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Longitudinal outcomes in pediatric- and adult-onset bipolar patients compared to healthy and schizophrenia controls

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Abstract

Objectives: Comparing outcomes of bipolar disorder (BD) with schizophrenia (SCZ) and psychiatrically healthy controls (PHC), contrasting pediatric-onset with adult-onset disorders.

Methods: A nationwide cohort study, including patients with an incident diagnosis of BD or SCZ registered in the Danish National Patient Registry and corresponding PHCs. Outcomes were 1) duration of hospitalization, 2) psychiatric admissions, 3) psychiatric outpatient contacts, 4) bone-fracture-related healthcare contacts, 5) self-harm-related healthcare contacts (including suicide and non-suicidal self-injuries), and 6) criminal charges. Incidence rate ratios (IRRs), adjusted for age at first psychiatric contact, substance abuse and parental psychiatric illness, were calculated, comparing pediatric-onset BD (5-17 years) and adult-onset BD (18-39 years) with age- and sex-matched SCZ patients and PHC.

Results: Pediatric-onset BD (n=349) performed better than 1:1-matched pediatric-onset SCZ (n=349) on all 6 outcomes (IRR=0.30 for self-harm-related contacts ($p<0.001$) to IRR=0.86 for criminal charges ($p=0.05$). Similar, but less pronounced results were observed comparing 1:1-matched adult-onset BD (n=5,515) with adult-onset SCZ (n=5,515) IRR=0.58 for psychiatric outpatient contact ($p<0.001$) to IRR=0.93 for criminal charges ($p<0.001$), except for more bone-fracture-related contacts in adult-onset BD (IRR=1.13, $p<0.01$). Comparing pediatric-onset BD (n=365) to 1:3-matched PHC (n=1,095), only self-harm-related contacts differed significantly

(IRR=2.80, p<0.001). Conversely, comparing adult-onset BD (n=6,005) with 1:3-matched PHC (n=18,015), self-harm-related contacts (IRR=16.68, p<0.001), bone fractures (IRR=1.74, p<0.001), and criminal charges (IRR=2.03, p<0.001) were more common in BD.

Conclusion: BD was associated with poorer outcomes than PHC, but better outcomes than SCZ. Furthermore, outcomes were more favorable in pediatric-onset BD when indirectly contrasted to adult-onset BD.

Key Words: bipolar disorder, schizophrenia, age-of-onset, outcome, criminality, self-harm, hospitalization, outpatient, bone-fractures,

Introduction

Bipolar disorder (BD) is a severe mental disorder affecting children, adolescents and adults, with both sexes being affected equally.[1] The estimated prevalence in adults is approximately 1.0% (BD-1 and BD-2)[2] and among adolescents it is 1.8% (threshold bipolar spectrum disorders)[3]. A recent nationwide Danish register-based study suggested an increasing incidence of diagnosed BD among children and adolescents over the past decade[4] , similar to findings from the USA showing an increase in rates of both psychiatric hospitalization[5,6] and outpatient treatment[7] in patients with pediatric-onset of BD.

An increased recognition and identification of pediatric-onset BD in the last two decades could be part of the reason for the observed increase in prevalence..[5,8] This perspective is supported by several studies of adults diagnosed with BD, showing that BD often debuts in late adolescence,

though the disorder is not diagnosed before adulthood,[9–11] and that the diagnosis is often delayed for years.[12,13] Goodwin and Jamison reported that most patients had onset of BD symptoms between the age of 15-19 years, with a relatively large group having first symptoms as early as 10-14 years of age.[1]

Pediatric-onset BD has been associated with poorer outcome, i.e., greater severity of depression and mania, larger number and longer duration of episodes, compared with adult-onset BD.[13–15] BD is associated with significant morbidity and mortality, has a reduced life-expectancy of 9-20 years,[16–18] and a more than ten-fold increased risk of suicide as cause of death compared to the general population.[17,19] Additionally, a recent nationwide study with 20 years of follow-up found an increasing standardized mortality ratio over the last twenty years in patients diagnosed with BD compared to the general population, with SMR being highest in the age group 15–29 years old.[20] Furthermore, patients with pediatric-onset BD are more likely to engage in suicidal behavior,[21] and pediatric-onset BD is also associated with a high rate of suicide attempts.[22,23].

Additionally, a strong association between criminal activity and BD has been shown, with substance abuse comorbidity being a mediating factor,[24,25] but a potentially increased risk of criminal acts has yet not been investigated in children and adolescents with BD. Lastly, Su et al. found BD in adults to be associated with a higher risk of fractures than matched controls.[26] Moreover, investigations of the relationship between self-harm acts and BD, stratified by age, based on comparisons to a psychiatric control group and a non-psychiatric control group is to our knowledge currently missing. Lastly, a possible association between pediatric-onset BD and risk of fracture has not yet been investigated.

Due to the scarcity of outcome studies in pediatric-onset BD as outlined above, we aimed at investigating the relative incidence rates of self-harm acts (including both suicide, suicidal behavior and non-suicidal self-injurious behavior), criminal charges, and health-care contacts due to bone fractures, comparing patients with incident BD to patients with incident schizophrenia (SCZ), and to psychiatrically healthy controls (PHC), stratifying on age-at-onset. Secondly, in the same way, we aimed to investigate psychiatric admissions and psychiatric outpatient contacts. Thirdly, we aimed at investigating the annual rate of days hospitalized in a psychiatric department over time. We compared pediatric-onset as well as adult-onset BD with SCZ and PHC, with the purpose of making an indirect comparison between age groups in BD.

Based on the prior literature, we hypothesized that independent of age-of-onset age group, outcomes in bipolar disorder would be more severe than in PHCs, but less unfavorable versus schizophrenia, and that pediatric-onset BD would have worse outcomes than adult-onset BD.

Methods

Design

A nationwide register-based cohort study, designed to indirectly compare outcomes of pediatric-onset BD with adult-onset BD over time, by using patients diagnosed with SCZ and PHCs as age-matched and age-of-onset-matched direct comparators, thereby partly removing the influence of differences in pediatric and adult services, as well as reducing the possible confounding effects of age.

Registers utilized

Data from registers were linked to the individual via the unique personal identification number (CPR number), assigned to all residents in Denmark at birth or upon immigration by the Civil Registration System.[27] The Danish Psychiatric Central Research Register (DPCRR)[28] contains information about all patients in contact with the hospital-based psychiatric services in Denmark from 1969 and onward. The Danish National Patient Register (NPR)[29] contains information from 1977 and onward concerning every contact with any type of hospital in Denmark, including psychiatric hospitals from 1995 and onward. The Danish Central Crime Register contains information from November 1st 1978 and onward on total number of criminal charges and convictions and dates of crimes and convictions.[30]

The Danish Register of Causes of Death contains information on causes of death on all citizens in Denmark.[31] From 1994 and onward the classification of cause of death is done by ICD-10 codes. Date of death was retrieved from the Civil Registration System.[27]

Study population

All patients diagnosed with incident BD from age five years until and including age 39 years, defined as an incident single manic episode or bipolar disorder (ICD-10: F30.X or F31.X),[32] diagnosed in the NPR[29] between January 1st 1995 and December 31st 2013, were included and followed for at least one year until December 31st 2014. Follow-up began at time of inclusion. Follow-up ended on December 31st 2014, or when the patient emigrated or died, whichever came first.

Patients were divided into two groups based on age at index diagnosis; a pediatric-onset group ranging from age 5 years to <18 years of age at index diagnosis, and an adult-onset group, ranging from 18 years to <40 years of age at index diagnosis.

The upper limit of <40 years old were chosen arbitrarily because of a possible increased risk of co-morbidities, as well as organic affective disorders in patients diagnosed at a later age. Patients with a BD diagnosis in the DPCRR[28] or in the NPR[29] (ICD-8: 296.1, 296.2, 296.3, 296.8, 296.9 and 298.1[33] or ICD-10:F30.x-F31.x)[32] prior to January 1st 1995 were excluded, as they would not have had an incident BD diagnosis between January 1st 1995 and December 31st 2013.

BD patients were matched on sex, date of birth within one year, and age at first time diagnosis within one year to patients diagnosed with incident schizophrenia (SCZ) (ICD-10: F20.X).[32] Again, patients with a SCZ diagnosis in the DPCRR[28] or in the NPR[29] (ICD-8: 295, excl. 295.7[33], or ICD-10 F20.x)[32] prior to January 1st 1995 were excluded, as they would not have had an incident SCZ diagnosis between January 1st 1995 and December 31st 2013.

Similarly, patients with BD were matched on sex and date of birth within one year to psychiatric healthy controls (PHC) from the general population, defined as having no psychiatric diagnosis prior to index date. Index for the PHC was defined as age of diagnosis for the corresponding BD match. PHC needed to be alive at defined time of diagnosis for the BD match.

Patients from the BD cohort later diagnosed with SCZ between January 1st, 1995 and December 31st, 2014 were counted in the group of patients with SCZ only. Likewise, patients from the SCZ cohort later diagnosed with BD between January 1st, 1995 and December 31st, 2014 were counted in the group of patients with BD only.

Patients were excluded if they were not registered in the Civil Registration System[27] at least five years prior to index.

Outcome measures

Annual rate of days hospitalized in a psychiatric ward, defined as the number of days hospitalized in a psychiatric ward after index, per calendar year. Contacts to a psychiatric ward was defined as being registered in the part of the NPR[29] containing psychiatric contacts or in the part of the NPR containing somatic contacts, with a primary diagnosis of any psychiatric disorder (ICD-10: Fxx.x), intentional self-harm acts (ICD-10: X60-X84) or an event of undetermined intent (ICD-10: Y10-Y34)[34].

Number of admissions in a psychiatric ward during the study period, defined as the number of admissions in a psychiatric ward after index during the study period, as defined above.

Number of psychiatric outpatient contacts in a psychiatric ward during the study period, defined as the number of outpatient contacts to a psychiatric facility after index during the study period, as defined above.

Number of self-harm acts, defined as the number of contacts to hospital-based treatment because of intentional self-harm acts (ICD-10: X60-X84) and event of undetermined intent (ICD-10: Y10-Y34),[34] including both suicide, suicidal behavior and non-suicidal self-injurious behavior, after index, during the study period. Data were retrieved from NPR[29] as defined above and from the Danish Register of Causes of Death.[31]

Number of health-care contacts as a result of a bone-fracture, defined as the number of contacts to hospital-based treatment because of; cranial fracture (ICD-10 S02), upper cervical fracture (ICD-10 S02), rib fracture (ICD-10 S12), lower cervical fracture (ICD-10 S22), shoulder fracture (ICD-10 S32), fracture of elbow or arm (ICD-10 S42), fracture of hand and wrist (ICD-10 S52), femur fracture (ICD-10 S62), fracture of knee (ICD-10 S72), lower leg and ankle fracture (ICD-10 S82) and fracture of the foot (ICD-10 S92).[34] Further, defined as the number of contacts to hospital-based treatment because of fracture surgery; in the spine (SKS: KNAJ), in the shoulder and upper arm (SKS: KNBJ), in the elbow and lower arm (SKS: KNCJ), in the hand and wrist (SKS: KNDJ), in the pelvis (SKS: KNEJ), in the upper leg (SKS: KNFJ), in the knee and lower leg (SKS: KNGJ), in the ankle and foot (SKS: KNHJ) and in the nose (SKS: KDJD30, KDJD40)[35] during the study period after index. Sundhedsvæsenets Klassifikations System (SKS) is the classification system used for surgery and procedures related to surgery in the Danish Health System. The SKS is maintained by the Danish Data Health Authorities who also support the SKS web browser, where any code related to surgery can be identified.[35] Data were retrieved from the NPR.[29]

Number of criminal charges, defined as the number of criminal charges for each participant received after index, during the study period. Data were retrieved from the Danish Central Crime Register.[30]

Confounding variables

Age at first psychiatric contact ever; data were retrieved from the DPCRR[28] and the NPR.[29]

Substance abuse, including alcohol (ICD-8: 291.0, 291.1, 291.2, 291.3, 291.9, 303.0, 303.1, 303.2, 303.9[33] or ICD-10: F10.X[32]), cannabis (ICD-8: 304.5[33] or ICD-10: F12.X[32]) or substances other than alcohol or cannabis (ICD-8: 294.3, 304.X, excl. 304.5[33], or ICD-10: F11.X, F13.X-F19.X[32]), dichotomized to misuse of one or more of the three above categories (yes/no). Substance abuse was implemented as a time-dependent variable. Data were retrieved from the DPCRR[28] and the NPR.[29]

Psychiatric family risk factors were defined as a sum score for the parent registered.

Firstly, the total psychiatric score for each parent was calculated as the number of diagnostic groups, that the parent had been ascribed. Parents could only receive points for one diagnosis within each diagnostic group.

Lastly, the mean psychiatric score was calculated as the sum of the psychiatric scores from parents divided by the number of parents registered.

This mean parental psychiatric illness score was used as a proxy measure of family disposition for psychiatric disorders.[36] Parents were identified from the CPR system,[27] where all children are linked to their mother and father, if possible. All parents were followed from start of the register until index date.

Psychiatric disorders were divided into the following five groups: Psychosis (ICD-8: 295, excl. 295.7 and 295.8, 297, 298, excl. 298.0 and 298.1, 299[33] or ICD-10: F20.X, F22.X-25.X, F28.X-29.X[32]), affective disorders (ICD-8: 296.0, 296.1, 296.2, 296.3, 296.8, 296.9, 298.0, 298.1, 300.4[33] or ICD-10: F30.X-F33.X[32]), substance misuse (ICD-8: 291.0, 291.1, 291.2, 291.3, 291.9, 294.3, 303.0, 303.1, 303.2, 303.9, 304[33] and ICD-10: F.1X.X[32]), other (ICD-8: 290 to 315 (excluding the above mentioned)[33] or ICD-10: Fxx.x (excluding the above-mentioned ones),[32] and intentional self-harm (ICD-8: E950-E959, E980-E989[33] or ICD-10: X60-X84, Y10-Y34[34]).

Data were retrieved from the DPCRR[28] and the NPR.[29]

Statistical analysis

Initially, we conducted descriptive analyses on baseline data using Fisher's exact test, or Students t-test where appropriate.

Secondly, we performed linear regression analyses on the annual number of days hospitalized in a psychiatric ward, comparing patients with incident BD to patients with incident schizophrenia. This analysis was performed both for the entire study period and also for only two years of follow-up to restrain follow-up within the pediatric-onset sample predominantly to pediatric services.

Additionally, we conducted multi-event Cox regression analyses on health-care contacts due to fractures, self-harm acts, criminal charges, psychiatric admissions and psychiatric outpatient contacts, comparing patients with incident BD to patients with incident SCZ, resulting in incidence rate ratios (IRR) for all outcomes. Analyses were adjusted for substance abuse, psychiatric family risk factors, and age in years at first psychiatric contact, employing restricted cubic splines for the age variable.

Thirdly, we performed multi-event Cox regression analyses on health-care contacts because of a fracture, self-harm acts and criminal charges, comparing patients with incident BD to PHCs, resulting in incidence rate ratios (IRR) for all outcomes. Analyses were adjusted for psychiatric family risk factors.

Psychiatric family risk factors were calculated by using the sum of the score ascertained by each parent, divided by the number of parents registered. In the analyses, this variable was considered as a linear continuous variable.

Moreover, as supplement to the Cox regression analyses, we constructed group-stratified histograms illustrating the distribution of number outcome events pr. subject, with zero events excluded to avoid inflation. For histograms comparing BD with PHC, we scaled the histograms for the BD group with a factor three in order to preserve between group comparisons. Utilizing anonymized healthcare register data prohibits us from publishing data in which single patients could be identified, and as a result, any frequency strata with less than four patients was not shown.

Lastly, we conducted sensitivity analyses for all of the regression analyses above, in which we did not adjust for psychiatric family risk factors or substance abuse. Furthermore, we conducted sensitivity analyses on health care contacts because of fractures, in which we conducted regression

analyses on healthcare contacts due to any fracture excluding cranial fracture and on healthcare contacts due to a cranial fracture only.

All analyses were stratified by age of onset at index, and subjects were followed from index date until end of study, emigration or death, whichever came first. P-values <0.05 were considered statistically significant. Statistical analyses were performed with Stata 15 (StataCorp. Stata Statistical Software. College Station, TX: StataCorp LLC. 2017; Release 15).

Results

Altogether, 6,370 patients with an incident diagnosis of BD were included in the study (adult-onset: n=6,005, pediatric-onset: n=365). We successfully matched 5,515 adults with incident BD to an equal number of adults diagnosed with incident SCZ, and 349 children and adolescents with incident BD to an equal number of incident SCZ. Furthermore, we successfully matched 1:3 all patients with BD to 19,110 PHC (adult-onset: n=18,015, pediatric-onset: n=1,095), as shown in figure 1.

The mean duration of follow up in the pediatric-onset and adult-onset BD groups matched with the PHC were 7.46 years (2,721 patient years) and 7.15 years (42,938 patient years), respectively. The mean duration of follow up in the pediatric and adult PHC groups were 7.20 years (7,887 patient years) and 7.08 years (127,619 patient years), respectively. The mean duration of follow up in the pediatric-onset and adult-onset BD groups matched with SCZ were 4.49 years (1,567 patient years) and 4.70 years (25,900 patient years), respectively. The mean duration of follow up in the pediatric-onset and adult-onset SCZ groups were 4.23 years (1,475 patient years) and 4.43 years (24,407 patient years), respectively.

Figure 2 and figure 3 demonstrate incident pediatric-onset and adult-onset BD subjects distributed by calendar year during the study period, and show that a more patients are diagnosed with BD late in the study period in both age groups as compared to early in the study period.

Mean age at first psychiatric contact for patients with pediatric-onset BD was 1.5 years lower than the mean age at first BD diagnosis, a similar 1.5 year diagnostic lag time existed in pediatric-onset SCZ. Mean age at first psychiatric contact for patients with adult-onset BD and SCZ were 4.2 and 4.6 years lower than the mean age at first BD and SCZ diagnoses, respectively (table 1). Furthermore, similar proportions of pediatric patients with BD (9.7%) and SCZ (9.5%) had substance abuse before the index diagnosis, but more were diagnosed with substance abuse at the time of or after index diagnosis in the SCZ (14.6%) than BD (11.8%) group. Approximately the same proportions of pediatric PHCs were diagnosed with substance abuse at time of or after index diagnose of corresponding matched BD patient (13.8%). Similar results were found for adult-onset disorders, with 27% and 30% of BD and SCZ patients, respectively, having a substance abuse diagnosis before index diagnosis, and more patients with SCZ (9.8%) than BD (8.1%) received a substance abuse diagnosis at time of or after index diagnosis. Only a minor proportion of adult PHCs were diagnosed with substance abuse at time of or after index diagnose of corresponding matched BD patient (2.6%) (table 1). Parental disposition for psychiatric disorder was similarly frequent across groups with BD and SCZ (31.2-36.7%), but expectedly significantly more frequent than in the PHC (16.0-16.2%) groups (table 1). Remaining confounding variables are shown in Table 1.

The mean annual number of days hospitalized for pediatric-onset BD (15.7 days) and adult-onset BD (13.1 days) during the entire study period was about half as much as for pediatric-onset SCZ (32.9 days, $p<0.001$) and adult-onset SCZ (27.9 days, $p<0.001$) groups (table 2).

Similarly, in the pediatric-onset and in the adult-onset group, the mean number of confounder-adjusted days psychiatrically hospitalized per year for the first two years after diagnosis was also about half and statistically significantly shorter in the BD than the schizophrenia group, although the annual number of hospital days was higher in the first two years than across the entire follow-up period (table 2).

In adjusted multi-event Cox regression models, all outcomes related to all-cause or cause-specific health contacts yielded significantly lower IRRs for pediatric-onset BD (n=349) than for 1:1-matched pediatric-onset SCZ (n=349) (IRR=0.30 for self-harm-related contacts ($p<0.001$) to IRR=0.86 for criminal charges ($p=0.05$) (table 3). Similar, but less pronounced results were observed comparing 1:1-matched adult-onset BD (n=5,515) with adult-onset SCZ (n=5,515) (IRR=0.58 for psychiatric outpatient contact ($p<0.001$) to IRR=0.93 for criminal charges ($p<0.001$), except for more bone-fracture-related contacts in adult-onset BD (IRR=1.13, $p<0.01$) (table 3).

Comparing pediatric-onset BD (n=365) to 1:3-matched PHC (n=1,095), only self-harm-related contacts differed significantly (IRR=2.80, $p<0.001$) (table 3). Conversely, comparing adult-onset BD (n=6,005) with 1:3-matched PHC (n=18,015), self-harm-related contacts (IRR=16.68, $p<0.001$), bone fractures (IRR=1.74, $p<0.001$), and criminal charges (IRR=2.03, $p<0.001$) were more common in BD (table 3).

Graphs showing the distribution of frequencies related to each outcome measure presented in Table 3 are shown in supplementary material. Utilizing anonymized healthcare register data prohibits us from publishing data in which single patients can be identified, and as a result, frequency strata with less than four patients are not shown.

Patients from the BD cohort later diagnosed with SCZ or vice versa were counted in the group in which they were diagnosed latest. Patients with BD matched 1:1 with SCZ diagnosed between January 1st 1995 and December 31st 2013 who earlier in this period had been diagnosed with SCZ comprised n=278 (5.04%) of the 18-39 years old and n=8 (3.15%) of the 5-17 years old subjects. Patients with SCZ matched 1:1 with BD diagnosed between January 1st 1995 and December 31st 2013 who earlier in this period had been diagnosed with BD comprised n=168 (3.05%) of the 18-39 years old and n=<4 of the 5-17 years old subjects.

Sensitivity analyses of all outcomes removing psychiatric family risk factors and substance misuse yielded similar results (data shown in supplementary material).

Likewise, shown in supplementary material are sensitivity analyses on healthcare contacts due to any fracture excluding cranial fracture and healthcare contacts due to a cranial fracture. The sensitivity analyses did not differ from the main analysis.

Discussion

In this study of 6,370 patients with BD, we found in the 365 patients with pediatric-onset BD compared to a 1:1 matched sample of pediatric-onset SCZ patients a 28% lower incidence rate of psychiatric outpatient contacts, 56% lower incidence rate of psychiatric admissions, 70% lower incidence rate of self-harm acts, 32% lower incidence rate of contacts due to bone fracture, and a 14% lowered incidence rate of criminal charges. Similarly, adult-onset BD versus matched SCZ

patients had a 42% lower incidence rate of psychiatric outpatient contacts, 28% lower incidence rate of psychiatric admissions, 15% lower incidence rate of intentional self-harm acts, 7% lower incidence rate of criminal charges, but a 13% higher incidence rate of healthcare contacts because of bone-fractures. Comparing pediatric-onset BD to matched PHC, an IRR of 2.80 for self-harm acts was found. In adult-onset BD this finding was more pronounced with an IRR of 16.68, and for this group, also higher healthcare contacts were observed due to bone-fractures and criminal charges compared to PHC.

In the current study, patients with BD had a lower incidence of psychiatric outpatient contacts and admissions compared to matched patients with SCZ in both the adult-onset and pediatric-onset groups. Regarding psychiatric outpatient contacts, the difference between BD and SCZ was largest in the adult-onset patients, whereas regarding psychiatric admissions, the difference was largest in the pediatric-onset patients. One possible explanation for these findings is that in children and adolescents BD often debuts with mixed episodes and depression rather than full blown mania,[37,38] and that these episodes are more likely to receive outpatient treatment, rather than inpatient treatment.

Furthermore, we found that, the incidence rate of self-harm acts was almost 17 times higher for patients with adult-onset BD compared to PHC. These findings are partly consistent with a study by Webb et al.[25] who reported an increased risk of attempted suicide with a risk ratio of 14.3. Self-harm in pediatric-onset BD has only scarcely been investigated previously, but a review by Hauser et al.[23] that investigated fourteen studies of children and adolescents with BD aged 18 or younger (mean age=14.4 years) showed a substantial risk of suicidal ideation and suicide attempts, with one out of two youth with BD having a past or current suicidal ideation, and one out of four having past or current suicide attempts in a population. In the current study, patients with pediatric-onset BD had an almost three-fold incidence of contacts due to deliberate self-harm acts than PHC. The

number of successful suicide attempts in the pediatric-onset BD group was too low to be investigated in the current study.

Consistent with our findings of increased healthcare contacts due to bone fractures in adults, Su et al. showed an increased risk of fractures in patients with BD compared with healthy controls.[26] In addition, Hsu et al. found that a BD diagnosis was an independent risk factor for bone-fractures, regardless of sex, age and comorbidities in a population of patients >16 years old.[39] To our knowledge, this is the first study to investigate the incidence of bone fractures in children and adolescents diagnosed with BD, and in contrast to the findings in adults, children and adolescents did not have an increased incidence of bone fractures compared to PHCs. Moreover, we observed a lower incidence of bone-fractures in children and adolescents diagnosed with BD compared to age- and sex-matched controls diagnosed with SCZ, whereas a higher incidence of bone-fractures was observed in adult-onset BD versus adult-onset SCZ.

The higher number of contacts due to bone-fractures in adult-onset BD versus SCZ and PHC in contrast to the findings in pediatric-onset BD could in part be explained by the age difference. The lifestyle of adults with BD is often characterized by poor diet[40], sedentary lifestyle with low physical activity[41], smoking[42] and substance misuse.[43] The relatively poorer physiological health in adults combined with risky, impulsive and sometimes even violent behavior, which is associated with BD especially in manic phases,[44,45] could also potentially increase the risk of fractures in adults with BD more than in youth. Furthermore, and maybe more importantly, another consequence of age is that adults unlike children and adolescents often live alone, and due to the episodic nature of BD contrary to schizophrenia, it can be difficult to provide sufficient social support at the right time. Hence, a severe mood episode in patients with BD living alone could more likely lead to behaviors resulting in a bone-fracture. It is unclear, however, why pediatric-onset SCZ is associated with a higher incidence rate of contacts due to bone-fractures than pediatric-onset BD, but this

might be explained by more disorganized behaviors and our result of increased self-injuries and suicidal behavior in pediatric-onset SCZ.

The correlation of criminal charges and pediatric BD has not been studied extensively. However, in the abovementioned study by Webb et al.[25] who included patients aged ≥15 years, an elevated risk of both violent crime and non-violent crime was found in cohort members with BD compared to the general population. Despite different methodologies, the findings by Webb et al.[25] are supported by the results in the current study with an incidence of criminal activity twice as high in adult-onset BD compared to PHC, but without a significant difference between pediatric-onset BD and PHC. Another study by Fazel et al.[24] investigated the association between BD and violent crime comparing patients with BD to the general population, and reported an adjusted odds ratio (OR) of 2.3 (95% CI: 2.0-2.6). However, the increased risk was attenuated in patients without a comorbid substance abuse diagnosis (OR=1.3 (95% CI: 1.0-1.5)). The findings were consistent with our results in adult-onset BD.

In general, contrasting the findings of IRR in pediatric-onset BD to adult-onset BD results show that compared to their matched psychiatrically ill SCZ as well as PHC, patients with adult-onset BD are doing worse than patients with pediatric-onset BD on all outcome measures except on number of outpatient contact. These findings are in contrast to several studies that have shown that pediatric-onset BD is generally associated with poorer outcomes than adult-onset BD.[12–14,46] However, results similar to ours were found in a 15-year follow-up study, where outcome in adolescents were better than outcomes in adults.[9] Possible explanations for the better outcomes in youth than adults with BD in this study include the far shorter gap between first psychiatric outpatient contact and diagnosis of BD in youth vs adults (1.5 to 4.5 years). Although we adjusted the statistical analyses for this dissimilarity, this systematic difference may not be fully adjustable and be related to other, unmeasured variables that significantly moderate or mediate outcomes, such

as closer contact to family members who can aide care and improve adherence to treatment. Further reasons for our different findings may include that in Denmark only very few youth are diagnosed with BD before age 15, a trend that is different in the US.[47] Other reasons could be that the outcome measures we include were somewhat different from outcome-measures used in other studies and that mean follow-up time was longer in our study. Furthermore, we were able to use a nationwide cohort that included all patients, and healthcare is free of charge, which both is not the case in the US studies.[5–7,12] Finally, to reliably compare outcomes of pediatric-onset and adult-onset BD over time, it is really necessary to make an indirect comparison, as pediatric and adult psychiatric services differ in content and intensity, and as service characteristics, including criteria for and duration of inpatient care, may also change over the time of the study period. Therefore, different from prior studies, we were able to contrast the differences between the pediatric-onset groups and the adult-onset groups by directly comparing the pediatric- and adult-onset BD groups with age-matched groups diagnosed with SCZ, thereby removing the influence of the differences in pediatric and adult services and also overcoming the influence of potential confounding effect of age.

The strength of this study lies in the use of the Danish healthcare registers, which enabled us to follow all people diagnosed with BD and SCZ with almost no loss to follow-up over extended periods of time owing to the systematic and mandatory reporting from clinicians to the registers. All data from in- and outpatient treatment from the public hospital-based healthcare system in Denmark is automatically send to the registers. Unfortunately, general practitioners and private psychiatrists do not report to the NPR, resulting in an underreporting of patients with less severe symptoms of psychiatric disorders, e.g., patients with only hypomanic episodes and milder depression and patients with less severe symptoms of schizophrenia. This limitation might have led to higher relative IRRs, yet results pertain to a clinically relevant sample requiring psychiatric care.

If healthcare is free of charge, nationwide register-based healthcare studies include patients independent of socioeconomic status. Since this is the case in Denmark, the present study included almost all people with at least a moderately severe psychiatric disorder, which is a strength of the study. However, generalizability to countries with less free access to healthcare services could be limited.

The relative good outcome of patients with pediatric-onset BD as compared to matched PHC versus that of adult-onset BD as compared to matched PHC could be a result of a relative intense treatment offered the young population in the Danish healthcare system. Likewise, our finding that pediatric-onset-BD differed more from pediatric-onset SCZ than adult-onset BD differed from adult-onset SCZ could at last in part be attributed to different services provided to these diagnostic groups, although it might also be explained by differential impact by the diagnoses per se. Taken together, special characteristics of the Danish healthcare system, for example that the healthcare is free of charge in contrast to many other countries, may limit the generalizability of our findings to other populations. However, it should be born in mind that direct comparison of our study findings to those of other studies conducted in other settings are not possible because of differences in study design.

The relatively larger group diagnosed with BD late in the study period contributed with relatively shorter follow-up time, however, this situation is not considered a problem for the results, as subjects are matched on sex, date of birth and date of diagnosis.

Furthermore, the clinical diagnoses from the registers might not have been valid in all patients. A few attempts have been made to investigate validity of the diagnoses used in the present study, which might indicate that the validity of diagnoses could be higher among adult-onset psychiatric disorders[48,49] than pediatric-onset psychiatric disorders.[50]

Finally, due to the observational study design, results consist of associations and causality cannot be inferred.

In conclusion, pediatric-onset BD appears to have a better prognosis at least as defined by lower psychiatric and fracture-related somatic service use as well as by fewer criminal charges compared to age-matched SCZ patients, used as psychiatric controls, but have a significantly worse prognosis than PHC on intentional self-harm acts. Likewise, adult-onset BD appears to have a better prognosis as defined by lower psychiatric service use and by fewer criminal charges compared to SCZ patients, but a worse prognosis than PHC, especially on intentional self-harm acts, but also on fracture-related somatic service use and on criminal charges.

. We compared pediatric-onset and adult-onset BD indirectly over time, through contrasting IRR of pediatric-onset BD and SCZ with IRR of adult-onset BD and SCZ, which showed that patients diagnosed with BD before age 18 had better outcomes than patients diagnosed with BD between age 18 and 39, relative to what was observed in the SCZ and the PHC controls. By comparing BD, SCZ and PHC, examining important outcomes, our results might contribute with evidence to future planning and distribution of resources for psychiatric specialized clinics. Furthermore, providing optimized and earlier interventions in both pediatric-onset BD and adult-onset BD will hopefully result in a better prognosis for both age groups.

Ethical considerations

The study was authorized by the Danish Data Protection Agency, id-number 2016-213. Approval of an ethical research committee was not required as data was anonymized and only used for research purposes.

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Table 1: Confounding variables in patients diagnosed with incident BD between January 1st 1995 and December 31st 2014, matched 1:1 with patients diagnosed with incident SCZ and 1:3 with PHC, stratified by age of onset.

	5-17 years						18-39 years					
	Bipolar disorder N=349		Schizophrenia N=349		PHC N=1,095		Bipolar disorder N= 5,515		Schizophrenia N=5,515		PHC N=18,015	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age at first psychiatric contact	14.57	3.29	14.53	3.34			25.45	7.42	24.63	7.25		
Age at index	16.03	1.76	16.08	1.66	15.32	2.14	29.65	6.18	29.26	6.21	30.19	6.48
Psychiatric family risk factors	0.32	0.51	0.29	0.53	0.13	0.34	0.31	0.55	0.29	0.53	0.13	0.35
	N	%	N	%	N	%	N	%	N	%	N	%
Females	212	60.74	212	60.74	648	59.18	3,121	59.59	3,121	59.59	10,821	60.07
Parents diagnosed with a psychiatric disorder prior to the patient's psychiatric diagnosis	128	36.68	112	32.09	177	16.16	1,811	32.84	1,721	31.21	2,885	16.01
Patients without a diagnosis of substance abuse	274	78.51	265	75.93			3,593	65.15	3,331	60.40		
Substance abuse before psychiatric diagnosis	34	9.74	33	9.46			1,477	26.78	1,642	29.77		
Substance abuse at time of or after the psychiatric diagnosis	41	11.75	51	14.61	151	13.79	445	8.07	542	9.83	461	2.56

Demographic data for children and adolescents (n=365) and adults (n=6,005) diagnosed with incident bipolar disorder matched 1:3 to PCH are not shown, as results are almost the same as for patients diagnosed with incident bipolar disorder matched 1:1 to incident SCZ.

BD= bipolar disorder
SCZ= schizophrenia
PHC= psychiatrically healthy controls

Table 2: Annual number of days of psychiatric hospitalization in patients diagnosed with incident bipolar disorder (BD) and schizophrenia (SCZ)

	5-17 years						18-39 years					
	Total study period			Max. two years after diagnosis			Total study period			Max. two years after diagnosis		
	Mean	95% CI	P	Mean	95% CI	P	Mean	95% CI	P	Mean	95% CI	P
Annual number of days psychiatrically hospitalized for patients with incident BD	15.7	12.7 18.8		25.6	20.8 30.3		13.1	12.5 13.9		20.4	19.3 21.6	
Annual number of days psychiatrically hospitalized for patients with incident SCZ	32.9	27.9 37.9		55.1	47.2 62.0		27.9	26.6 29.2		41.9	40.0 43.8	
Adjusted mean difference between patients with incident BD vs incident SCZ	-17.3	-23.2 -11.5	<0.001	-29.5	-38.7 -20.3	<0.001	-14.5	-16.0 -12.9	<0.001	-21.2	-23.4 -19.0	<0.001

Table 3: Incidence rate ratios of outcomes comparing patients with incident bipolar disorder (BD) to patients with incident schizophrenia (SCZ) and to psychiatrically healthy controls (PHC), stratified by age of onset. A multi-event analysis adjusted for psychiatric family risk factors when comparing BD with PHC, and adjusted for substance abuse, psychiatric family risk factors, and age in years at first psychiatric contact when comparing BD to SCZ.

	5-17 years										**18-39 years**									
	Bipolar disorder (n=349) versus schizophrenia (n=349)					**Bipolar disorder (n=365) versus PHC (n=1,095)**					**Bipolar disorder (n=5,864) versus schizophrenia (n=5,864)**					**Bipolar disorder (n=6,005) versus PHC (n=18,015)**				
	Event	**IRR**	**95% CI**		**P**	**Event**	**IRR**	**95% CI**		**P**	**Event**	**IRR**	**95% CI**		**P**	**Event**	**IRR**	**95% CI**		**P**
Contacts to an outpatient psychiatric department	16,126 vs 22,278	0.72	0.71	0.74	<0.001						307,550 vs 551,411	0.58	0.57	0.58	<0.001					
Psychiatric admissions	884 vs 2,091	0.44	0.41	0.48	<0.001						18,117 vs 27,084	0.72	0.71	0.73	<0.001					
Healthcare contacts because of intentional self-harm acts	41 vs 147	0.30	0.21	0.42	<0.001	42 vs 33	2.80	1.75	4.48	<0.001	590 vs 743	0.85	0.76	0.95	<0.01	617 vs 105	16.68	13.54	20.55	<0.001
Healthcare contacts because of a fracture	75 vs 112	0.68	0.50	0.91	<0.01	92 vs 288	0.93	0.73	1.18	0.553	1,559 vs 1,456	1.13	1.05	1.22	<0.01	1,616 vs 2,679	1.74	1.63	1.85	<0.001
Criminal charges	324 vs 413	0.86	0.74	0.99	<0.05	337 vs 988	0.93	0.82	1.05	0.254	5,966 vs 7,020	0.93	0.90	0.97	<0.001	6,084 vs 8,234	2.03	1.97	2.10	<0.001

Event are accounted during the entire study period from January 1st till December 31st 2014.