |  | Incidence in bipolar disorder | Incidence in major depressive disorder | Odds ratio (95% CI)     |
| Parkinson's disease             | 2,050 (0.37%)                 | 955 (0.17%)                            | <b>2.15 (1.99-2.33)</b> |  | 1,626 (0.31%)                 | 826 (0.16%)                            | <b>1.97 (1.81-2.14)</b> |
| Dementia (any)                  | 4,372 (0.78%)                 | 3,119 (0.56%)                          | <b>1.40 (1.34-1.47)</b> |  | 3,714 (0.71%)                 | 2,550 (0.49%)                          | <b>1.46 (1.39-1.53)</b> |
| Alzheimer's disease             | 753 (0.13%)                   | 674 (0.12%)                            | <b>1.12 (1.01-1.24)</b> |  | 630 (0.12%)                   | 520 (0.10%)                            | <b>1.21 (1.08-1.36)</b> |
| Vascular dementia               | 819 (0.15%)                   | 601 (0.11%)                            | <b>1.36 (1.23-1.51)</b> |  | 670 (0.13%)                   | 484 (0.09%)                            | <b>1.38 (1.23-1.56)</b> |
| Unspecified dementia            | 2,993 (0.53%)                 | 2,084 (0.37%)                          | <b>1.44 (1.36-1.52)</b> |  | 2,575 (0.49%)                 | 1,694 (0.32%)                          | <b>1.52 (1.43-1.62)</b> |
| Cerebrovascular disease         | 12,697 (2.27%)                | 12,062 (2.16%)                         | <b>1.05 (1.03-1.08)</b> |  | 11,189 (2.14%)                | 11,112 (2.12%)                         | 1.01 (0.98-1.03)        |
| Stroke                          | 5,824 (1.04%)                 | 6,018 (1.08%)                          | 0.97 (0.93-1.00)        |  | 5,026 (0.96%)                 | 5,590 (1.07%)                          | <b>0.90 (0.86-0.93)</b> |
| Death                           | 13,753 (2.46%)                | 11,400 (2.04%)                         | <b>1.21 (1.18-1.24)</b> |  | 12,819 (2.45%)                | 10,261 (1.96%)                         | <b>1.26 (1.22-1.29)</b> |

†Values below 0.1 indicate matching between cohorts.

‡W: Caucasian; AA: Black or African American; O: other or not known

§Most recent value at cohort entry

**Table 3. Bipolar disorder compared to schizophrenia: cohorts and outcomes**

|                                 | <b>Full cohorts</b>           |                            |                                  |  | <b>Lithium-free cohorts</b>   |                            |                                  |
|---------------------------------|-------------------------------|----------------------------|----------------------------------|--|-------------------------------|----------------------------|----------------------------------|
| <b>Baseline characteristics</b> | Bipolar disorder              | Schizophrenia              | Standard difference <sup>†</sup> |  | Bipolar disorder              | Schizophrenia              | Standard difference <sup>†</sup> |
| Number                          | 131,795                       | 131,795                    |                                  |  | 128,767                       | 128,767                    |                                  |
| Age at index (y; mean [SD])     | 43.1 [16.1]                   | 43.3 [15.7]                | <0.02                            |  | 43.3 [16.2]                   | 43.4 [15.7]                | <0.01                            |
| Sex (M:F)                       | 65%:35%                       | 65%:35%                    | <0.01                            |  | 65%:35%                       | 65%:35%                    | <0.01                            |
| Race‡                           | 50% W, 31% AA, 19% O          | 50% W, 32% AA, 18% O       | <0.02                            |  | 50% W, 32% AA, 18% O          | 50% W, 32% AA, 18% O       | <0.01                            |
| Blood pressure§                 | 125/75                        | 125/75                     | <0.03                            |  | 125/75                        | 125/75                     | <0.04                            |
| BMI§ (mean [SD])                | 28.8 [7.9]                    | 29.6 [8.0]                 | <0.02                            |  | 29.5 [8.0]                    | 28.6 [8.0]                 | 0.10                             |
| <b>Outcomes</b>                 | Incidence in bipolar disorder | Incidence in schizophrenia | Odds ratio (95% CI)              |  | Incidence in bipolar disorder | Incidence in schizophrenia | Odds ratio (95% CI)              |
| Parkinson's disease             | 586 (0.44%)                   | 465 (0.35%)                | <b>1.26 (1.12-1.42)</b>          |  | 516 (0.40%)                   | 434 (0.34%)                | <b>1.19 (1.05-1.35)</b>          |
| Dementia (any)                  | 1,413 (1.07%)                 | 1,470 (1.11%)              | 0.96 (0.89-1.03)                 |  | 1,326 (1.03%)                 | 1,415 (1.10%)              | 0.94 (0.87-1.01)                 |
| Alzheimer's disease             | 249 (0.19%)                   | 217 (0.16%)                | 1.15 (0.96-1.38)                 |  | 230 (0.18%)                   | 214 (0.17%)                | 1.07 (0.89-1.29)                 |
| Vascular dementia               | 242 (0.18%)                   | 237 (0.18%)                | 1.02 (0.85-1.22)                 |  | 249 (0.19%)                   | 222 (0.17%)                | 1.12 (0.94-1.34)                 |
| Unspecified dementia            | 981 (0.74%)                   | 1,065 (0.81%)              | 0.92 (0.84-1.00)                 |  | 923 (0.72%)                   | 1,034 (0.80%)              | <b>0.89 (0.82-0.97)</b>          |
| Cerebrovascular disease         | 3,609 (2.74%)                 | 2,688 (2.04%)              | <b>1.35 (1.29-1.42)</b>          |  | 3,388 (2.63%)                 | 2,598 (2.02%)              | <b>1.31 (1.25-1.38)</b>          |
| Stroke                          | 1,632 (1.24%)                 | 1,216 (0.92%)              | <b>1.25 (1.25-1.45)</b>          |  | 1,488 (1.16%)                 | 1,181 (0.92%)              | <b>1.26 (1.17-1.36)</b>          |
| Death                           | 4,078 (3.09%)                 | 5,236 (3.97%)              | <b>0.77 (0.74-0.80)</b>          |  | 4,164 (3.23%)                 | 5,124 (3.98%)              | <b>0.81 (0.77-0.84)</b>          |

<sup>†</sup>Values below 0.1 indicate matching between cohorts.

<sup>‡</sup>W: Caucasian; AA: Black or African American; O: other or not known

<sup>§</sup>Most recent value at cohort entry

**Table 4. Age at diagnosis of neurodegenerative outcomes**

| <b><i>Age at diagnosis (y)</i></b> | Bipolar disorder |      | Mixed disorders |      | Major depressive disorder |      | Schizophrenia |      |
|------------------------------------|------------------|------|-----------------|------|---------------------------|------|---------------|------|
|                                    | Mean             | S.D. | Mean            | S.D. | Mean                      | S.D. | Mean          | S.D. |
| Parkinson's disease                | 64.9             | 12.0 | 72.5            | 12.4 | 69.3                      | 11.1 | 64.7          | 12.2 |
| Dementia                           | 67.3             | 13.0 | 73.4            | 13.0 | 73.0                      | 11.9 | 68.8          | 11.7 |
| Cerebrovascular disease            | 56.3             | 14.0 | 60.9            | 15.6 | 62.4                      | 13.8 | 60.5          | 12.8 |