

# Diagnostic conversion from unipolar depression to bipolar disorder, schizophrenia, or schizoaffective disorder: A nationwide prospective 15-year register study on 43 495 inpatients

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## Abstract

**Objective:** To examine temporal patterns and predictors for diagnostic conversion from unipolar depression (UD) to bipolar disorder (BD), schizophrenia, and schizoaffective disorder (SAD).

**Methods:** A prospective nationwide register-based cohort (n = 43 495) of all first psychiatric hospitalizations due to UD during 1996-2011 was followed up to 15 years. We used cumulative incidence function (CIF) analyses and the Fine-Gray subdistribution model to define the cumulative incidence of the conversions and subdistribution hazard ratios (SHRs) for predictors.

**Results:** The overall 15-year cumulative incidence of conversion was 11.1% (95% CI 10.7-11.6); 7.4% (95% CI 7.0-7.8) for BD, 2.5% (95% CI 2.3-2.7) for schizophrenia, and 1.3% (95% CI 1.1-1.4) for SAD. The highest crude incidence rate emerged during the first year. Psychotic depression predicted higher conversion risk to BD (SHR = 2.0, 95% CI 1.5-2.7), schizophrenia (SHR = 5.3, 95% CI 3.3-8.7), and SAD (SHR = 10.6, 95% CI 4.0-28.4) than mild depression. Female sex, greater overall disturbance, and comorbid personality disorder predicted conversion to BD, whereas young age and male sex to psychotic disorders.

**Conclusions:** Among patients with first hospitalization due to UD, approximately one in nine converts to another major psychiatric disorder during 15 years, with the highest risk occurring within the first year. Patients with psychotic depression are particularly vulnerable for conversion to other major psychiatric disorders. Conversion to psychotic disorders occurs earlier than to BD. Males are at higher risk for progression to psychotic disorders, whereas females, patients with recurrent depressive episodes, severe disturbance of overall functioning, and personality disorder are at higher risk for converting to BD.

## KEYWORDS

bipolar disorder, diagnostic conversion, schizoaffective disorder, schizophrenia, unipolar depression

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## 1 | INTRODUCTION

Unipolar depression (UD), bipolar disorder (BD), and schizophrenia, prevalent major psychiatric disorders,<sup>1-4</sup> are leading contributors to functional and vocational disability worldwide<sup>5</sup> and to deaths by suicide.<sup>6</sup> Although early diagnosis and treatment of these disorders would significantly reduce their enormous burden, apparent phenomenological similarity in the prodromal phases and clinicians' limited ability to predict the development of psychopathology on the individual level often challenge recognition of the major psychiatric disorders in clinical practice. Depressive symptoms and syndromes are common at the initial stages of both BD<sup>7-9</sup> and psychotic disorders.<sup>10,11</sup> As BD and schizophrenia differ in their prognosis and treatment approaches, knowing how commonly patients initially diagnosed with UD will subsequently convert to BD and psychotic disorders, when the diagnostic conversion will commonly occur, and what factors predict the conversion are critical for identifying depressed patients at risk.

The meta-analysis of Kessing et al showed that in 11 studies using survival analysis, the 10-year cumulative risk for conversion from UD to BD was 12.9%, with the highest conversion risk emerging during the first few years of follow-up.<sup>12</sup> A comparable finding arose from the meta-analysis of Ratheesh et al<sup>13</sup> However, both authors emphasized high variation in the finding of conversion risk across studies. Among factors underlying this divergence, several are of particular importance when examining the diagnostic conversion incidence and its temporal patterns. First, as the conversion from UD to BD is more likely to occur within 5 years of the first episode of depression, studies following depressed patients from their first episodes probably report more accurate cumulative conversion incidence than studies on patients with multiple recurrent episodes of UD. Second, retrospective study design commonly yields a higher conversion risk than prospective design, possibly due to a risk of recall or selection bias. Third, type of outcome and setting are crucial. As mania often requires hospitalization, studies including only inpatients may underestimate the conversion to BD type 2 since the diagnostic conversion occurring in outpatient care remains undetected. Finally, although clinical cohort studies produce diagnostically more accurate data, register-based studies may produce representative national-level generalizable data. Thus, when characterizing the temporal patterns of the diagnostic conversion, a prospective design, a large sample size, and a long follow-up of patients with UD from their initial phase of illness are vital.

Evidence on predictors of the conversion from UD to BD is also inconsistent.<sup>12,13</sup> The meta-analysis of Kessing et al found no risk factors that were consistently confirmed across studies.<sup>12</sup> Factors comparable to those influencing divergence on the conversion risk from UD to BD across studies are likely to also explain varying findings on the risk factors.<sup>12</sup> While prospective clinical cohort studies may examine the predictive values of broad sets of risk factors,<sup>14</sup> large-scale register-based studies can commonly investigate only a limited number of predictors. Moreover, as longitudinal studies following patients from their first depressive episode estimate conversion risk more accurately, it is likely that these studies also estimate more accurately the predictive values of risk factors for it.<sup>12</sup> Consequently, prospective studies with a large

sample size, following the patients from their first depressive episodes for a long time are needed to estimate the predictive values of the risk factors. To our knowledge, no longitudinal register-based study has explored potential secular trends in risk of conversion. The reasons for examining them include deinstitutionalization and reductions in available hospital beds, and abundant epidemiological evidence for under-recognition of BD, also from Finland.<sup>15</sup> Improvements in diagnostic procedures could significantly increase the rates of conversion over time. The use of antidepressants has been associated with emergence of hypomania or mania,<sup>16</sup> and has also markedly increased in Finland between 1990 and 2010.<sup>17</sup> Therefore, comparing rates of conversion between time periods is warranted.

Depressive symptoms and UD frequently precede both schizophrenia<sup>11,18,19</sup> and schizoaffective disorder (SAD),<sup>20</sup> and ultra-high-risk (UHR) patients often seek treatment due to depressed mood. UD per se appears to predict conversion to psychosis in UHR patients.<sup>10</sup> The Danish prospective register-based study on transition from UD to schizophrenia showed that the 18.5-year cumulative incidence of conversion from UD to schizophrenia was more than 8% in men and almost 6% in women.<sup>21</sup> As in conversion to BD, the highest conversion to schizophrenia occurred within the first years of follow-up. Younger age, greater depression severity, inpatient treatment, and psychotic depression were among the predictors for conversion from UD to schizophrenia. Overall, these risk factors appear partially overlapping with the predictors for conversion to BD. To our knowledge, the findings by Musliner et al have not been replicated in nationwide register studies, and no register-based studies on conversion to SAD exist.

The aim of this Finnish nationwide prospective register-based study on patients with first hospitalization due to UD is (a) to investigate cumulative incidence of diagnostic conversion from UD to BD, schizophrenia, or SAD over a period of up to 15 years, (b) to characterize the temporal pattern of diagnostic conversion, and (c) to examine five putative predictors of diagnostic conversion. In addition, we examined whether the hazard for conversion differed between time periods 1996-2003 and 2004-2011.

## 2 | METHODS

### 2.1 | Study design and data

This study uses data from the MERTTU research project, the background and methodology of which have been reported in detail elsewhere.<sup>22-24</sup> In our study, the data are based on the Finnish Hospital Discharge Register (FHDR), maintained by the Finnish Institute of Health and Welfare, which includes all psychiatric and somatic hospitalizations since 1969, and the Causes of Death Register of Statistics Finland. Permission to use the data was provided by the registers. FHDR includes data on, for example, admission and discharge dates, diagnoses, operations, hospital, and specialty; quality of data in the register is known to be good.<sup>25</sup> Since 1994, also information on psychiatric admissions, including data on treatments and admission as well as status of overall functioning, has been collected. The overall

functioning is assessed by the attending doctor using the Global Assessment Scale (GAS).<sup>26</sup> The Finnish personal identity codes enabled us to connect these registers at the individual level, resulting in a comprehensive dataset on all inpatient psychiatric hospitalizations from 1980 to 2011. No private psychiatric hospitals exist in Finland. No data on outpatient settings were available for the current study.

## 2.2 | Settings and sample selection

From the database, we identified a cohort of inpatients who had been treated in a psychiatric hospital or a psychiatric ward of a general hospital for the International Classification of Diseases, 10th edition (ICD-10)<sup>27</sup> diagnoses of UD (ICD-10 codes F32-F33) since the start of 1996 ( $n = 86\,581$ ). In Finland, the ICD-10 diagnoses have been used since 1996. To identify the first lifetime admissions and to avoid confusion due to differences in ICD-8, ICD-9, and ICD-10, we excluded all patients with any psychiatric hospitalizations (since 1980) within a 16-year clearance period before their first UD admission since the beginning of 1996, leaving 54 974 patients. Additionally, we excluded patients aged <13 years or more than 60 years (remaining  $n = 45\,944$ ) as well as patients who were not discharged alive from the episode or had comorbid diagnoses of neurodegenerative disorders (ICD-10: F00-09), schizophrenia or other non-affective psychosis (F20-29), or manic/mixed affective states (F30-31, F38.00). The final number of inpatients in the study was 43 495 (see Figure 1).

## 2.3 | Outcome

The outcomes were defined by the diagnoses of hypomania or mania (F30.x), BD (F31.x), schizophrenia (F20.x), or SAD (F25.x) according to the ICD-10. We used a minimum time period of 2 weeks between the discharge from the first hospitalization due to UD, to the admission of the following hospitalization with diagnostic conversion registered at discharge. Subsequent hospitalizations with time interval

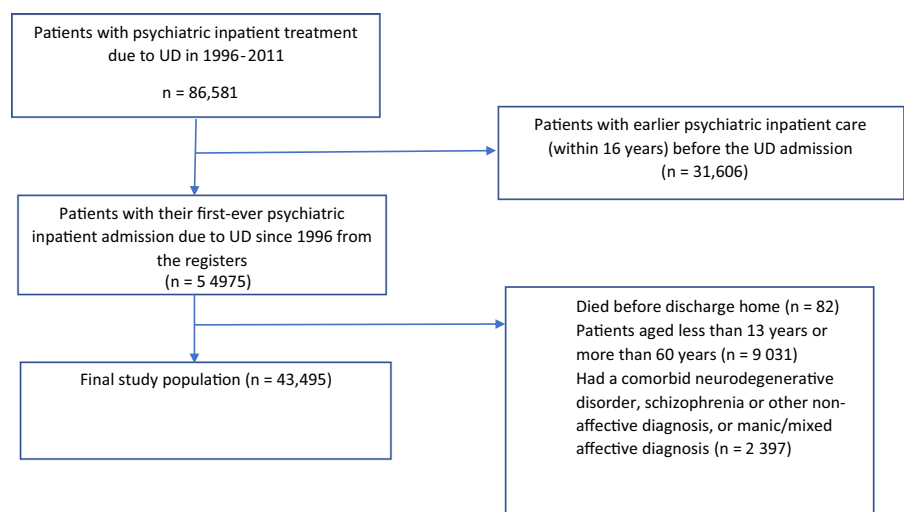
shorter than 14 days were treated as one hospitalization. The follow-up was ceased when one (the first) of these outcome diagnoses occurred. Due to high heterogeneity among patients with SAD, we also used a dichotomous outcome in the sensitivity analyses: BD (including patients with a manic and mixed type of SAD) and schizophrenia (including patients with a depressive type of SAD).

## 2.4 | Predictors

We investigated the effect of the following predictors on the conversion risk from UD to the major psychiatric disorders: sex, first (single) depressive episode vs recurrent depression, severity of depression (mild, moderate, severe without psychotic symptoms, severe with psychotic symptoms), age at first depressive episode, presence of personality disorder, GAS score at first hospitalization due to UD and two time periods of 1996-2003 and 2004-2011.

## 2.5 | Statistical analysis

Data preprocessing was carried out in SAS 9.4 and statistical analysis in R 3.6.1 with extension packages *survival*, *cmprsk*, *fastcmprsk*, *SurvR*, *Epi*, and *popEpi*. Crude incidence rates were obtained by dividing the number of events of interest by the total follow-up time measured in person-years over a set period. For the estimation of cumulative incidence and predictor-related risks, a competing risk approach for survival analysis was used. Follow-up started from the discharge of first UD episode and ended at the first psychiatric inpatient admission with a diagnosis of any of the outcomes (hypomania or mania, BD, schizophrenia, SAD), competing risks (death, neurodegenerative diagnosis), or date of administrative censoring on the final day of the year 2011, whichever occurred first. We used techniques focusing on cause-specific hazards (Kaplan-Meier and multivariable Cox regression with adjustment for all the included predictors) and direct models for CIFs (CIF analyses and Fine-Gray subdistribution model); we report only the results of the latter ones as they fit the



**FIGURE 1** Flow chart yielding the final cohort of 43 495 inpatients with first hospitalization due to UD since 1996. UD, unipolar depression

current situation better, and there were no essential differences.<sup>28,29</sup> We checked the proportional hazards assumption using Schoenfeld residuals and concluded that subdistribution hazard ratios (SHRs) should be interpreted as the average effects over time.

### 3 | RESULTS

#### 3.1 | Sample characteristics

The clinical characteristics of the patients are presented in Table 1. The mean age was 34.4 (SD 13.9) years, and the majority of patients were females (59%). Almost 85% of the patients received a diagnosis of single depression at their first hospitalization, and the rest had probably been diagnosed with depression earlier in outpatient care. Of depression diagnoses, 13% were characterized as psychotic, 35% as severe without psychotic symptoms, and the remainder as mild

(4%), moderate (28%), or not otherwise specified (20%). More than 70% of patients were assessed as having a severe functional impairment (GAS < 47) on admission.

#### 3.2 | Conversions to major psychiatric disorders

The sample was followed for a total of 294 992 person-years. The mean follow-up was 6.78 years, the median 6.37 years. Overall, the cumulative conversion incidence during a 15-year follow-up of patients with UD to other major psychiatric disorders was 11.1% (95% CI 10.7-11.6). The overall cumulative incidences for all major psychiatric disorders are shown in Figure 2.

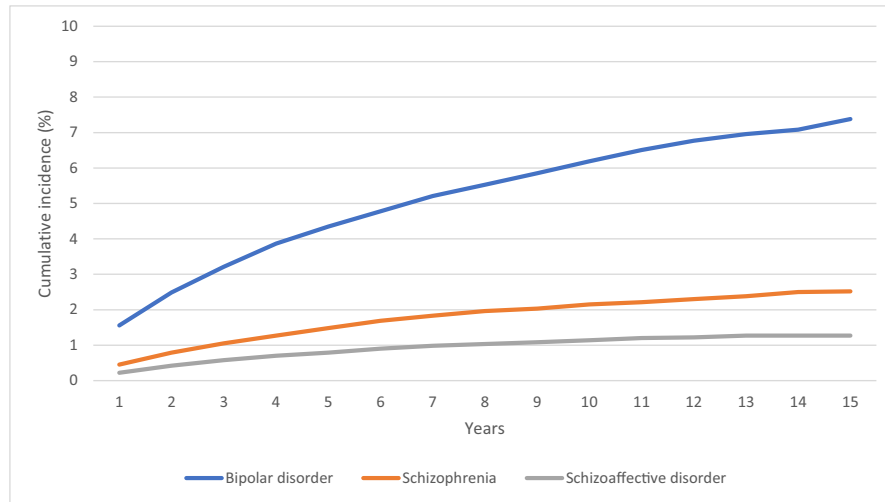
#### 3.3 | Conversion to BD

The cumulative incidence of conversion from UD to BD was 7.4% (95% CI 7.0-7.8) during a 15-year follow-up. Separately, the

Characteristic	All patients n (%)	Males n (%)	Females n (%)
N	43 495 (100)	17 775 (100)	25 720 (100)
Recurrence of unipolar depression			
Single depressive episode (F32.x)	36 487 (84)	15 188 (85)	21 299 (83)
Recurrent depressive disorder (F33.x)	7008 (16)	2587 (15)	4421 (17)
Severity of depression			
Mild	1704 (4)	767 (4)	937 (4)
Moderate	12 199 (28)	4753 (27)	7446 (29)
Severe without psychotic symptoms	15 211 (35)	5928 (33)	9283 (36)
Severe with psychotic symptoms	5517 (13)	2186 (12)	3331 (13)
Unspecified	8864 (20)	4141 (23)	4723 (18)
Age, y			
Mean (SD)	34.4 (13.9)	34.4 (13.9)	34.4 (13.9)
13-17	6366 (15)	1502 (8)	4864 (19)
18-22	5920 (14)	2285 (13)	3635 (14)
23-29	5765 (13)	2345 (13)	3420 (13)
30-39	7969 (18)	3539 (20)	4430 (17)
40-49	9299 (21)	4368 (25)	4931 (19)
50-60	8176 (19)	3736 (21)	4440 (17)
GAS at admission			
Mild impairment (63-100)	1074 (2)	445 (3)	629 (2)
Moderate impairment (47-62)	10 343 (24)	4439 (25)	5904 (23)
Severe impairment (0-46)	30 798 (71)	12 378 (70)	18 420 (72)
Missing	1280 (3)	513 (3)	767 (3)
Comorbid personality disorder			
Yes	4227 (10)	1644 (9)	2583 (10)
No	39 268 (90)	16 131 (91)	23 137 (90)

**TABLE 1** Clinical and demographic characteristics of the patients with first hospitalization due to unipolar depression since 1996

Abbreviation: GAS, Global Assessment Scale.



**FIGURE 2** Cumulative conversion incidences from unipolar depression (UD) to the major psychiatric disorders during a 15-year follow-up of inpatients with their first hospitalization due to UD (n = 43 495)

cumulative conversion incidence for successive hospitalizations due to first hypomania, mania, or mixed episode was 2.7% (95% CI 2.5-2.9) and for a depressive episode of BD 4.7% (95% CI 4.4-5.0) (see Figure S1 for details). The highest yearly crude incidence rate for BD emerged within the first year of follow-up: 16.0 (95% CI 14.9-17.3) per 1000 person-years; specifically, the crude incidence rate at 0-3, 3-6, and 6-9 months since the start of follow-up was 23.0 (95% CI 20.3-26.0), 14.9 (95% CI 12.8-17.5), and 13.3 (95% CI 11.2-15.7) per 1000 person-years, respectively (Figure 3).

### 3.4 | Conversion to psychotic disorders

#### 3.4.1 | Schizophrenia

The cumulative conversion incidence for schizophrenia was 2.5% (95% CI 2.3-2.7) during a 15-year follow-up (Figure 1). As for conversion to BD, the highest crude incidence rate, that is, 4.6 (95% CI 4.0-5.3) per 1000 person-years, emerged at the first year of follow-up; the crude incidence rate at 0-3, 3-6, and 6-9 months since the start of follow-up was 4.6 (95% CI 3.5-6.1), 4.7 (95% CI 3.5-6.2), and 4.9 (95% CI 3.7-6.4) per 1000 person-years, respectively. The crude incidence rate then continued to decrease over time and was zero person-years at year 15 (Figure 3).

#### 3.4.2 | Schizoaffective disorder

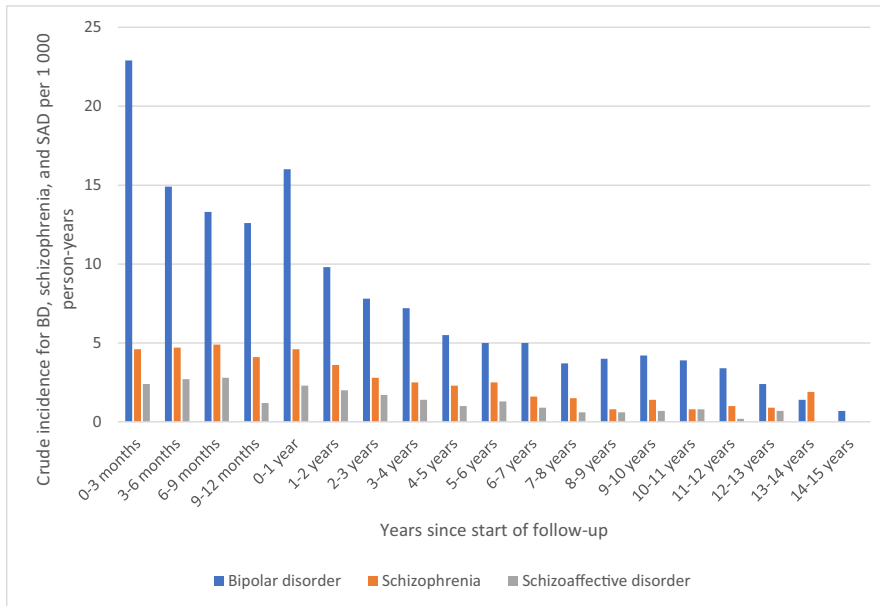
The cumulative conversion incidence for SAD was only 1.3% (95% CI 1.1-1.4) after 15 years of follow-up (see Figure 2). At the first year of follow-up, the crude incidence rate was at its highest, that is, 2.3 (95% CI 1.9-2.8) per 1000 person-years. Crude incidence rate at 0-3, 3-6, and 6-9 months since the start of follow-up was 2.4 (95% CI 1.9-2.8), 2.7 (95% CI 1.8-3.9), and 2.8 (95% CI 1.9-4.0) per 1000 person-years, respectively. The yearly crude incidence rate progressively declined after year 1 (see Figure 3).

### 3.5 | Conversion to major psychiatric disorders for patients with first hospitalization due to psychotic depression

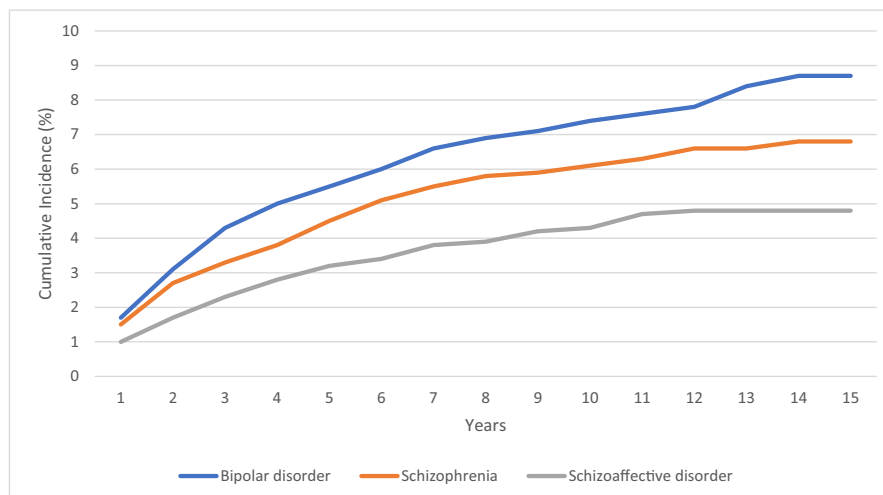
The overall cumulative incidence for conversion to all major psychiatric disorders among patients with first hospitalization due to psychotic depression was 19.2% (95% CI 17.9-20.7). The cumulative incidence for conversion to BD was 8.2% (95% CI 7.2-9.2) (manic, hypomanic, or mixed episode 3.8% (95% CI 3.1-4.5); depressive episode 4.5% (95% CI 3.7-5.2); to schizophrenia 6.5% (95% CI 5.7-7.3), and to SAD 4.6% (95% CI 3.9-5.2) during a 15-year follow-up (Figure 4).

### 3.6 | Predictors of conversion to major psychiatric disorders

SHRs for predictors of conversion from UD to the major psychiatric disorders are presented in Table 2. Overall, females were at higher risk to convert from UD to BD or SAD than males, whereas males were at higher risk to progress to schizophrenia than females. Patients with moderate and severe psychiatric impairment measured by GAS had approximately two times higher risk for conversion to BD than patients with mild impairment. Compared with mild depression, psychotic depression was a consistent predictor for conversion to manic, hypomanic, and mixed forms of BD (SHR = 2.4, 95% CI 1.4-3.9), depressive form of BD (SHR = 1.7, 95% CI 1.1-2.4), schizophrenia (SHR = 5.3, 95% CI (3.3-8.7)), and SAD (SHR = 10.6, 95% CI 4-28.4). Patients with a single depressive episode had a lower risk for further conversion to depressive form of BD than patients with preceding, non-hospitalized episodes, that is, recurrent UD (SHR = 0.7, 95% CI 0.6-0.8). Age 18-49 years was a stronger predictor for conversion to BD than age 13-18 years. Patients aged 30-49 years had a lower risk of



**FIGURE 3** Yearly crude incidence rate for the conversion from unipolar depression (UD) to bipolar disorder (BD), schizophrenia, and schizoaffective disorder (SAD) during a 15-y follow-up of inpatients after their first hospitalization due to UD (n = 43 495)



**FIGURE 4** Cumulative conversion incidence to bipolar disorder, schizophrenia, and schizoaffective disorder during a 15-y follow-up of inpatients with first hospitalization due to psychotic depression (n = 5517)

converting to schizophrenia than people aged 13-29 years, and patients aged 40-60 years had a lower risk of converting to SAD than patients aged 13-39 years. The cumulative conversion incidence of UD to BD, schizophrenia, and SAD in different age groups is shown in Figures S2-S7. The risk for subsequent hospitalization due to schizophrenia and SAD was higher during 1996-2003 than during 2004-2011 (SHR = 2.0, 95% CI 1.7-2.4; SHR = 1.7; 95% CI 1.4-2.2, respectively). The risk for hospitalization due to a depressive episode of BP was lower within the time period 1996-2003 than 2004-2011 (SHR = 0.9, 95% CI 0.8-0.97), but not for bipolar conversion overall.

We have also conducted sensitivity analyses with a multivariable Cox regression using different time periods from 2 weeks to 6 months between the first hospitalization due to UD and occurrence of the diagnostic conversion. All cause-specific hazard ratios

of the predictors remained within the confidence intervals demonstrated in our sample (with the original definition of the minimum of 2 weeks interval between the first hospitalization due to UD and the diagnostic conversion). The results are available on request.

### 3.7 | Sensitivity analysis for dichotomous outcome

We also conducted the sensitivity analysis using a dichotomous outcome. The cumulative conversion incidence for BD (including patients with ICD-10 diagnosis of a manic or mixed type of SAD) was 7.7% (95% CI 7.4-8.1) and for schizophrenia (including patients with ICD-10 diagnosis of depressive type of SAD) 3.4% (95% CI 3.2-3.7). In terms of predictors, no significant differences between the findings for the three outcomes emerged (see Table S1).

**TABLE 2** SHRs for predictors of conversion from unipolar depression to major psychiatric disorders after first hospitalization (n = 43 495)

Predictors	Bipolar disorder hypomanic, manic or mixed episode SHR (CI)	Bipolar disorder depressive episode SHR (CI)	All bipolar disorders SHR (CI)	Schizophrenia SHR (CI)	Schizoaffective disorder SHR (CI)
<b>Gender</b>					
Male	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Female	<b>1.2 (1.07-1.4)</b>	<b>1.3 (1.1-1.4)</b>	<b>1.3 (1.2-1.4)</b>	<b>0.6 (0.5-0.7)</b>	<b>1.4 (1.2-1.8)</b>
<b>Recurrence of depression</b>					
Recurrent depression	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Single depression	1.0 (0.8-1.2)	<b>0.7 (0.6-0.8)</b>	0.8 (0.7-0.9)	1.2 (0.9-1.5)	1.05 (0.8-1.5)
<b>GAS</b>					
Mild	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Moderate GAS	<b>2.1 (1.0-4.1)</b>	<b>1.8 (1.1-3.0)</b>	<b>1.9 (1.3-2.9)</b>	1.4 (0.7-3.0)	2.0 (0.3-12.3)
Severe GAS	<b>2.3 (1.2-4.5)</b>	<b>2.0 (1.2-3.3)</b>	<b>2.1 (1.5-3.1)</b>	1.8 (0.9-3.8)	2.5 (0.4-16.1)
Missing GAS	<b>2.3 (1.03-5.2)</b>	1.6 (0.9-2.9)	<b>1.8 (1.1-3.0)</b>	1.5 (0.6-3.5)	3.1 (0.4-20.9)
<b>Personality disorders</b>					
No	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Yes	1.2 (0.9-1.5)	<b>1.2 (1.01-1.4)</b>	<b>1.2 (1.03-1.3)</b>	1.2 (0.97-1.5)	1.0 (0.7-1.4)
<b>Severity of depression</b>					
Mild	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Moderate depression	1.5 (0.94-2.5)	<b>1.5 (1.05-2.1)</b>	<b>1.5 (1.1-2.1)</b>	1 (0.6-1.6)	1.5 (0.5-4.0)
Severe depression	1.5 (0.95-2.5)	<b>2.0 (1.4-2.9)</b>	<b>1.9 (1.4-2.5)</b>	1.2 (0.8-2.0)	1.9 (0.7-5.0)
Psychotic depression	<b>2.4 (1.4-3.9)</b>	<b>1.7 (1.1-2.4)</b>	<b>2.0 (1.5-2.7)</b>	<b>5.3 (3.3-8.7)</b>	<b>10.6 (4-28.4)</b>
Unspecified	1.3 (0.8-2.1)	1.3 (0.9-1.9)	1.3 (0.9-1.9)	1.4 (0.8-2.3)	1.5 (0.5-4.0)
<b>Age, y</b>					
13-17	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
18-22	1.3 (0.93-1.7)	<b>1.4 (1.2-1.8)</b>	<b>1.4 (1.2-1.7)</b>	1.1 (0.9-1.4)	1.1 (0.8-1.6)
23-29	<b>1.5 (1.1-2.0)</b>	<b>1.8 (1.5-2.3)</b>	<b>1.7 (1.4-2.1)</b>	0.9 (0.7-1.1)	1.3 (0.9-1.8)
30-39	<b>1.6 (1.2-2.0)</b>	<b>1.6 (1.3-2.0)</b>	<b>1.6 (1.4-1.9)</b>	<b>0.5 (0.4-0.6)</b>	0.7 (0.5-1.0)
40-49	<b>1.7 (1.3-2.2)</b>	<b>1.3 (1.04-1.6)</b>	<b>1.4 (1.2-1.7)</b>	<b>0.2 (0.15-0.3)</b>	<b>0.4 (0.3-0.5)</b>
50-60	1.0 (0.7-1.3)	0.9 (0.7-1.1)	0.9 (0.8-1.1)	0.1 (0.09-0.2)	<b>0.3 (0.2-0.54)</b>
<b>Time periods</b>					
2004-2011	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1996-2003	1.1 (0.96-1.3)	<b>0.9 (0.8-0.97)</b>	0.95 (0.9-1.0)	<b>2.0 (1.7-2.4)</b>	<b>1.7 (1.4-2.2)</b>

Note: Bolded text indicates  $P \leq .05$ .

Abbreviations: GAS, Global Assessment Scale; ref, reference; SHR, Subdistribution hazard ratio.

## 4 | DISCUSSION

In this prospective nationwide register study, which covered all first psychiatric hospitalizations due to UD in Finland (n = 43 495) between 1996 and 2011, the overall 15-year cumulative incidence of conversion to another major psychiatric disorders was 11.1%. More specifically, the 15-year cumulative incidences of conversion to BD, schizophrenia, and SAD were 7.4%, 2.5%, and 1.3%, respectively. The highest cumulative incidence for all of the major psychiatric disorders occurred during the first years of follow-up, thereafter decreasing with time. The most consistent predictor for conversion to a manic, hypomanic, or mixed episode of BD,

schizophrenia, or SAD was severe depression, particularly psychotic depression. In patients hospitalized due to psychotic depression, the cumulative risk for conversion to any of the major psychiatric disorders was almost twofold higher than in patients with mild depression. Risk for progression to schizophrenia and SAD was several times higher than in patients with mild depression. Patients with recurrent episodes of depression are more likely than those with a single episode to progress to BD. Females were at higher risk of converting to BD, whereas males had a higher risk of converting to psychotic disorders. Greater psychiatric disturbance within depression predicted diagnostic conversion to BD. Finally, the risk for conversion to the psychotic disorders

was higher during 1996-2003 than during 2004-2011, whereas the risk for conversion to a depressive episode of BD was higher during 2004-2001, than 1996-2003.

Our register-based prospective study has several strengths. First, we were able to investigate the cumulative incidence of diagnostic conversion and its temporal patterns and predictors in a large representative national Finnish cohort ( $n = 43\,465$ ) of patients with UD. Therefore, our findings are generalizable within Finland and likely to the other Nordic countries with broadly similar healthcare services. Generalizability to other settings remains to be investigated. Second, our dataset included adolescents in the age group of 13-17 years. As BD type 1 and schizophrenia may manifest before the age of 18 years,<sup>30,31</sup> we were able to investigate the conversion risk in this particularly vulnerable age group. Third, prospective design of the study is an obvious strength when examining the incidence of diagnostic conversion and the predictive value of risk factors. Fourth, a long follow-up is a strength, allowing us to describe the temporal trajectory of the cumulative conversion incidences for the major psychiatric disorders. Fifth, availability of data on the level of overall functioning of the patients during their hospitalization enabled us to examine its predictive value for diagnostic conversion. Sixth, to our knowledge, this is the first register-based prospective study examining the conversion from UD to SAD. The inclusion of all three major psychiatric disorders allowed us to compare their cumulative conversion incidences and their predictors.

Our study also has limitations. First, our dataset is limited to information available on psychiatric hospitalizations. Thus, diagnostic conversions detected in relation to treatment in outpatient psychiatric, primary care, and private psychiatric settings remain unknown, unless the patients were later rehospitalized. Therefore, our dataset presumably consists of patients with the most severe mood and psychotic disorders, and the less severe disorders are not included. As hypomania, as opposed to mania, rarely requires hospitalization, we assume that our findings reflect the diagnostic conversion to BD type 1 more precisely than the conversion to BD type 2. Second, the diagnoses are clinical and unverified by structured clinical interviews, which may result in diagnostic inaccuracy. A considerable delay in recognition of BD<sup>15,32</sup> or psychotic disorders<sup>33</sup> and the low diagnostic reliability of SAD<sup>34</sup> are well-known clinical problems. However, previous research has shown a relatively good diagnostic accuracy of register-based studies,<sup>25,35</sup> particularly for psychotic disorders in Finland.<sup>36,37</sup> In addition, we suppose that clinicians do not always correctly classify single vs recurrent depression in clinical practice, which may affect our findings in terms of predictive value of single vs recurrent depression. Moreover, we were unable to follow patients from their first depressive episode if it did not require hospitalization. Third, only a limited range of risk factors could be investigated. For instance, data on family history of mental health disorder, a previously reported important predictor for conversion to both BD and schizophrenia,<sup>21,38</sup> were not available. Fourth, as the risk for conversion to BD may persist over the lifespan,<sup>39</sup> the results of a 15-year

follow-up are an underestimate of lifetime diagnostic changes. However, since the highest rate of conversions was found to occur early, the rate of late diagnostic change after 15 years is likely to be low in BD and negligible in schizophrenia and SAD.

#### 4.1 | Cumulative incidence and its temporal patterns for diagnostic conversion from UD to BD, schizophrenia, and SAD

In our study, the cumulative incidence of conversion from UD to BD during a 15-year follow-up (7.4%) is lower than reported in the meta-analyses by Kessing et al<sup>12</sup> and Ratheesh et al<sup>13</sup> but in line with the findings from the largest register-based study of Musliner et al<sup>38</sup> showing a 21-year cumulative incidence of conversion of 8.7% in women and 7.7% in men. Notably, although relatively low lifetime prevalence of BD has been reported in Finland,<sup>40,41</sup> the cumulative conversion incidence is comparable to the conversion risk reported in Denmark. However, the conversion incidence to schizophrenia was approximately two and half times lower than in the Danish register study.<sup>21</sup> Since lifetime prevalence of schizophrenia in Finland was reported to be even higher than in other Nordic countries,<sup>42,43</sup> this finding is unexpected. We presume that the lack of data on outpatient units and private settings, the register-based design, and the exclusion of patients with previous hospitalizations due to unspecified psychosis may partly explain this discrepancy. In addition, slight differences may exist in the mental health service structures between these countries.

In our study, the risk for transition to psychotic disorder was higher during 1996-2003 than during 2004-2011. This finding accords with the previously reported decline in the incidence of schizophrenia in Finland.<sup>44</sup> The risk for subsequent hospitalization due to a depressive episode of BD was slightly higher during the time period 2004-2011 than 1996-2003, whereas the risk for hospitalization due to a manic, hypomanic, or mixed episode remained the same, as did risk of bipolar conversion overall. Improved recognition of BD type 2 by clinicians at outpatient settings during the later time period may underlie this finding. The low conversion risk for SAD corresponds to a low lifetime prevalence of SAD.<sup>45</sup> Moreover, low diagnostic reliability of SAD in clinical practice may underlie the low conversion risk<sup>34</sup> in our study. The yearly crude incidence rate for all major psychiatric disorders appeared highest in the first year after hospitalization due to UD, thereafter decreasing with time.

#### 4.2 | Predictors for diagnostic conversion

Predictors associated with conversion to the major psychiatric disorders in our study corresponded to the predictors reported in the studies of the Danish group on conversion to BD<sup>38,46</sup> and schizophrenia.<sup>21</sup> Severe depression, especially psychotic depression, was the most consistent predictor for conversion to any major psychiatric disorder. In our study, one of five patients with a history of



hospitalization due to psychotic depression progressed to a major psychiatric disorder. Compared with patients with mild depression, patients with psychotic depression had approximately a fivefold risk for progression to schizophrenia. The hazard ratio for psychotic depression to progress to SAD was exceptionally high, 10.6 (CI 95% 4.0-28.4). This finding may reflect the previously reported frequent shift from psychotic depression to SAD,<sup>20</sup> although the wide confidence interval indicates uncertainty in the actual size of the risk. In addition to severity of depression, patients with moderate and severe psychiatric disturbance during UD had an approximately two-fold higher risk for conversion to BD than patients with mild disturbance. Furthermore, as in earlier studies,<sup>9</sup> we found patients with recurrent (previously non-hospitalized) depression to have higher risk of converting to BD than patients with a single episode. As in the study of the Danish group, females were at higher risk of conversion to BD than males.<sup>38</sup> However, in line with the previous studies in patients with UD<sup>21</sup> and UHR patients,<sup>10</sup> males had a higher risk of converting to schizophrenia than females. Although young age was a significant predictor for conversion to BD in the meta-analysis by Ratheesh (2018), in our study, patients aged 23-49 years had a higher risk of converting to BD than patients aged 13-17 years. A similar finding arose from the study by Musliner et al (2018) and our previous study.<sup>14</sup> Consistent with Musliner et al (2018), we hypothesize that delays in recognition of BD may partly underlie this finding. We have previously shown that the earlier the onset of a mood disorder episode, the longer the delay from the first episode to correct diagnosis of BD.<sup>47</sup> Poor recognition of BD in adolescence may be partly explained by overlapping symptoms of BD and comorbid disorders such as attention-deficit hyperactivity disorder.<sup>48</sup> In addition, clinical presentation of UD in adolescence may differ from UD in adults, resulting in misdiagnosis of UD in young people.<sup>49</sup> Therefore, exclusion of all psychiatric hospitalizations before the first inpatient treatment due to UD may underestimate the effect of age on conversion. In contrast, corresponding to studies in UHR patients,<sup>10,11</sup> patients aged 13-17 years were at higher risk of converting to psychotic disorders than patients aged 40-60 years. This finding might be explained by the fact that depressive symptoms and diagnosed depressive disorders are common in the prodromal phase of psychotic disorders in young people.<sup>50</sup> Thus, conversion to psychotic disorders seems to occur earlier than to BD in patients with their first hospitalization due to UD. Finally, patients with comorbid personality disorder were at higher risk of diagnostic conversion to BD. This probably reflects the association between comorbid personality disorder and increased risk for chronicity, recurrence, and severity of depression during a mood disorder episode.<sup>51</sup> Taken together, although prediction of further development of psychopathology is challenging on the individual level, patients with a history of a hospitalization due to psychotic depression, recurrent episodes, and greater psychiatric disturbance within depression are particularly vulnerable for further conversion from UD to BD or psychotic disorder during the first years after the hospitalization. These findings should be taken into consideration when planning the outpatient follow-up of the patients discharged from the hospitalization due to UD.

To conclude, in Finland, among patients with first psychiatric hospitalization due to UD, approximately one in nine seems to convert to a major psychiatric disorder during a 15-year follow-up. The cumulative conversion incidence for BD was 7.4%, corresponding to the previously reported conversion incidence from UD to BD in Denmark. However, the cumulative incidence of conversion to psychotic disorders was relatively low: 2.5% for schizophrenia and 1.3% for SAD. Patients suffering from psychotic depression represent a vulnerable group for conversion, with a higher risk for psychotic disorders than for BD. The highest risk for conversion emerged within the first years of follow-up. Males were at higher risk than females for progression to schizophrenia, whereas females were at higher risk for conversion to BD and SAD. Greater psychiatric disturbance during UD or presence of a comorbid personality disorder predicted conversion to BD. Patients with recurrent depression were at higher risk for conversion to BD than patients with a single depression episode. Patients aged 13-17 years were at higher risk for progression to psychotic disorders than older patients. In contrast, patients older than 18 years were at higher risk for conversion to BD than younger patients. Finally, during a 15-years follow-up, in patients with their first hospitalization due to UD, the risk for the subsequent hospitalization due to schizophrenia and SAD was somewhat higher during the first half of the time period, whereas for bipolar depression during the latter. Thus, time period of investigation may have some influence on observed hospitalization-based rates of diagnostic conversion.

## CONFLICT OF INTEREST

None declared.

## DATA AVAILABILITY STATEMENT

Due to limitations imposed by research permit and legislation, data not available.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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