



## Multiple sclerosis and psychiatric disorders: comorbidity and sibling risk in a nationwide Swedish cohort

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Keywords:	Multiple sclerosis, Bipolar disorder, Depression, Schizophrenia, Genetic liability, Cohort study
Abstract:	<p>Abstract</p> <p>Background: Psychiatric disorders are known to be prevalent in Multiple Sclerosis (MS).</p> <p>Objective: To study comorbidity between MS and bipolar disorder, schizophrenia and depression in a nation-wide cohort and to determine whether shared genetic liability underlies the putative association.</p> <p>Methods: We identified ICD-diagnosed patients with MS (n=16,467), bipolar disorder (n=30,761), schizophrenia (n= 22,781) and depression (n=172,479) in the Swedish National Patient Register and identified their siblings in the Multi-Generation Register. The risk of MS was compared in psychiatric patients and in matched unexposed individuals. Shared familial risk between MS and psychiatric disorders was estimated by sibling</p>

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	<p>comparison.</p> <p>Results: The risk of MS was increased in patients with bipolar disorder (hazard ratio [HR] 1.8, 95% confidence interval [CI] 1.6-2.2, <math>p &lt; 0.0001</math>) and depression (HR 1.9, 95% CI 1.7-2.0, <math>p &lt; 0.0001</math>). MS risk in schizophrenia was decreased (HR 0.6, 95% CI 0.4-0.9, <math>p = 0.005</math>). The association between having a sibling with a psychiatric disorder and developing MS was not significant.</p> <p>Conclusion: We found a strong positive association between MS and bipolar disorder and depression that could not be explained by genetic liability. The unexpected negative association between MS and schizophrenia might be spurious or indicate possible protective mechanisms that warrant further exploration.</p>

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4 **nationwide Swedish cohort**  
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40 Christina M. Hultman were responsible for the study design and interpretation of the results.  
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42 Paul Lichtenstein was responsible of the preparation of the data. Viktoria Johansson, Cecilia  
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44 Lundholm and Christina M. Hultman worked with the data analysis and Cecilia Lundholm  
45  
46 provided biostatistical expertise. Viktoria Johansson was responsible for literature search.  
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48 Viktoria Johansson and Christina M. Hultman worked with the preparation of figures and  
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50 tables. Viktoria Johansson, Cecilia Lundholm, Jan Hillert, Thomas Masterman, Paul  
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52 Lichtenstein, Mikael Landén and Christina M. Hultman worked with the writing of the  
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54 manuscript.  
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**Key words:**

Multiple Sclerosis, Bipolar disorder, Depression, Schizophrenia, Genetic liability, Cohort study

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## Multiple sclerosis and psychiatric disorders: comorbidity and sibling risk in a nationwide

### Swedish cohort

#### Abstract

**Background:** Psychiatric disorders are known to be prevalent in Multiple Sclerosis (MS).

**Objective:** To study comorbidity between MS and bipolar disorder, schizophrenia and depression in a nation-wide cohort and to determine whether shared genetic liability underlies the putative association.

**Methods:** We identified ICD-diagnosed patients with MS (n=16,467), bipolar disorder (n=30,761), schizophrenia (n= 22,781) and depression (n=172,479) in the Swedish National Patient Register and identified their siblings in the Multi-Generation Register. The risk of MS was compared in psychiatric patients and in matched unexposed individuals. Shared familial risk between MS and psychiatric disorders was estimated by sibling comparison.

**Results:** The risk of MS was increased in patients with bipolar disorder (hazard ratio [HR] 1.8, 95% confidence interval [CI] 1.6-2.2,  $p < 0.0001$ ) and depression (HR 1.9, 95% CI 1.7-2.0,  $p < 0.0001$ ). MS risk in schizophrenia was decreased (HR 0.6, 95% CI 0.4-0.9,  $p = 0.005$ ). The association between having a sibling with a psychiatric disorder and developing MS was not significant.

**Conclusion:** We found a strong positive association between MS and bipolar disorder and depression that could not be explained by genetic liability. The unexpected negative association between MS and schizophrenia might be spurious or indicate possible protective mechanisms that warrant further exploration.

## Introduction

Multiple sclerosis (MS) is an inflammatory autoimmune disease resulting in demyelination and axonal loss of the central nervous system (CNS), which lead to disability with detrimental effects on quality of life (1). Emerging evidence suggests that inflammation also plays an important role in psychiatric disorders such as bipolar disorder, schizophrenia and depression (2). Several studies have shown increased rates of depression and bipolar disorder in patients with MS (3-14). In some studies, MS has also been associated with an increased risk of schizophrenia and non-affective psychosis (11, 15-17), while in other studies no association was demonstrated (14, 18).

The association between MS and these psychiatric disorders might be explained by shared familial liability. Family, twin and adoption studies in MS, as well as in bipolar disorder, depression and schizophrenia, indicate moderate to high degrees of genetic influence; and moderate to high genetic correlations have been observed between the psychiatric diagnoses (19-21). In a population-based cohort study of parents and siblings to MS patients, an increased risk of schizophrenia, but not bipolar disorder, was found (7, 17), and in another study depression was not more common in first-degree relatives of MS patients (n=221) than in unexposed individuals (10).

Some of these previous studies have had limited statistical power due to modestly sized data sets (10), while others have arrived at contradictory results with regard to non-affective psychosis and schizophrenia (11, 14-18) or failed to report risks for matched population controls. Here, with a view to studying the relationship between MS and bipolar disorder, schizophrenia and depression, we sought to overcome these limitations by using a Swedish national database, which constitutes, to our knowledge, the largest cohort ever employed for this purpose. In addition, we used a

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3 matched cohort sibling design to investigate whether shared genetic liability might underlie the  
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5 putative comorbidity between MS and the psychiatric disorders.  
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## 10 **Materials and Methods**

### 11 12 13 14 15 *Data sources*

16  
17 The study was approved by the ethics committee of Karolinska Institutet. The Swedish National  
18 Patient Register (NPR, National Board of Health and Welfare, <http://www.socialstyrelsen.se>) is a  
19 nationwide register containing information on inpatient care (psychiatric diagnoses from 1973 and  
20 MS from 1987) and specialist care (from 2001). It has a high level of agreement with medical and  
21 psychiatric diagnoses (22). The Swedish MS Register (SMSreg; <http://www.msreg.net>) was started  
22 in 1996 and includes information on 13,558 unique individuals registered prior to January 1, 2010;  
23 MS diagnosis are decided by consultant neurologists (23). The Swedish Multi-Generation Register  
24 (Statistics Sweden, <http://www.scb.se>) is a national database with coverage of individuals born in  
25 Sweden since 1932 and living in Sweden after 1960, and of immigrants who became Swedish  
26 citizens before the age of 18. The Cause of Death Register (National Board of Health and Welfare)  
27 provides data regarding all deaths, and the Total Population Register (Statistics Sweden) contains  
28 information on immigration and emigration from the country.  
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### 48 *Disease classification*

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50 Using codes from the International Classification of Diseases (ICD 8-10), we identified in the NPR  
51 patients diagnosed with bipolar disorder, schizoaffective disorder, schizophrenia, depression and  
52 MS (Table 1). We identified a subgroup of patients with bipolar disorder who had experienced one  
53 or more episodes of mania (designated bipolar disorder type I), and a subgroup of subjects with  
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3 depression who had experienced at least one episode of severe depression (designated severe  
4 depression). A validation study of the bipolar diagnosis in the NPR found that two independent  
5 inpatient admissions generated a positive predictive value of 0.81 (24). A requirement of two  
6 diagnoses to define schizophrenia resulted in frequencies comparable to internationally reported  
7 lifetime prevalence percentages (25). To secure diagnostic specificity, we required two or more  
8 diagnoses from the NPR for all diagnostic categories. To differentiate between bipolar disorder,  
9 schizophrenia and schizoaffective disorder, we did not allow any overlap between the three  
10 diagnoses, and subjects with more than one of these diagnoses were classified in a separate mixed  
11 category (designated mixed bipolar/psychosis).  
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27 We used the SMSreg to verify the quality of the MS diagnoses from the NPR where individuals are  
28 coded as having MS according to the McDonald criteria (26). 96% of the patients with a diagnosis  
29 of MS in the NPR were registered as having MS in the SMSreg.  
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### 36 *Study population and design*

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38 To study associations between psychiatric disorders and MS, we used a matched cohort design  
39 based on individuals and pairs of siblings living in Sweden, whom we had identified from, register  
40 linkages with the help of the unique personal identification number assigned to each Swedish  
41 resident.  
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51 In a “comorbidity cohort” we assessed the association between a psychiatric diagnosis (exposure  
52 directly to the particular disorder) and risk of MS (outcome), and in a “sibling cohort” (familial  
53 analysis) we assessed the association between having a sibling with a psychiatric disorder  
54 (exposure to an inherited or environmentally mediated liability to the particular disorder) and risk  
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3 of MS (outcome; Figure 1). In the comorbidity cohort, we identified the exposed patients and 10  
4 randomly selected unexposed individuals per patient, matched by birth year and sex. Unexposed  
5 individuals had not received an exposure diagnosis prior to the date of the patient's first diagnosis  
6 or start of follow-up, if it occurred later. In the sibling cohort all pairwise combinations of sibling  
7 pairs were considered. For each sibling pair exposed to the disorder of interest, we randomly  
8 selected 10 unexposed sibling pairs, matched for birth year and sex (for both individuals in the  
9 pair). The index person of the selected unexposed pairs was required to be alive, living in Sweden  
10 and free of the diagnosis of the exposed index person at the start of follow-up.  
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24 The analyses were also performed in reverse order, to assess the association between MS or having  
25 a sibling with MS (exposure) and the risk of a psychiatric disorder (outcome; Figure 2).  
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### 32 *Analysis by time period*

33 To address the influence of ascertainment bias in the comorbidity analysis, we analyzed the risk of  
34 MS in three different time windows, as in Figure 3 and an alternative analysis, as in Figure 4.  
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### 41 *Sensitivity analysis*

42 To test the sensitivity of our results, we performed several additional analyses; patients with  
43 schizophrenia were analyzed without exclusion of cases with additional diagnoses of  
44 schizoaffective or bipolar disorder; individuals born between 1969 and 1991 were analyzed  
45 separately; the data was re-analyzed, with MS as exposure and the start of follow-up as 2001; the  
46 depression cohort was reanalyzed including patients with single diagnosis of depression; to assure  
47 the accuracy of the MS diagnoses, we analyzed the data using diagnostic information first from the  
48 SMSreg alone and then in combination with diagnostic information from the NPR.  
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### *Statistical analysis*

Descriptive statistics are presented as means and standard deviations for continuous data and frequencies and percentages for categorical data. Estimates for the risk of being diagnosed with an event among exposed individuals were obtained by calculating hazard ratios (HR) with 95% confidence intervals (CI) by a Cox regression model using SAS version 9.3. To compensate for the clustering effect in the sibling analysis, we used robust sandwich estimates. Follow-up started in 1987 (or age 18) when MS was the event and in 1973 (or age 18) when psychiatric disorder was the event. Subjects were followed until an event occurred or until the subject was censored due to death, emigration or end of follow-up on December 31, 2009. Two-tailed probability values were calculated, with values less than 0.05 regarded as significant. In both the comorbidity and the sibling analyses, we adjusted for immigration status (born in or born outside of Sweden); effect modification was tested for by including interaction terms between sex and exposure.

### **Results**

We identified 8,193,579 individuals born between 1932 and 1991 who were alive and residing in Sweden at the start of follow-up, Table 2.

#### *Comorbidity cohort—analysis of psychiatric disorders and MS*

We found a statistically significantly increased risk of MS in the patients with bipolar disorder as well as in the subcategory classified as bipolar disorder type I, Figure 5. In patients with schizophrenia, the risk of MS was significantly decreased. In schizoaffective disorder, MS risk was non-significantly decreased, whereas the risk in the mixed category did not differ from that of

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3 unexposed subjects. In individuals with depression, MS risk was increased and the results  
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5 remained significant in the subgroup of severely depressed patients. Adjustment for immigration  
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7 status did not change the overall results. **There was no evidence of sex-specific effects except for in**  
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9 **bipolar disorder type I where the risk of MS was increased in males compared to females**  
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11 **(interaction effect  $p=0.0008$ ), Table 3.** The results were similar when the risk of psychiatric  
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13 disorders in the cohort of MS patients was analyzed, Table 4.  
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### 18 19 20 ***Comorbidity cohort—analysis by time period***

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22 The risk of MS was significantly higher in all three time windows (explained in Figure 3), and was  
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24 not found to be associated with the date of onset of bipolar disorder, bipolar disorder type I and  
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26 depression (explained in Figure 4), Table 5. The results for schizophrenia were not significant. The  
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28 results remained unchanged when analyzed in the reverse direction.  
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### 33 34 ***Sibling cohort—analysis of psychiatric disorders and MS***

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36 The risk of MS in siblings to subjects with bipolar disorder, schizophrenia or depression did not  
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38 differ from the risk in siblings to unexposed individuals, Figure 5. Sibling analyses were performed  
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40 in the reverse direction, with similar results, Table 4.  
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### 45 46 ***Sensitivity analysis***

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48 Patients with schizophrenia, defined more widely, with inclusion of cases with additional  
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50 diagnoses of schizoaffective or bipolar disorder, showed no significantly decreased risk of MS (HR  
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52 0.8, 95% CI: 0.7-1.0,  $p=0.1$ ). To ensure that individuals would be no older than 18 years of age  
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54 when entering the study in 1987 subjects born between 1969 and 1991 were analyzed. The results  
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56 were in agreement with the main results but, in some cases, failed to reach statistical significance,  
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3 presumably due to lack of power. The outpatient register was started in 2001, which means that  
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5 milder cases of depression might have been included from 2001 and onwards. To avoid selection  
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7 bias, the comorbidity cohort was analyzed with MS as exposure, and the start of follow-up as 2001.  
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9 The increased risk of depression in MS patients remained significant. We also analyzed the effect  
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11 of depression on MS risk, including individuals with a single depression. In total, 303,763  
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13 individuals with depression were identified, and the increased risk of MS remained significant (HR  
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15 2.0 95% CI: 1.9-2.1,  $p < 0.0001$ ). Finally, using diagnostic information from the SMSreg alone and  
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17 in combination with information from the NPR, we obtained similar results as in the main analysis.  
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## 24 Discussion

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29 Comorbidity and familial liability between MS and bipolar disorder, schizophrenia and depression  
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31 were studied in a nationwide Swedish cohort—to our knowledge, the largest study to date of MS  
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33 and psychiatric conditions. A statistically significantly increased risk of comorbid MS was found in  
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35 bipolar disorder and depression, but a significantly decreased risk of MS was found in  
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37 schizophrenia. Compared to risks in unexposed siblings, the risk of MS was not increased in  
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39 siblings to subjects with bipolar disorder, schizophrenia or depression, and the risk of these  
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41 psychiatric disorders was not increased in siblings to MS patients. Our main conclusion is,  
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43 therefore, that the associations between MS and the psychiatric disorders are not confounded by  
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45 familial factors.  
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53 There are several strengths in this study: The large study base allowed us to perform analyzes by  
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55 time period and to analyze subcategories such as bipolar disorder type I and severe depression.  
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57 Potential confounders were accounted for by matching for age and sex and the data was analyzed  
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3 bidirectional. The quality of the MS diagnoses was assured by sensitivity analyses, using MS  
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5 diagnosis from both the NPR and SMSreg. Limitations in our study include the circumstance that  
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7 depression diagnoses in the NPR are not validated. Our lack of access to primary-care register data  
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9 regarding depression may have resulted in a selective bias, in that we may have missed less severe  
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11 cases of depression and therefore underestimated the magnitude of increased risks. However,  
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13 inclusion of patients with a single depression diagnosis did not substantially affect estimates of MS  
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15 risk. **We were not able to adjust for socioeconomic status in childhood, but recent data indicate that**  
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17 **socioeconomic status is not associated with MS (27) and it is not very likely that our results would**  
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19 **be affected.**  
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27 The comorbidity between MS and bipolar or depressive disorder were in agreement with previous  
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29 studies in the field (3-14) and may be explained by several hypothetical mechanisms. First, the  
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31 pathogenic events in MS, including the inflammatory process in the CNS, might give rise to  
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33 depressive or even manic symptoms. Second, affective symptoms might be triggered by the  
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35 psychological trauma of having been diagnosed with chronic, disabling disease such as MS.  
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37 However, the analysis of the MS risk by time period revealed no temporal association between the  
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39 occurrence of bipolar disorder or depression and the onset of MS, which argues against the role of  
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41 purely psychological factors, Table 5. Also the increased risk of MS in the severe subgroups  
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43 (bipolar disorder type I and severe depression) suggests involvement of biological mechanisms  
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45 such as inflammation rather than psychological factors. Thirdly, the increased comorbidity could  
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47 be an effect of ascertainment bias; however, the results from the analysis by time period do not  
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49 support this explanation. A fourth possibility is that comorbidity is triggered by MS medications,  
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51 such as interferon beta and corticosteroids, both known to cause psychiatric side effects (28), but  
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53 again the results from the analysis by time period do not support this explanation. According to a  
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3 fifth possible mechanism, changes in behavior resulting from psychiatric disorders, such as  
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5 increased smoking or reduced exposure to ultraviolet light, might lead to reduced synthesis of  
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7 vitamin D, thus increasing the risk of MS (29). However, the notion that increased MS risk in  
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9 psychiatric conditions is mediated by smoking is not supported by our finding of decreased MS risk  
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11 in schizophrenia, given the high rate of tobacco smoking in patients with schizophrenia, compared  
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13 to rates in the general population (29). We also found gender differences as males with bipolar  
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15 disorder type I were at higher risk of MS compared to females, Table 3. The finding might deserve  
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17 further investigation.  
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24 The decreased risk of MS in patients with schizophrenia deviates from the findings of previous  
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26 studies (6, 11, 15-18) and there might be several reasons for the disparate results. The large  
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28 advantage with our data is the population-based approach, the large sample size and the limitation  
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30 to schizophrenia patients who did not exhibit overlap with schizoaffective disorder and bipolar  
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32 disorder. The significant negative association was only seen when no diagnostic overlap was  
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34 allowed, indicating that the results are specific to a particular schizophrenia phenotype lacking  
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36 bipolar affective symptoms. A negative association with schizophrenia has been observed in other  
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38 disorders mediated by inflammation, such as rheumatoid arthritis (30, 31). Like rheumatoid  
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40 arthritis, schizophrenia and MS have been shown to be associated with polymorphisms at human  
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42 leucocyte antigen (32, 33). Although no decreased familial risk was found between MS and  
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44 schizophrenia, it is tempting to speculate that risks conferred by alleles at HLA loci might explain  
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46 part of the negative association between MS and schizophrenia—as has previously been  
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48 demonstrated for *DRB1\*1501*, which is a risk allele in MS and a protective allele in diabetes  
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50 mellitus type 1 (34). Finally protective effects, with regard to MS risk, of treatment with  
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3 antipsychotic medications or the possibility that patients with severe mental illness have a reduced  
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5 ability to recognize and report symptoms to the healthcare-system, might also explain the findings.  
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10 Previous studies found no familial relationship between MS and bipolar disorder or  
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12 depression—which is in accordance with our findings—but an increased risk of schizophrenia has  
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14 been previously reported in patients with a family history of MS (7, 10, 17). Using a method with  
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16 matched sibling controls, we found no significant familial link between MS and schizophrenia.  
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## 20 21 22 **Conclusion** 23

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27 There is an increased risk of MS in bipolar disorder and depression, including bipolar disorder type  
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29 I and severe depression, and, conversely, an increased risk of these psychiatric conditions in MS  
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31 patients. In contrast to previous findings, in the present study, the risk of MS was found to be  
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33 decreased in patients with schizophrenia, and the risk of schizophrenia decreased in patients with  
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35 MS. However, MS was not found to be underrepresented in siblings to schizophrenic patients, nor  
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37 was schizophrenia found to be underrepresented in siblings to MS patients—findings suggesting  
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39 the involvement of other mechanisms than genetically determined liability. Clinicians should be  
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41 aware of the increased risk of bipolar disorder and depression in patients with MS and pay  
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43 particular attention to neurological symptoms in patients with schizophrenia.  
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## References

1. Compston A, Coles A. Multiple sclerosis. *Lancet*. 2002 Apr 6;359(9313):1221-31.
2. Najjar S, Pearlman DM, Alper K, Najjar A, Devinsky O. Neuroinflammation and psychiatric illness. *J Neuroinflammation*. 2013;10:43.
3. Surridge D. An investigation into some psychiatric aspects of multiple sclerosis. *The British journal of psychiatry : the journal of mental science*. 1969 Jul;115(524):749-64.
4. Schiffer RB, Wineman NM, Weitkamp LR. Association between bipolar affective disorder and multiple sclerosis. *The American journal of psychiatry*. [Research Support, U.S. Gov't, P.H.S.]. 1986 Jan;143(1):94-5.
5. Fis KJ, Morehouse SA, Brown MG, Skedgel C, Murray TJ. Hospital-based psychiatric service utilization and morbidity in multiple sclerosis. *The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques*. [Research Support, Non-U.S. Gov't]. 1998 Aug;25(3):230-5.
6. Marrie RA, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. The burden of mental comorbidity in multiple sclerosis: frequent, underdiagnosed, and undertreated. *Mult Scler*. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2009 Mar;15(3):385-92.
7. Eaton WW, Pedersen MG, Nielsen PR, Mortensen PB. Autoimmune diseases, bipolar disorder, and non-affective psychosis. Bipolar disorders. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2010 Sep;12(6):638-46.
8. Thielscher C, Thielscher S, Kostev K. The risk of developing depression when suffering from neurological diseases. *German medical science : GMS e-journal*. 2013;11:Doc02.
9. Pine DS, Douglas CJ, Charles E, Davies M, Kahn D. Patients with multiple sclerosis presenting to psychiatric hospitals. *The Journal of clinical psychiatry*. 1995 Jul;56(7):297-306; discussion 7-8.
10. Sadovnick AD, Remick RA, Allen J, Swartz E, Yee IM, Eisen K, et al. Depression and multiple sclerosis. *Neurology*. [Comparative Study Research Support, Non-U.S. Gov't]. 1996 Mar;46(3):628-32.
11. Kang JH, Chen YH, Lin HC. Comorbidities amongst patients with multiple sclerosis: a population-based controlled study. *European journal of neurology : the official journal of the European Federation of Neurological Societies*. [Research Support, Non-U.S. Gov't]. 2010 Sep;17(9):1215-9.
12. Schiffer RB, Babigian HM. Behavioral disorders in multiple sclerosis, temporal lobe epilepsy, and amyotrophic lateral sclerosis. An epidemiologic study. *Archives of neurology*. 1984 Oct;41(10):1067-9.
13. Patten SB, Svenson LW, Metz LM. Descriptive epidemiology of affective disorders in multiple sclerosis. *CNS Spectr*. 2005 May;10(5):365-71.
14. Marrie RA, Fisk JD, Yu BN, Leung S, Elliott L, Caetano P, et al. Mental comorbidity and multiple sclerosis: validating administrative data to support population-based surveillance. *BMC Neurol*. 2013;13:16.
15. Patten SB, Svenson LW, Metz LM. Psychotic disorders in MS: population-based evidence of an association. *Neurology*. 2005 Oct 11;65(7):1123-5.
16. Benros ME, Nielsen PR, Nordentoft M, Eaton WW, Dalton SO, Mortensen PB. Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. *The American journal of psychiatry*. 2011 Dec;168(12):1303-10.



17. Benros ME, Pedersen MG, Rasmussen H, Eaton WW, Nordentoft M, Mortensen PB. A Nationwide Study on the Risk of Autoimmune Diseases in Individuals With a Personal or a Family History of Schizophrenia and Related Psychosis. *The American journal of psychiatry*. 2013 Oct 16.
18. Eaton WW, Byrne M, Ewald H, Mors O, Chen CY, Agerbo E, et al. Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. *The American journal of psychiatry*. 2006 Mar;163(3):521-8.
19. Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nat Rev Genet*. 2012 Aug;13(8):537-51.
20. Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet*. 2013 Sep;45(9):984-94.
21. Westerlind H, Ramanujam R, Uvehag D, Kuja-Halkola R, Boman M, Bottai M, et al. Modest familial risks for multiple sclerosis: a registry-based study of the population of Sweden. *Brain*. 2014 Mar;137(Pt 3):770-8.
22. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. *BMC public health*. [Validation Studies]. 2011;11:450.
23. Ahlgren C, Oden A, Lycke J. High nationwide prevalence of multiple sclerosis in Sweden. *Multiple sclerosis*. 2011 Aug;17(8):901-8.
24. Sellgren C, Landen M, Lichtenstein P, Hultman CM, Langstrom N. Validity of bipolar disorder hospital discharge diagnoses: file review and multiple register linkage in Sweden. *Acta psychiatrica Scandinavica*. [Research Support, Non-U.S. Gov't]. 2011 Dec;124(6):447-53.
25. Lichtenstein P, Bjork C, Hultman CM, Scolnick E, Sklar P, Sullivan PF. Recurrence risks for schizophrenia in a Swedish national cohort. *Psychological medicine*. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2006 Oct;36(10):1417-25.
26. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Annals of neurology*. [Guideline Research Support, Non-U.S. Gov't]. 2001 Jul;50(1):121-7.
27. Nielsen NM, Jorgensen KT, Bager P, Stenager E, Pedersen BV, Hjalgrim H, et al. Socioeconomic factors in childhood and the risk of multiple sclerosis. *Am J Epidemiol*. 2013 Jun 1;177(11):1289-95.
28. Patten SB. Psychiatric side effects of interferon treatment. *Current drug safety*. 2006 May;1(2):143-50.
29. Beary M, Hodgson R, Wildgust HJ. A critical review of major mortality risk factors for all-cause mortality in first-episode schizophrenia: clinical and research implications. *J Psychopharmacol*. 2012 May;26(5 Suppl):52-61.
30. Mors O, Mortensen PB, Ewald H. A population-based register study of the association between schizophrenia and rheumatoid arthritis. *Schizophrenia research*. 1999 Nov 9;40(1):67-74.
31. Chen SJ, Chao YL, Chen CY, Chang CM, Wu EC, Wu CS, et al. Prevalence of autoimmune diseases in in-patients with schizophrenia: nationwide population-based study. *The British journal of psychiatry : the journal of mental science*. [Research Support, Non-U.S. Gov't]. 2012 May;200(5):374-80.
32. Kodavali CV, Watson AM, Prasad KM, Celik C, Mansour H, Yolken RH, et al. HLA associations in schizophrenia: Are we re-discovering the wheel? *Am J Med Genet B Neuropsychiatr Genet*. 2013 Oct 19.
33. Suzuki A, Kochi Y, Okada Y, Yamamoto K. Insight from genome-wide association studies in rheumatoid arthritis and multiple sclerosis. *FEBS Lett*. 2011 Dec 1;585(23):3627-32.
34. Svejgaard A. The immunogenetics of multiple sclerosis. *Immunogenetics*. 2008 Jun;60(6):275-86.

**Table 1** Diagnostic codes for disease classification according to International Classification of Diseases (ICD).

	<b>ICD 8 (1969-1986)</b>	<b>ICD 9 (1987-1996)</b>	<b>ICD 10 (1997-)</b>
<b>Bipolar disorder</b> a, b	296.0-296.3, 296.8, 296.9	296.0-296.6, 296.8, 296.9	F30.0-F30.2, F30.8, F30.9, F31.1-F31.9
<b>Schizophrenia</b>	295.0-295.6, 295.8, 295.9	295.0-295.6, 295.8, 295.9	F20
<b>Schizoaffective disorder</b>	2957	2957	F25
<b>Depression</b> <sup>c</sup>	296.0, 300.4, 298	296.1, 300.4, 311, 298.0	F32, F33
<b>Multiple sclerosis</b>	340.99	340	G35

a Patients with only one code of bipolar disorder from ICD 8 and ICD 9 were classified as bipolar disorder if they had one or more of the following diagnosis (ICD8: 296.0, 296; ICD9: 2961)

b Patients who fulfilled the criteria of bipolar disorder and presented at least one of the following codes for several manic episodes (ICD8: 296.1; ICD9: 296.0, 296.2, 296.8, ICD10: F301, F302, F311, F312) were classified in the subgroup bipolar disorder type I

c Patients who fulfilled the criteria of depression and presented at least one of the following codes for severe depression (ICD8: 296.0, 298; ICD9: 296.1, 298.0; ICD10: F322, F323, F332, F333) were classified in the subgroup severe depression

**Table 2** Characteristics for the patients with psychiatric disorders, multiple sclerosis and their siblings

Psychiatric disorder as exposure and multiple sclerosis as the event								
	Patients with a psychiatric disorder					Siblings to patients with a psychiatric disorder		
	No of patients	Males/ Females	Age of onset in years <sup>a</sup>	Age of onset in years - born 1969-1991 <sup>a</sup>	Follow-up time in days - 1987-2009	No of siblings to patients	Males/ Females	Follow-up time in days - 1987-2009
	N	%	Mean (SD)	Mean (SD)	Mean (SD)	N	%	Mean (SD)
<b>All psychotic disorders</b>	71134	48.7/51.3	37.8 (12.7)	26.4 (6.12)	7078.8 (2200.3)	118374	46.1/50.9	7227.0 (2162.1)
<i>Bipolar disorder</i>	30761	40.4/59.6	40.0 (13.3)	27.0 (6.3)	6901.2 (2352.9)	51979	39.7/60.3	6967.5 (2357.0)
<i>Bipolar type I</i>	8695	41.8/58.2	37.5 (11.9)	24.2 (5.8)	7185.6 (2166.7)	13875	41.9/58.1	7547.6 (1882.2)
<i>Schizophrenia</i>	22781	63.8/36.2	35.3 (11.8)	25.9 (5.8)	7116.9 (2123.8)	37390	65.5/34.5	7366.5 (2034.1)
<i>Schizo-affective disorder</i>	1816	38.7/61.29	40.2 (12.5)	28.1 (5.7)	7104.5 (2116.7)	2759	37.9/62.1	6896.9 (2328.5)
<i>Mixed category</i>	15776	44.2/55.8	34.6 (10.7)	24.3 (5.4)	7366.9 (1964.9)	26246	45.4/54.6	7577.2 (1822.8)
<b>Depression</b>	172479	39.6/60.4	39.2 (14.4)	25.6 (6.6)	6682.6 (2502.5)	280577	39.6/60.4	6707.7 (2504.8)
<i>Severe depression</i>	48329	40.8/59.2	40.4 (13.9)	25.9 (6.5)	6965.2 (2293.5)	77849	40.7/59.3	6903.7 (2386.0)
Multiple sclerosis as exposure and psychiatric disorder as the event								
	Patients with multiple sclerosis					Sibling to patients with multiple sclerosis		
	No of patients	Males/ Females	Age of onset in years <sup>a</sup>	Age of onset in years - born 1969-1991 <sup>a</sup>	Follow-up time in days - 1973-2009	No of siblings to patients	Males/ Females	Follow-up time in days - 1973-2009
	N	%	Mean (SD)	Mean (SD)	Mean (SD)	N	%	Mean (SD)
<b>All psychotic disorders</b>	16467	30.9/69.1	43.8 (11.9)	28.1 (5.6)	10505.4 (3421.3)	26506	30.8/69.2	10429.1 (3726.5)
<b>Depression</b>	16446	30.9/69.1	43.8 (11.9)	28.1 (5.6)	10320.3 (3516.9)	26474	30.8/69.2	10357.0 (3751.1)

<sup>a</sup> Age of onset defined as age of the first healthcare contact due to the disorder.

**Table 3** The risk of multiple sclerosis (MS) in patients with psychiatric disorders stratified by sex.

	Risk of MS in patients with PD				
	Sex	Patients, n (MS affected, n)	HR	95% CI	p-value
<b>All psychotic diagnosis</b>	Male	34,628 (67)	1.24	0.97-1.60	0.0876
	Female	36,506 (182)	1.29	1.11-1.50	0.0008
Bipolar disorder	Male	12,420 (42)	2.31	1.67-3.21	<.0001
	Female	18,341 (111)	1.70	1.40-2.06	<.0001
<i>Bipolar type I</i>	Male	3631 (23)	4.76	2.94-7.70	<.0001
	Female	5064 (39)	1.76	1.27-2.44	0.0007
Schizophrenia	Male	14,525 (16)	0.71	0.43-1.18	0.1838
	Female	8256 (20)	0.56	0.36-0.88	0.0122
<b>Depression</b>	Male	68,300 (202)	2.20	1.90-2.54	<.0001
	Female	104,179 (563)	1.77	1.63-1.92	<.0001
Severe depression	Male	19,733 (48)	1.84	1.40-2.44	<.0001
	Female	28,596 (137)	1.36	1.15-1.60	0.0003

Hazard Ratios (HR) and 95% confidence limits (95% CI). The hazard ratios are not adjusted for immigration status.

**Table 4** The risk of psychiatric disorders (PD) in patients with multiple sclerosis (MS) and siblings to patients with MS. (MS as exposure and PD as event)

	Risk of PD in patients with MS				Risk of PD in siblings to patients with MS			
	Patients, n (PD affected, n)	HR	95% CI	p-value	Siblings to patients, n (PD affected, n)	HR	95% CI	p-value
<b>All psychotic disorders</b>	16,467 (250)	1.37	1.20-1.56	<.0001	26506 (306)	0.96	0.85-1.08	0.4665
Bipolar disorder	16,467 (154)	1.86	1.56-2.20	<.0001	26506 (126)	0.93	0.77-1.11	0.4157
<i>Bipolar type I</i>	16,467 (62)	2.37	1.79-3.12	<.0001	26506 (31)	0.77	0.53-1.10	0.1513
Schizophrenia	16,467 (36)	0.71	0.51-1.00	0.0478	26506 (93)	0.88	0.71-1.09	0.4424
Schizoaffective disorder	16,467 (3)	0.64	0.20-2.09	0.4629	26506 (4)	0.67	0.24-1.85	0.0411
Mixed category	16,467 (57)	1.28	0.97-1.68	0.0815	26506 (83)	1.15	0.92-1.45	0.2242
<b>All depression</b>	16,446 (763)	1.86	1.72-2.01	<.0001	26474 (681)	1.02	0.95-1.11	0.5524
Severe depression	16,446 (180)	1.52	1.30-1.78	<.0001	26474 (191)	0.99	0.85-1.15	0.8985

Hazard Ratios (HR) and 95% confidence limits (95% CI). The hazard ratios are not adjusted for immigration status.

**Table 5** Risk of multiple sclerosis (MS) in patients with psychiatric disorders (PD), and risk of PD in patients with MS, by time period.

	Up to 2 years prior to date of PD onset <sup>a</sup>		Date of onset of PD $\pm$ 2 years <sup>a</sup>		2 years after PD onset and onwards <sup>a</sup>		From PD onset and onwards <sup>b</sup>	
<b>Risk of MS in patients with PD</b>	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
<b>All psychotic disorders</b>	<b>1.63</b>	1.27-2.09	<b>1.73</b>	1.28-2.34	1.16	0.97-1.39	1.10	0.93-1.30
Bipolar disorder	<b>2.09</b>	1.59-2.74	<b>2.14</b>	1.47-3.11	<b>1.76</b>	1.35-2.30	<b>1.64</b>	1.29-2.08
Bipolar type I	<b>6.05</b>	3.44-10.63	<b>2.74</b>	1.31-5.73	<b>1.87</b>	1.32-2.64	<b>1.79</b>	1.29-2.49
Schizophrenia	0.54	0.22-1.34	0.79	0.34-1.81	0.62	0.41-0.95	<b>0.55</b>	0.37-0.84
<b>All depression</b>	<b>2.01</b>	1.79-2.27	<b>2.63</b>	2.27-3.04	<b>1.86</b>	1.62-2.12	<b>1.51</b>	1.35-1.69
Severe depression	<b>1.32</b>	1.03-1.70	<b>2.30</b>	1.76-3.00	<b>1.68</b>	1.31-2.14	<b>1.33</b>	1.08-1.64
<b>Risk of PD in patients with MS</b>	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
	Up to 2 years prior to date of MS onset <sup>a</sup>		Date of onset of MS $\pm$ 2 years <sup>a</sup>		2 years after MS onset and onwards <sup>a</sup>		From MS onset and onwards <sup>b</sup>	
<b>All psychotic disorders</b>	<b>1.38</b>	1.20-1.58	<b>1.74</b>	1.28-2.36	<b>1.61</b>	1.25-2.08	<b>1.74</b>	1.41-2.15
Bipolar disorder	<b>1.82</b>	1.52-2.18	<b>1.98</b>	1.35-2.89	<b>1.93</b>	1.45-2.57	<b>2.08</b>	1.63-2.65
Bipolar type I	<b>2.25</b>	1.69-3.01	<b>2.76</b>	1.25-6.12	<b>4.93</b>	2.69-9.05	<b>4.76</b>	2.85-7.97
Schizophrenia	0.73	0.51-1.02	0.91	0.39-2.11	0.74	0.32-1.70	0.89	0.48-1.65
<b>All depression</b>	<b>1.53</b>	1.33-1.76	<b>2.78</b>	2.39-3.22	<b>1.80</b>	1.58-2.04	<b>2.13</b>	1.93-2.36
Severe depression	<b>1.44</b>	1.11-1.88	<b>2.72</b>	2.07-3.59	1.08	0.81-1.44	<b>1.55</b>	1.25-1.92

Hazard Ratios (HR) and 95% confidence limits (95% CI). Significant HRs are indicated by bold text. The hazard ratios are not adjusted for immigration status.

a Analysis as described in Figure 3

b Analysis as described in Figure 4

## Figure legends

**Figure 1** Flowchart of the study population in the comorbidity and the sibling cohorts (psychiatric disorders as exposure and multiple sclerosis as outcome).

**Figure 2** Flowchart of the study population in the comorbidity and the sibling cohorts (multiple sclerosis as exposure and psychiatric disorders as outcome).

**Figure 3** Analysis by time period of multiple sclerosis (MS) risk in the comorbidity cohort with psychiatric disorder (PD) as exposure:

MS risk was analyzed: A) from entry date until two years before date of PD onset; B) from two years before until 2 years after date of PD onset; C) from two years after date of PD onset until end of follow-up. The analyses were performed in a reverse manner, whereby PD risk was analyzed with MS as exposure.

**Figure 4** MS risk was analyzed after date of onset (entry date) of the psychiatric disorder (PD), until an event occurred or the subject was censored. Patients with an MS event before entry date were censored. The analyses were performed in a reverse manner, whereby PD risk was analyzed with MS as exposure.

**Figure 5** Boxplot showing the risk of multiple sclerosis (MS) in patients with a psychiatric disorder and in siblings to patients with a psychiatric disorder. HR = hazard ratio; CI = confidence interval. The hazard ratios are not adjusted for immigration status.

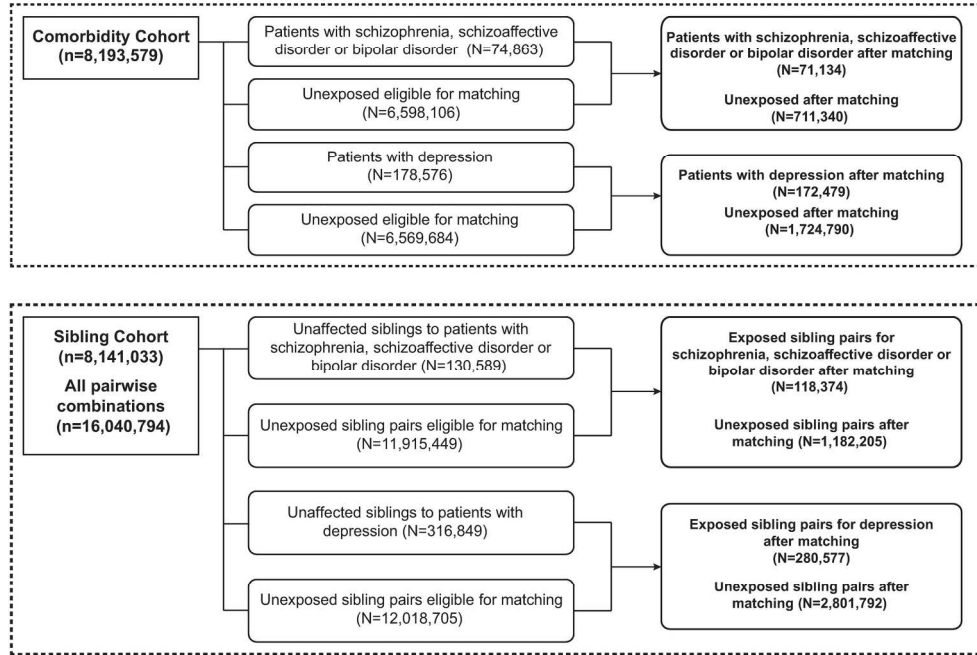


Figure 1 Flowchart of the study population in the comorbidity and the sibling cohorts (psychiatric disorders as exposure and multiple sclerosis as outcome).  
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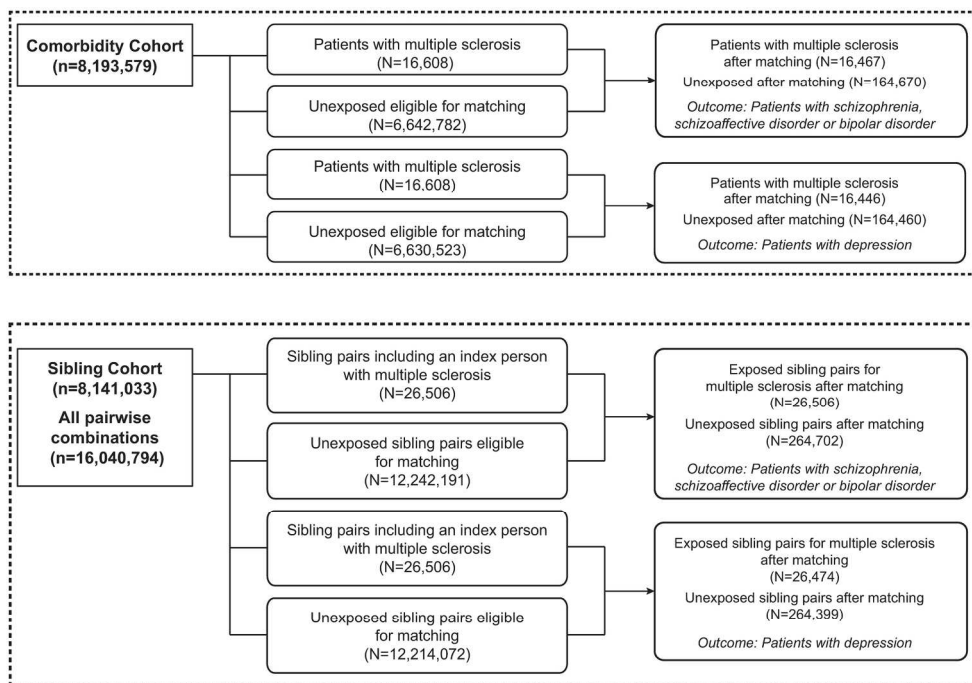


Figure 2 Flowchart of the study population in the comorbidity and the sibling cohorts (multiple sclerosis as exposure and psychiatric disorders as outcome).  
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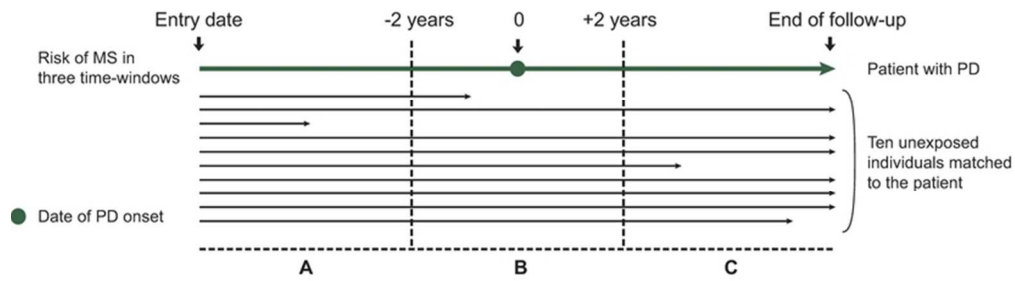
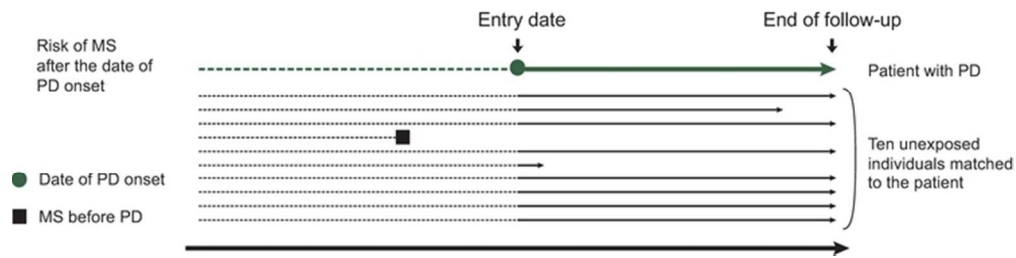


Figure 3 Analysis by time period of multiple sclerosis (MS) risk in the comorbidity cohort with psychiatric disorder (PD) as exposure:

MS risk was analyzed: A) from entry date until two years before date of PD onset; B) from two years before until 2 years after date of PD onset; C) from two years after date of PD onset until end of follow-up. The analyses were performed in a reverse manner, whereby PD risk was analyzed with MS as exposure.  
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16 Figure 4 MS risk was analyzed after date of onset (entry date) of the psychiatric disorder (PD), until an  
 17 event occurred or the subject was censored. Patients with an MS event before entry date were censored.  
 18 The analyses were performed in a reverse manner, whereby PD risk was analyzed with MS as exposure.  
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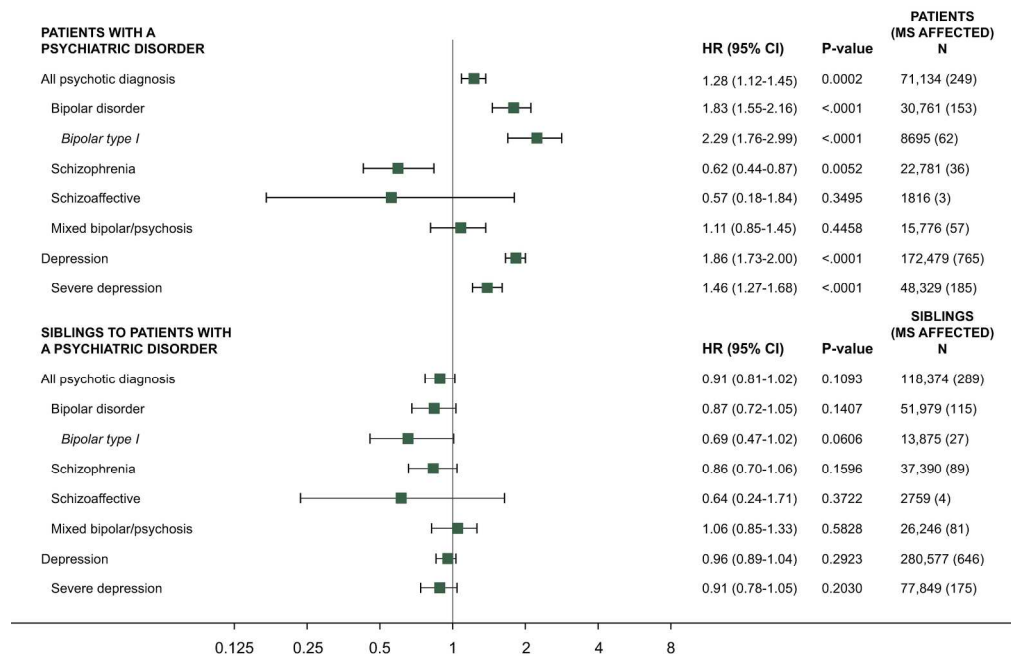


Figure 5 Boxplot showing the risk of multiple sclerosis (MS) in patients with a psychiatric disorder and in siblings to patients with a psychiatric disorder. HR = hazard ratio; CI = confidence interval. The hazard ratios are not adjusted for immigration status.  
208x136mm (300 x 300 DPI)