Patterns and predictors of conversion to bipolar disorder in 91,587 individuals diagnosed with unipolar depression

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Abstract (200 words)

Objective: Conversion from unipolar depression (UD) to bipolar disorder (BD) is a clinically important event that should lead to treatment modifications. Unfortunately, recognition of this transition is often delayed. Therefore, the objective of this study was to identify predictors of diagnostic conversion from UD to BD.

Method: Historical prospective cohort study based on 91,587 individuals diagnosed with UD in Danish hospital psychiatry between 1995 and 2016. The association between a series of potential predictors and the conversion from UD to BD during follow-up (702,710 person years) was estimated by means of Cox regression with death as competing risk.

Results: During follow-up, 3,910 individuals with UD developed BD. The cumulative incidence of conversion was slightly higher in females (8.7%, 95%CI: 8.2-9.3) compared to males (7.7%, 95% CI: 7.0-8.4). The strongest predictor of conversion from UD to BD was parental history of BD (adjusted hazard ratio (aHR)=2.60, 95%CI: 2.20-3.07). Other notable predictors included psychotic depression at the index UD diagnosis (aHR=1.73, 95%CI: 1.48-2.02), a prior/concomitant non-affective psychosis (aHR=1.73, 95%CI: 1.51-1.99) and inpatient treatment at index diagnosis (aHR=1.76, 95% CI: 1.63-1.91).

Conclusion: Diagnostic conversion from UD to BD is predicted by severe depression requiring inpatient treatment, psychotic symptomatology, and parental history of BD.

Key words

Depression, Affective disorders, Bipolar disorder, Diagnosis, Alcohol

Significant outcomes

- The overall cumulative incidence of conversion from unipolar depression (UD) to bipolar disorder (BD) diagnosis was 8.7% in females and 7.7% in males.

- The strongest predictor of conversion from UD to BD was parental history of BD. Other significant predictors included psychotic depression at the index UD diagnosis, inpatient or emergency treatment at UD diagnosis, recurrent depressive disorder at the index UD diagnosis, greater severity at UD diagnosis, a prior/concomitant non-affective psychosis, a prior/concomitant alcohol abuse disorder and parental history of UD.

- Patients with UD that have comorbid psychotic symptomatology and a parental history of BD are at increased risk of conversion to BD. Since this replicates the findings from a recent meta-analysis, it appears that these risk factors are now so well established that they can be used clinically to identify UD patients at elevated risk of developing BD.

Limitations

- Diagnostic data from primary care was not available in this study.

- Diagnoses are made in a real-world clinical setting and are potentially subject to bias. E.g. individuals with a parental history of BD may be more likely to receive a BD diagnosis.

- Not all diagnoses in the Danish Central Psychiatric Research Register have been validated, but the validity of both UD and BD diagnoses has been shown to be high.

Introduction

In most individuals who develop bipolar disorder (BD), depression is the first episode of illness [1,2]. Since the bipolar nature of the disorder has not manifested at this stage, these individuals are correctly diagnosed with unipolar depression (UD). The subsequent transition from UD to BD, with the occurrence of the first episode of hypomania, mania or mixed symptoms, is a clinically important event that should be followed by modifications in psychopharmacological treatment (less use of antidepressants and addition of a mood-stabilizing agent) [3,4] .

Unfortunately, the conversion from UD to BD often goes undetected, resulting in long periods of untreated BD, which are known to affect the prognosis negatively [5,6]. In order to decrease the duration of untreated illness by facilitating early detection, many efforts have been made to identify risk factors for the conversion of UD to BD [7-11]. In a recent paper published in this journal, Ratheesh et al. [9] systematically reviewed the literature on this topic and, via a meta-analysis, identified three predictors that were significantly associated with conversion from UD to BD, namely early age of onset of UD, presence of psychotic symptoms and having a family history of BD.

In this study we aimed to determine whether the results from the meta-analysis of Ratheesh et al. could be reproduced in a large nationwide sample of patients with UD based on data from Danish registers [12]. In order to be able to identify other predictors of the conversion from UD to BD than those found by Ratheesh et al. and to adjust for potential confounding our analyses included a series of clinical covariates that could also be linked to BD.

Materials and Methods

Study design and data

We conducted a historical prospective cohort study using de-identified data extracted from the Danish Civil Registration System (DCRS) [13] and the Danish Central Psychiatric Research Register (DCPRR) [14] . The DCRS was established in 1969 and includes information such as sex, place of birth, date of birth, mother and father's ID and vital status (i.e. whether the individual is alive or dead) for all individuals living in Denmark [13]. The DCPRR contains information including the admission and discharge dates and the diagnosis given at discharge by the treating psychiatrist for all inpatient visits to psychiatric treatment facilities from 1969 onwards and all outpatient and psychiatric emergency room visits from 1995 onwards [14]. The DCPRR does not include diagnoses given in primary care settings. Diagnoses in the DCPRR were made based on the International Classification of Diseases 8th edition (ICD-8) [15] until 1994, when psychiatrists in Denmark adopted the International Classification of Diseases 10th edition (ICD-10) [16] . Complete information from the DCRS and DCPRR were available through December 31, 2016. For the diagnostic variables in this study, we considered DCPRR main diagnoses assigned in relation to inpatient, outpatient and emergency room assessment/treatment at psychiatric hospitals throughout Denmark (including Greenland or the Faroe Islands).

Sample selection

We began by identifying all individuals who received their first diagnosis of unipolar depression (UD) (ICD-10 codes F32, F33) in a psychiatric hospital in Denmark (including Greenland or the Faroe Islands) after January 1, 1995 who were discharged from their index UD diagnosis at least 8 weeks before the date of administrative censoring (December 31, 2016) (N=167,277). We then restricted the sample to individuals who were at least 10 years old on the date of their first UD diagnosis (depression diagnoses are very rarely assigned prior to this age in Danish hospital psychiatry – see Pedersen et al. [17]), were

born in 1955 or later, had links to both parents in the DCRS, and had no prior records of bipolar disorder (ICD-8 codes 296.19, 296.39, 298.19; ICD-10 codes F30-F31) schizophrenia (ICD-8 codes 295.x9 [excluding 295.79]; ICD-10 code F20) or schizoaffective disorder (ICD-8 codes 295.79, 296.89; ICD-10 code F25) (N=94,601) (see Figure 1). An additional 141 individuals were removed due to missing or unknown place of birth, or because their date of UD diagnosis occurred after they were recorded as having died or emigrated (likely an administrative error). Finally, 1,091 individuals were removed either because they received a BD diagnosis within 8 weeks of the discharge date of their index UD diagnosis (n=828) or because they died or emigrated within 8 weeks of the discharge date of their index UD diagnosis (n=263). The final sample consisted of 91,587 individuals with UD.

Figure 1 approximately here

Predictors

We examined the effects of the following predictor variables on hazard of conversion from UD to BD: sex (male/female); Geographic area of birth (Capital/suburb of capital, Provincial city/town, Rural area, Born outside Denmark); treatment setting at index UD diagnosis (outpatient, inpatient, emergency room); Recurrent depressive disorder vs. single (i.e. first) depressive episode at index diagnosis; Severity at index diagnosis (Mild, Moderate, Severe without psychotic symptoms, Severe with psychotic symptoms); Age at index UD diagnosis (10-19 years, 20-29 years, 30-39 years, 40-49 years, and 50-61 years); Other diagnoses of mental disorders on or before the date of index UD diagnosis (any mental disorder other than mood disorders, substance abuse disorder (excl. alcohol), alcohol abuse disorder, non-affective psychotic disorders excluding schizophrenia/schizoaffective disorder (i.e. non-affective psychosis), Neurotic, stress-related, and somatoform disorders (excl. obsessive compulsive disorder) (i.e. anxiety disorders), obsessive compulsive disorder (OCD), anorexia nervosa, personality disorders, mental

retardation, autism spectrum disorders, attention-deficit hyperactivity disorder (ADHD), and behavioral and emotional disorders in childhood (excl. ADHD)); and records of psychiatric diagnoses in the subjects' parents (any mental disorder in a parent, substance abuse disorder (excl. alcohol), alcohol abuse disorder, Schizophrenia and related disorders (i.e. psychotic disorders), BD, UD, anxiety disorders, OCD, anorexia nervosa, personality disorders, mental retardation, autism spectrum disorders, ADHD, and behavioral and emotional disorders in childhood (excl. ADHD)). These potential predictors were chosen based on prior studies of the transition from UD or other high-risk phenotypes to BD [8-10,18,19] and our recent analogue study of the transition from UD to schizophrenia [20]. Information on sex and place of birth were obtained from the DCRS. All other predictor variables were obtained using information from the DCPRR. Diagnostic categories (See Supplementary Table 1) were based on the diagnostic classification of mental disorders for the DCPRR outlined in Pedersen et al. [17].

Outcome

The outcome of interest (BD) was defined by a diagnosis of mania/hypomania (ICD-10 code: F30) or BD (ICD-10 code: F31) in the DCPRR [17,21] occurring at least 8 weeks after the discharge date of the index UD diagnosis. This 2-month "grace period" was included to ensure that we were indeed studying diagnostic conversions from a separate episode of UD to a subsequent (first) episode of BD, i.e., to avoid that the index UD diagnosis was actually a misclassified episode of BD.

Statistical Analysis

Analyses were conducted in SAS 9.4. Follow-up began 8 weeks after the discharge date of the index UD diagnosis and ended at first BD diagnosis, death, emigration or December 31, 2016, whichever came first. Because UD cases that die during follow-up may not have the same risk for conversion to BD as cases who do not die, we incorporated death as a competing event in all models. The cause-specific

cumulative incidence function was calculated using the "%cif" macro. Hazard ratios for predictor variables were calculated using Fine and Gray's extension of the Cox model for competing risks [22] implemented in SAS (PROC PHREG). We calculated crude hazard ratios for each predictor variable, as well as adjusted hazard ratios from a model containing all other predictor variables as well as calendar year at index UD diagnosis.

Results

Sample characteristics

Characteristics of the study sample are shown in Table 1. The sample was 63% female, with an average age at index UD diagnosis of 31 years (SD=11 years). Over half (57%) of the sample received treatment for their index UD diagnosis in an outpatient setting. Seventy one percent received a diagnosis of single depressive episode and the remainders were diagnosed with recurrent depressive disorder. Sixteen percent of the index UD diagnoses were characterized as mild, 44% as moderate, 13% as severe without psychotic symptoms, 4% as severe with psychotic symptoms and 24% received no severity specification.

Table 1 approximately here

Thirty-nine percent of the cohort members were diagnosed with a mental disorder other than a mood disorder on or prior to the date of their index UD diagnosis. The most common comorbid diagnoses were neurotic, stress-related and somatoform disorders excluding OCD (i.e. anxiety disorders): a quarter of the UD cases received a diagnosis from this category either on before the date of their index UD diagnosis. All other diagnoses were relatively rare (0.6-6.8%). Twenty seven percent of the sample had a

parental history of mental disorder, most commonly unipolar depression (10%) and anxiety disorders (12%). As very few individuals had a parental history of mental retardation (0.07%), anorexia nervosa (0.07%) or autism spectrum disorder (0.01%), we did not include these three variables in further analyses.

Conversion to bipolar disorder

The cohort was followed for a total of 702,710 person years. Length of follow-up ranged from 1 day to 7975 days (22 years). Average length of follow-up was 7.7 years (SD = 5.4 years). Of the 91,587 UD cases in the sample, 3,910 converted to BD during follow-up, 3,092 died and the remainder was administratively censored due to emigration or end of follow-up. The yearly and overall cumulative incidences of conversion from UD to BD are shown in Figure 2. Overall, the cumulative incidence of conversion was 8.4% (95%CI: 7.9-8.8). The cumulative incidence of conversion was slightly higher in females (8.7%, 95%CI: 8.2-9.3) compared to males (7.7%, 95%CI: 7.0-8.4). The yearly incidence of conversion to BD was highest in the first year of follow-up (Females: 1.07%, 95%CI: 0.99-1.16. Males: 1.02%, 95%CI: 0.92-1.13). The decrease in conversion rate was most pronounced between the first and second year, however the rate of conversion continued to decrease in later years, albeit to a lesser degree (Figure 2). No BD diagnoses occurred after 20 years from the index UD diagnosis.

Figure 2 approximately here

Predictors of conversion to bipolar disorder

Crude and adjusted hazard ratios for predictors of conversion from UD to BD are shown in Figure 3. The strongest predictor of conversion from UD to BD was parental history of BD (crude Hazard Ratio (HR)=2.99, 95%CI: 2.58-3.46; adjusted HR=2.60, 95%CI: 2.20-3.07). Among individuals with a parental

history of bipolar disorder, the 20-year cumulative incidence of conversion to BD was 25% (95%CI: 19.5-31.2) (see Figure 4). Other notable predictors included psychotic depression at index UD diagnosis (crude HR=2.31, 95%CI: 1.99-2.68; adjusted HR=1.73, 95%CI: 1.48-2.02), prior or concomitant diagnosis with a non-affective psychosis (crude HR=2.14, 95%CI: 1.88-2.43; adjusted HR=1.73, 95%CI: 1.51-1.99) and inpatient treatment at index UD diagnosis (crude HR=1.91, 95%CI: 1.77-2.05; adjusted HR=1.76, 95%CI: 1.63-1.91). Other predictor variables with statistically significant but smaller effect sizes included female sex; birthplace in a provincial town/city (relative to the capital); emergency room treatment at index UD diagnosis (relative to outpatient); recurrent depressive disorder (relative to single depressive episode) at index UD; moderate, severe without psychotic symptoms and unspecified severity at index UD diagnosis (relative to mild); prior or concomitant diagnosis of alcohol abuse disorders; and parental history of unipolar depression (Figure 3). All other variables were not significant after adjusting for other predictors.

Figure 3 and Figure 4 approximately here

Post hoc analysis

We conducted a post hoc analysis to investigate the extent to which the effect of a prior or concomitant diagnosis of non-affective psychosis was driven by a diagnosis of "Acute polymorphic psychotic disorder without symptoms of schizophrenia" (ICD-8 code 298.29; ICD-10 code F23.0). Individuals suffering from this disorder often display "Emotional turmoil, characterized by intense feelings of happiness or ecstasy, or overwhelming anxiety or marked irritability" [16] and therefore bipolar disorder is a common differential diagnosis. Of the 2,737 individuals with a prior or concomitant diagnosis of a non-affective psychosis, 237 (8.7%) received this diagnosis. The effect of acute polymorphic psychotic disorder on the hazard of conversion from UD to BD was strong (crude HR=4.87, 95% CI: 3.65-6.48). The effect of the

non-affective psychosis category was attenuated after removal of these individuals (from crude HR=2.14, 95% CI: 1.88-2.43 to crude HR=1.85, 95%CI: 1.61-2.14), suggesting that this diagnosis was driving some, but not all, of the effect.

Discussion

In this study of 91,587 individuals with UD followed up for a total of 702,710 person years, the cumulative incidence of conversion was 8.7% (95%CI: 8.2-9.3) in females and 7.7% (95% CI: 7.0-8.4) in males. The incidence of conversion to BD decreased most prominently after the first year of follow-up and the conversion rate was almost constant after the 5th year following the UD diagnosis. The strongest predictor of conversion from UD to BD was parental history of BD. Other significant predictors included psychotic depression at the index UD diagnosis, inpatient or emergency treatment at UD diagnosis, greater severity at UD diagnosis, recurrent depressive disorder, a prior/concomitant non-affective psychosis, a prior/concomitant alcohol abuse disorder and parental history of UD.

That the risk for conversion from UD to BD was most pronounced in the first year, and was then slightly decreasing) after the 5th year following the UD diagnosis, is in agreement with the findings from the meta-analyses by Kessing et al. [8] and Ratheesh et al. [9]. Our conversion rates were however lower than those generally reported elsewhere [8,9,23], which is most likely to be due to the fact that we could only include information on the development of BD from registers (when patients got readmitted, received outpatient treatment or were seen in the psychiatric emergency room), while for instance Angst et al. performed systematic follow-up of the UD patients over time [23]. The latter approach is likely to be more sensitive and will thus identify more cases. In support of this explanation, James et al.

[11] recently reported that the overall BD conversion rate in their 12-year register-based follow-up study of patients with UD was 5.7%, which is in agreement with our findings.

In our analysis of predictors of conversion from UD to BD, parental history of BD had the strongest signal. As demonstrated by the meta-analysis of Ratheesh et al. [9], this finding is perhaps the most consistent one across studies. This is in line with the very high heritability (heritability estimates of approximately 0.85) of bipolar disorder [24]. A parental history of psychotic disorder (including schizophrenia and schizoaffective disorder) was not associated with conversion from UD to BD. Interestingly, these findings are completely opposite to those from our analogue study of conversion from UD to schizophrenia [20] where a parental history of schizophrenia, but not bipolar disorder, was among the significant predictors. They also lend some support to the Kraepelinian dichotomy, which states that the affective psychoses and schizophrenia are distinct syndromes [25]. Of course, this difference is likely to be partly due to the treating psychiatrist's awareness of the parental history of mental disorder when assigning a diagnosis. A UD patient having a parent with BD may be relatively more likely to get a BD diagnosis compared to a UD patient having a parent with schizophrenia, who will be more likely to get a schizophrenia diagnosis. However, it seems unlikely that this should account for a large proportion of the observed difference in our studies as the diagnostic criteria for bipolar disorder and schizophrenia differ substantially.

Another finding from our study that overlapped with those reported in the meta-analysis by Ratheesh et al. [9] was that psychotic depression at index was associated with subsequent BD. This association has been reported consistently over decades based on studies of both clinical and epidemiological cohorts [7,26-33]. In further support of the close connection between psychotic depression and BD, prior studies have shown that when relatives of patients with BD become depressed, they have an increased prevalence of psychotic symptoms compared to depressed relatives of individuals without BD [34] and

that a parental history of BD is an independent risk factor for psychotic depression, but not for non-psychotic (severe) depression [30].

In addition to psychotic depression, we also found that recurrent depressive disorder was associated with conversion to BD. This has been reported before [10,23] and indicates that there is a kindling effect operating across the spectrum of affective disorders [35]. More broadly speaking, our results suggest that patients with a severe presentation of UD (severe depression, recurrent depression, psychotic depression, comorbid alcohol abuse and need for inpatient treatment) are at increased risk of converting to BD. This seems to resonate well with experiences from clinical practice.

Our finding that age at diagnosis was not associated with risk for conversion to BP is inconsistent with prior research, including the meta-analysis by Ratheesh et al. [9], which typically find that younger age at UD diagnosis is associated with increased risk for conversion. We believe that this result is due to the fact that until recently, diagnoses of BD were very rarely assigned to individuals below the age of 18 in Danish hospital psychiatry [21]. The finding from our register-based study is also in agreement with the register-based study by James et al. [11], who found the lowest conversion rate to BD in individuals diagnosed with UD between the age of 10 and 14 years. Hence, it seems likely that register-based studies may underestimate the BD transition rate in pediatric UD populations compared to clinical studies with more systematic follow-up examination of the patients [9]. This hypothesis is supported by findings from the clinical Jorvi Bipolar Study in Finland showing that onset of BD prior to the age of 18 was associated with delay of treatment [36]. In a register–based study such as ours, which rely solely on hospital diagnoses, the finding from the Jorvi Bipolar Study would translate into underestimation of BD transition rates in children and adolescents with UD.

We found that having had a non-affective psychosis (not schizophrenia/schizoaffective disorder) was associated with transition from UD to BD. This seems to be consistent with studies of individuals at Ultra-High-Risk for psychosis, who are also at high risk of developing affective psychoses, including BD [37,38] . Our post hoc analysis revealed that the diagnosis "Acute polymorphic psychotic disorder without symptoms of schizophrenia" was particularly strongly associated with subsequent BD. The clinical presentation of this disorder, i.e. "Emotional turmoil, characterized by intense feelings of happiness or ecstasy, or overwhelming anxiety or marked irritability" [16], can be very difficult to differentiate from a manic or a mixed affective episode. Also, it is possible that acute polymorphic psychotic disorder without symptoms of schizophrenia represents a developmentally modified presentation of early stages of BD. Either way, it would seem that clinicians should be extra attentive of other risk factors for BD [7,37] in individuals who present with acute polymorphic psychotic disorder without symptoms of schizophrenia.

A noteworthy finding of this study was that having been diagnosed with alcohol abuse and not drug abuse was associated with increased risk of converting from UD to BD. Interestingly, we found the exact opposite in our study of conversion from UD to schizophrenia where those diagnosed with drug abuse and not substance abuse were at elevated risk of converting from UD to schizophrenia [20]. A possible explanation for this difference could be that while alcohol abuse in individuals with UD that are later diagnosed with BD may represent a consequence of emerging manic/hypomanic/mixed symptoms [18,39-41], substance abuse (of cannabis for instance) in individuals with UD that are later diagnosed with schizophrenia could be an outright etiological factor [42,43]. In a recent study of young individuals with high-prevalence mental disorders, alcohol abuse was also strongly associated with progression to bipolar disorder [18].

There are a number of limitations to the register-based approach used in this study that deserve mentioning. First and foremost, our dataset is restricted to diagnoses assigned in relation to assessment and treatment of mental disorder performed at psychiatric hospitals (and not in primary care settings) in Denmark. As such, our findings are probably most generalizable to relatively severe UD in populations with universal/free access to psychiatric care. Furthermore, not all diagnoses in the source register (the DPCRR) have been validated, but the validity of for instance the UD, BD and schizophrenia diagnoses in the DPCRR have been found to be quite high [44-46]. Finally, as mentioned previously, the diagnoses in the DPCRR are potentially subject to bias. E.g. individuals with parental history of BD may be more likely to receive a BD diagnosis.

The register-based approach also has obvious strengths, most importantly it enabled us to follow a very large and nationally representative cohort of individuals with UD (n=91,587) for an extensive period of time (702,710 person years), which to our knowledge, makes this one of the largest studies of the conversion from UD to BD to date [9].

In conclusion, patients with UD that have severe depression requiring inpatient treatment, recurrent depression, prior or comorbid psychotic symptomatology, and those with a parental history of BD are at increased risk of conversion to BD. This replicates the findings from a recent meta-analysis [9]. It appears that these risk factors are now so well established that they can be used clinically to identify UD patients at elevated risk of developing BD.

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Declaration of interest

The authors declare no conflicts of interest.

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Table 1. Sample characteristics for UD cases that did and did not convert to BD

			Converted to Bipolar Disorder			
	Total sample		No		Yes	
Characteristics	*Number*	*%*	*Number*	*%*	*Number*	*%*
Sex						
Female	57,914	63.23	55,336	63.11	2,578	65.93
Male	33,673	36.77	32,341	36.89	1,332	34.07
Place of birth						
Capital or suburb of the Capital	23,916	26.11	22,942	26.17	974	24.91
Provincial town/city	40,146	43.83	38,244	43.62	1,902	48.64
Rural area	23,023	25.14	22,161	25.28	862	22.05
Born outside of Denmark	4,502	4.92	4,330	4.94	172	4.40
Treatment setting						
Outpatient	52,515	57.34	50,949	58.11	1,566	40.05
Inpatient	19,464	21.25	18,146	20.70	1,318	33.71
Emergency	19,608	21.41	18,582	21.19	1,026	26.24
Recurrence						
Single (first) depressive episode	65,374	71.38	62,852	71.69	2,522	64.50
Recurrent depressive disorder	26,213	28.62	24,852	28.31	1,388	35.50
Severity						
Mild	14,357	15.68	13,829	15.77	528	13.50
Moderate	40,311	44.01	38,574	44.00	1,737	44.42
Severe without psychotic symptoms	11,712	12.79	11,118	12.68	594	15.19
Severe with psychotic symptoms	3,352	3.66	3,088	3.52	264	6.75
Unspecified severity	21,855	23.86	21,068	24.03	787	20.13
Age						
10-19 years	16,724	18.26	16,252	18.54	472	12.07
20-29 years	28,103	30.68	26,850	30.62	1,253	32.05
30-39 years	24,479	26.73	23,208	26.47	1,271	32.51
40-49 years	17,006	18.57	16,250	18.53	756	19.34
50-61 years	5,275	5.76	5,117	5.84	158	4.04
Other psychiatric disorders:						
Any psychiatric disorder excluding mood disorders	35,493	38.75	33,765	38.51	1,728	44.19
Substance abuse disorders (excl. alcohol)	2,112	2.31	1,985	2.26	127	3.25
Alcohol abuse disorders	3,308	3.61	3,082	3.52	226	5.78
Non-affective psychosis	2,737	2.99	2,482	2.83	255	6.52
Anxiety disorders excluding OCD	23,088	25.21	22,017	25.11	1,071	27.39
OCD	838	0.91	801	0.91	37	0.95
Anorexia nervosa	583	0.64	562	0.64	21	0.54
Personality disorders	6,239	6.81	5,880	6.71	359	9.18
Mental retardation	365	0.40	349	0.40	16	0.41
Autism spectrum disorders	709	0.77	693	0.79	16	0.41
ADHD	976	1.07	952	1.09	24	0.61
Other behavioral and emotional disorders in childhood	1,943	2.12	1,871	2.13	72	1.84
Parental history of psychiatric diagnoses						
Any parental psychiatric disorder	24,799	27.08	23,599	26.92	1,200	30.69
Illicit substance abuse disorders	1,586	1.73	1,521	1.73	65	1.66
Alcohol abuse disorders	5,388	5.88	5,130	5.85	258	6.60
Psychotic disorders	3,177	3.47	2,983	3.40	194	4.96
Bipolar disorder	1,622	1.77	1,435	1.64	187	4.78
Unipolar depression	9,438	10.30	8,913	10.17	525	13.43
Anxiety disorders excluding obsessive compulsive disorder	11,389	12.44	10,928	12.46	461	11.79
Obsessive compulsive disorder	173	0.19	165	0.19	8	0.20
Anorexia nervosa	64	0.07	63	0.07	<5	-
Personality disorders	5,814	6.35	5,508	6.28	306	7.83
Mental retardation	67	0.07	62	0.07	5	0.13
Autism spectrum disorders	11	0.01	11	0.01	<5	-
Attention deficit hyperactivity disorder (ADHD)	157	0.17	154	0.18	<5	-
Behavioral and emotional disorders in childhood (not ADHD)	242	0.26	232	0.26	10	0.26

Figure 1. Sample Selection

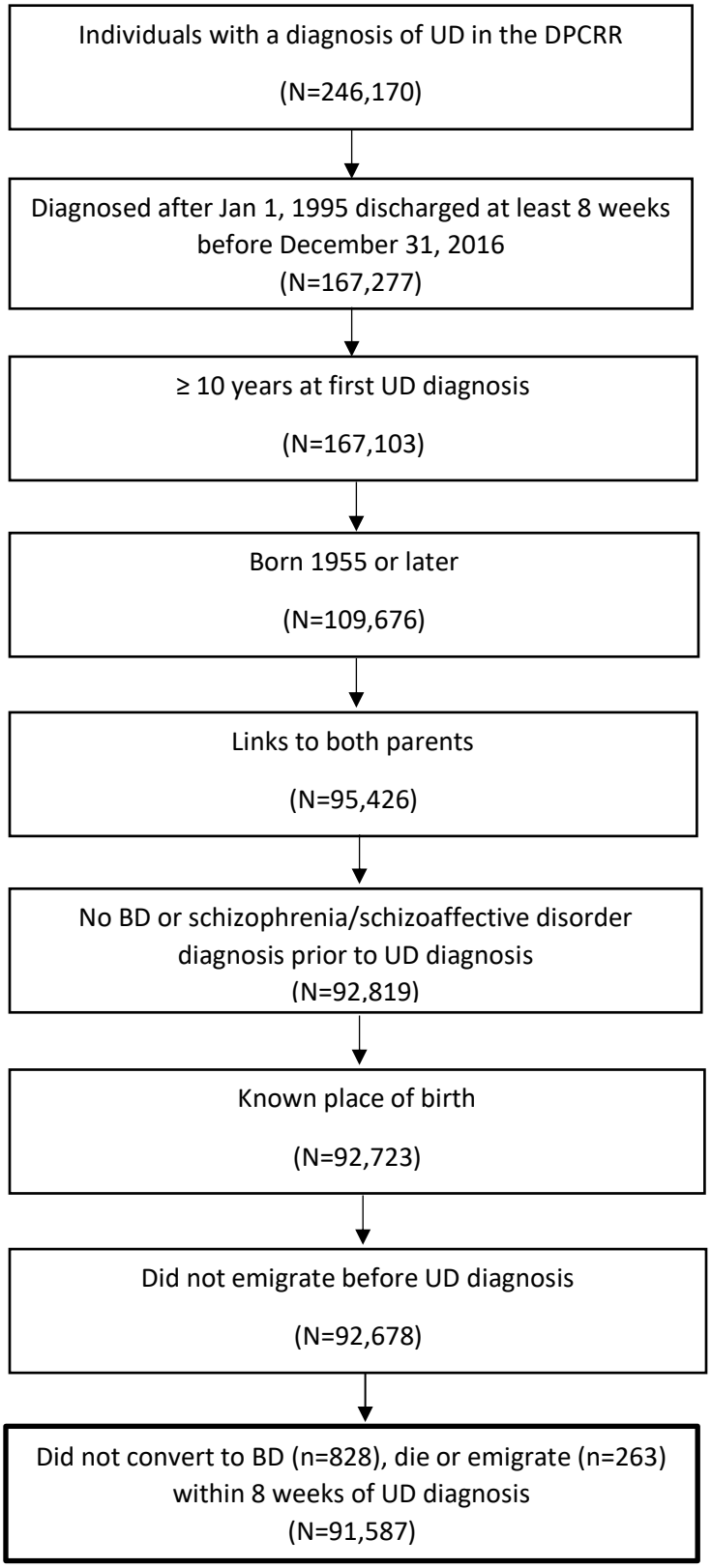
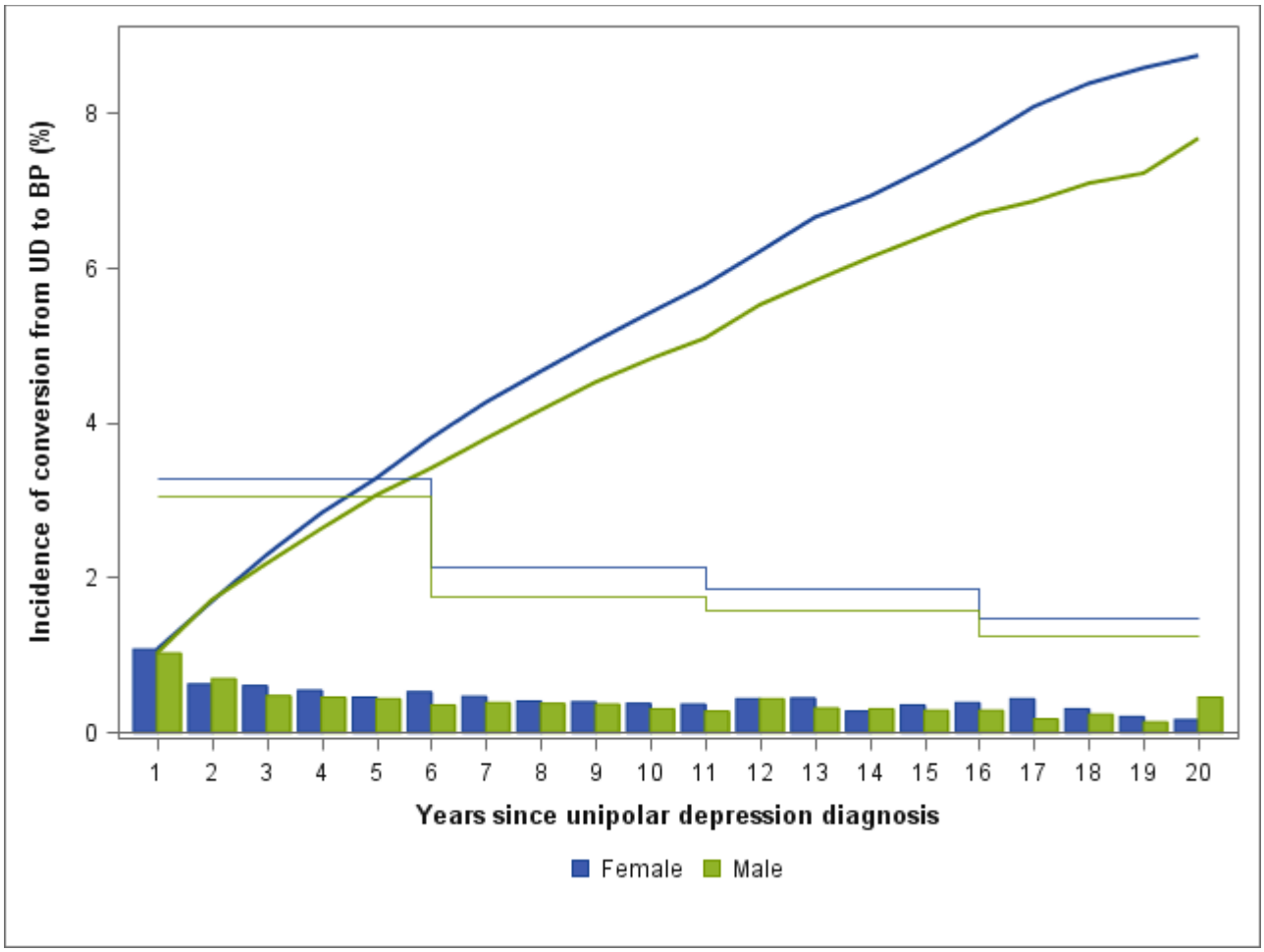
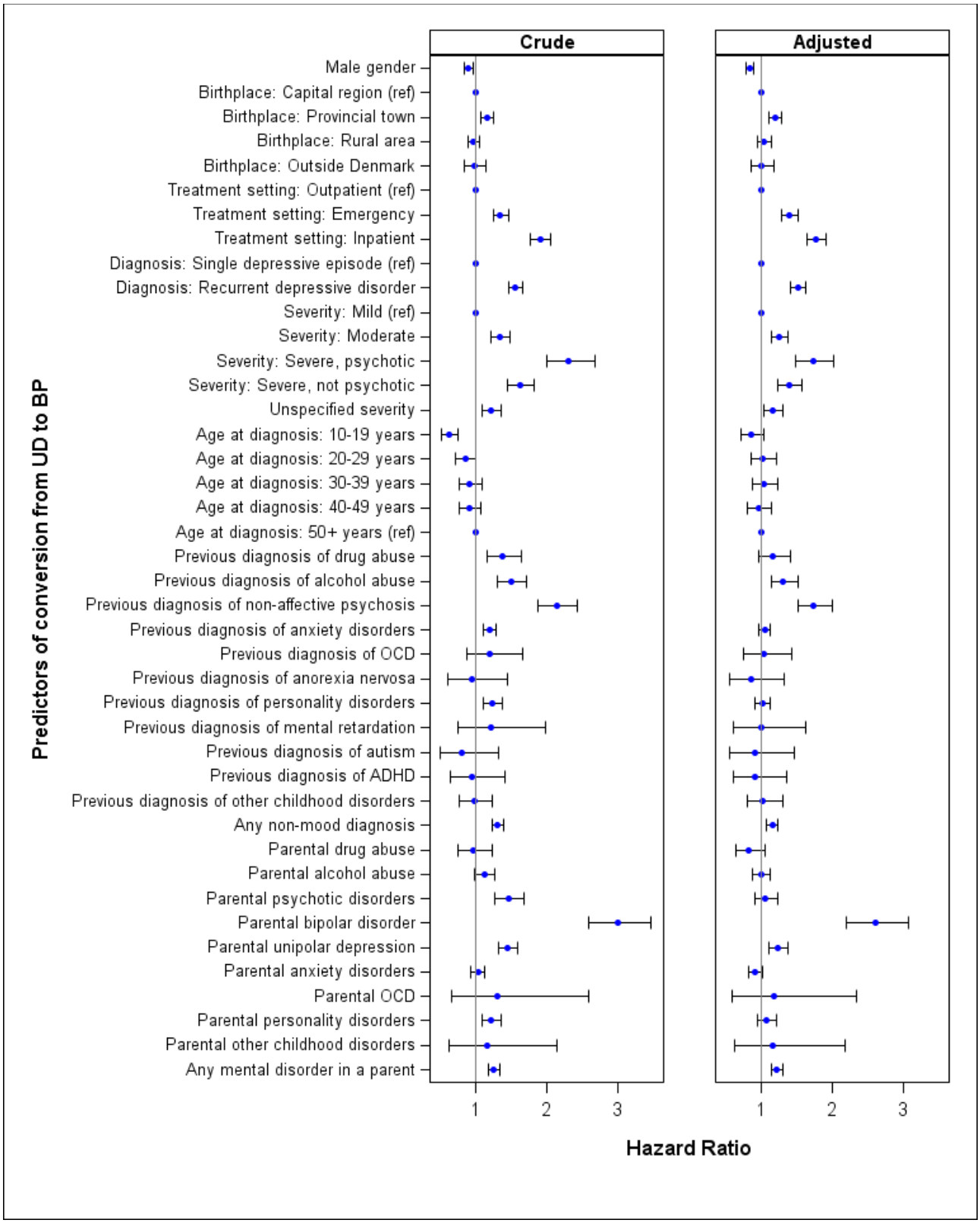


Figure 2. Incidence of conversion from UD to BD



UD = unipolar depression; BD = bipolar disorder. Bars represent the yearly incidence of conversion from UD to BD. Thin lines represent the incidence of conversion in 5-year blocks (e.g. the incidence of conversion between 6 and 10 years after the index UD diagnosis). Thick lines represent the overall cumulative incidence of conversion over the 20-year follow-up period.

Figure 3: Crude and adjusted hazard ratios for predictors of conversion from UD to BD



UD = unipolar depression, BD = bipolar disorder, OCD = obsessive compulsive disorder, ADHD = attention-deficit hyperactivity disorder

Figure 4: Cumulative incidence of conversion to bipolar disorder among patients with unipolar depression with different characteristics