

Higher socio-economic status of parents may increase risk for bipolar disorder in the offspring

KENJI J. TSUCHIYA*, ESSEN AGERBO, MAJELLA BYRNE
AND PREBEN B. MORTENSEN

*Department of Psychiatry and Neurology, Hamamatsu University School of Medicine, Hamamatsu, Japan;
National Centre for Register-based Research, University of Aarhus, Denmark*

ABSTRACT

Background. There are conflicting data regarding the socio-economic risk factors for bipolar disorders. The aim of the present study was to explore the association between the socio-economic status of an individual or the parent and the risk for bipolar disorder.

Method. Two Danish registers were merged. From the data source, we extracted those born in 1960 or later, and those with a first-ever admission to, or contact with, Danish psychiatric facilities during 1981–1998 with a diagnosis of bipolar disorder. Fifty time-matched controls per case were chosen by the incidence-density sampling method. Effects of marital status, occupation, education, income, and wealth, of both subjects and the parents, were estimated using conditional logistic regression.

Results. A total of 947 cases were matched to 47 350 controls. Those at high risk of bipolar disorders were: single subjects, those in receipt of social assistance, pension or sickness payments, unemployed, subjects with a shorter educational history, and subjects with lower income. Conversely, parental higher education and higher level of paternal wealth were associated with increased risk. These associations remained significant after adjustment for gender, family history of psychiatric diagnoses, and other socio-economic variables, and are unlikely to be explained by known biases.

Conclusions. The associations of lower socio-economic indices of subjects may be explained as a consequence of the disease. The association of higher socio-economic indices of parents may be explained by socio-economic achievement in the family of origin.

INTRODUCTION

Early studies have implied that bipolar disorders (BPD) are more prevalent in subjects with higher socio-economic status (SES), e.g. longer history of education, executive professionals (Hirschfeld & Cross, 1982; Goodwin & Jamison, 1990; Bebbington & Ramana, 1995). Recent findings do not support this, suggesting rather that shorter educational history, lower income, and unemployment are associated with an increased risk for BPD (Weissman *et al.* 1991;

Kessler *et al.* 1997). Regarding this discrepancy, a methodological issue should be addressed, as the prodrome or earlier course of the illness, prior to the first clinical referral, might have led the affected individual to social decline prior to the measurement of SES (Bebbington & Ramana, 1995; Tsuchiya *et al.* 2003). Studies examining parental SES might have excluded this effect (Eisemann, 1986; Coryell *et al.* 1989; Lewinsohn *et al.* 1995; Verdoux & Bourgeois, 1995); however, consensus has not been drawn from these studies because of the inconsistent results (Tsuchiya *et al.* 2003). This inconsistency might have arisen from lack of an adjustment for family history of psychiatric diagnoses,

* Address for correspondence: Dr Kenji J. Tsuchiya, Department of Psychiatry and Neurology, Hamamatsu University School of Medicine, Handayama 1, Hamamatsu 4313192, Japan.
(Email: tsuchiya@zah.att.ne.jp)

a major risk factor for BPD (Berrettini, 2000; Mortensen *et al.* in press). Furthermore, these studies might have suffered from small sample sizes and have compromised the precision.

In the present study, we used marital status, occupation, education, annual income, and wealth of both subjects and the parents as indices for SES. Using a nested case-control study design, we investigated the associations between the indices and the risk for the later occurrence of BPD with large-scale population registers.

METHOD

Data source

Two Danish population-based registers were linked by a unique personal identifier (CPR number) assigned to each individual, either Danish-born or immigrant. This number has been logically checked for errors and thus re-identification across registers is almost 100% correct.

The Danish Psychiatric Central Register, including psychiatric in-patients since 1938, has been computerized for all in-patients since 1969, and for all out-patients since 1995, who have been referred to psychiatric facilities in Denmark (Munk-Jørgensen & Mortensen, 1997). There are no private psychiatric hospitals in Denmark, and all treatment is free of charge. All diagnoses included in the Register were based on the WHO International Classification of Diseases (WHO, 1967), which was replaced by the tenth version (WHO, 1992) on 1 January 1994, and were established by trained psychiatrists. The Integrated Database for Longitudinal Labour Market Research has provided yearly status of demographic and socio-economic indices for each individual since 1980 (Danmarks Statistik, 1991). Linking information between mothers and children relies basically on midwifery reports, and all biological mothers of subjects can be identified, although this does not hold true for all biological fathers. The registration of subjects had been non-randomly incomplete until the late 1950s, and we excluded subjects born before 1960.

The data source, a combination of the two registers, is a well-defined open cohort, and thus consists of individuals born in or after 1960, with a registered link to the biological mother.

Cases and controls

We chose a design of a nested case-control study. Cases were those aged 10 years or older with a history of first-ever admission during the years 1981–1994, or with a history of first-ever clinical contact during the years 1995–1998, diagnosed with BPD (296.1x, 296.3x in ICD-8; F30.xx, F31.xx in ICD-10) by the end of 1998 or before loss to follow-up, whichever came first. As clinical diagnosis was uniquely provided in a hierarchical manner (Mortensen *et al.* in press), those with a history of diagnosis of schizophrenia or schizoaffective disorder (295.xx in ICD-8; F20.xx, F25.xx in ICD-10) were not selected as cases, but those with a history of both BPD and other diagnoses were treated as cases. Date of occurrence of BPD was conventionally determined as the date of the first-ever admission (1981–1994) or contact (1995–1998) irrespective of the first-ever diagnosis. Fifty time-matched controls per case were randomly selected by means of an incidence-density sampling method (Flanders & Louv, 1986), as those at risk on the particular date of occurrence of BPD, and at risk at the particular age in days without a prior history of psychiatric admission.

Covariates (risk factors)

We assigned a unique value of each SES index to cases and controls, recorded in the data source as that on a fixed date in the year prior to the year of first admission or contact. Included were marital status, occupation, education, annual income, and wealth (property and debt; lower and upper half according to national statistics) of each subject and of the parents. Sickness payment in the previous year was only measured in subjects. With regard to demographic variables to be controlled for, we included: gender, citizenship, country of birth, subject's place of residence, age of parents, lack of link with parents in the previous year (mainly due to a long absence from Denmark, parental death, etc.), and the number of siblings and children born before the first-ever admission or contact. Family history of psychiatric diagnoses in first-degree relatives (father, mother, and siblings) was uniquely assigned to each subject as being a main psychiatric diagnosis in a hierarchical manner. Schizophrenia or schizoaffective disorders (295.xx in ICD-8; F20.xx, F25.xx in

ICD-10) had the highest priority, followed by BPD (296.1x, 296.3x in ICD-8; F30.xx, F31.xx in ICD-10), major depressive disorder (296.xx in ICD-8; F3x.xx in ICD-10, with the exception of BPD), other psychiatric diagnoses, and no diagnosis respectively.

Data analysis

After the linkage was completed, all personally identifiable information was removed and all data were processed in an anonymized form. Data were analysed using conditional logistic regression analyses with the STATA software version 7.0 (Stata Corporation, 2000), first in a crude model without any adjustment, then in a model with gender and family history of psychiatric diagnoses controlled (first adjustment), and, finally, in a model with all available covariates controlled (full adjustment). The incidence-density sampling method allowed the estimation of unbiased odds ratios (ORs) independent of competing risks between exposed and unexposed categories. We did not consider omitting covariates from the model after full adjustment because obtaining a predictive model was beyond the scope of our study. A statistical significance level for risk estimates was set at 5%, and 95% confidence intervals (CI) were also presented.

RESULTS

A total of 947 cases and 47 350 time-matched controls were included in the analysis. A higher proportion of female subjects was identified in cases (60%, $n=567$) than in controls (49%, $n=23\,265$). Consistent with previous studies (Berrettini, 2000; Mortensen *et al.* in press), subjects having first-degree relatives with psychiatric diagnoses are highly associated with the risk after full adjustment, as follows: family history of BPD (OR 20.09, 95% CI 15.39–26.23); family history of schizophrenia and schizoaffective disorder (OR 5.73, 95% CI 4.07–8.05); family history of major depression (OR 3.63, 95% CI 2.78–4.72); family history of other psychiatric diagnoses (OR 1.70, 95% CI 1.37–2.11). No obvious difference regarding citizenship, country of birth, parental age, and urban–rural distribution was found, but more cases than expected were found in Frederiksberg, the largest city in the Greater Copenhagen area

other than Copenhagen, and in Aarhus, the second largest city in Denmark (not shown in the Tables). This may be related to mobility, organizational pattern, diagnostic tradition, etc., however, we have no evidence to support any of these hypotheses. We treated these variables in the full-adjustment model as confounders.

SES of subjects

ORs after a full adjustment (shown in Table 1) indicated that single persons aged 18 years and over were at increased risk for BPD. The categories of self-employed, student and homemaker, receipt of social assistance, receipt of disability pension, unemployed for more than 20% of the previous year, shorter educational history, lower annual income, and receipt of sickness payment were all associated with an increased risk for BPD. Level of wealth was not associated with an increased risk for BPD.

SES of parents

Lack of link with father in the previous year was associated with an increased risk for BPD, whereas lack of link with mother was not (Table 2).

Having father as self-employed, or as a student and a homemaker, and having father with a higher level of wealth were associated with an increased risk for BPD. Longer educational history of both father and mother were associated with an increased risk for BPD as was implied in previous studies (Eisemann, 1986; Coryell *et al.* 1989; Verdoux & Bourgeois, 1995).

DISCUSSION

Limitations of the study

To our knowledge, this is the first national register study for socio-economic risk factors for BPD. The study is of note for its high statistical power and multivariable adjustment, including family history of psychiatric diagnoses. On the other hand, generalizability of the results is limited because the sample stems from a Danish population, which has a relatively high divorce rate and a high proportion of women in the labour force. The registered diagnostic information we used does not distinguish between bipolar I and bipolar II disorders. One concern

Table 1. *Socio-economic status of subjects in relation to the risk for bipolar disorder: number of subjects, odds ratios, and 95% confidence interval*

	No. of exposed cases	No. of exposed controls	Crude	First adjustment (by gender and family history)	Full adjustment (by all covariates available)
Marital status					
Single (age < 18 years)	130	6527	0.46 (0.06–3.43)	0.45 (0.06–3.43)	0.53 (0.07–4.08)
Single (age ≥ 18 years)	552	22925	1.83 (1.56–2.15)	2.02 (1.71–2.39)	1.80 (1.50–2.16)
Cohabiting*	265	17898	1	1	1
Occupation					
Self-employed	20	800	1.56 (0.99–2.47)	1.80 (1.13–2.87)	1.60 (1.00–2.57)
Student and homemaker	180	7165	1.69 (1.38–2.07)	1.59 (1.29–1.95)	1.26 (1.02–1.55)
Social assistance	30	518	3.68 (2.51–5.39)	3.08 (2.08–4.55)	2.36 (1.57–3.55)
Disability pension	12	240	3.14 (1.74–5.67)	3.07 (1.68–5.61)	2.50 (1.34–4.66)
Unemployed (0–20%)	93	5729	1.03 (0.82–1.29)	0.99 (0.78–1.24)	0.99 (0.78–1.26)
Unemployed (> 20%)	212	7482	1.80 (1.52–2.14)	1.66 (1.39–1.98)	1.48 (1.22–1.79)
Paid worker*	400	25416	1	1	1
Education					
Longer (Bachelor level and above)	71	4471	0.76 (0.59–0.98)	0.74 (0.57–0.96)	0.65 (0.50–0.85)
Not available, including subjects before graduation	33	1543	1.18 (0.67–2.06)	1.17 (0.66–2.07)	0.93 (0.52–1.65)
Shorter*	843	41336	1	1	1
Income					
Upper half	219	16423	0.48 (0.40–0.56)	0.53 (0.45–0.63)	0.75 (0.62–0.91)
Lower half*	728	30927	1	1	1
Wealth					
Upper half	503	25693	0.95 (0.82–1.09)	0.96 (0.83–1.11)	0.88 (0.76–1.02)
Lower half*	444	21657	1	1	1
Sickness payment					
Yes	119	4537	1.37 (1.12–1.67)	1.27 (1.04–1.56)	1.34 (1.07–1.66)
None*	828	42813	1	1	1

* Reference category.

about our method of case ascertainment is that we might have included those converting from depression to hypomania or mania, such as drug-induced hypomania. Whether such a psychopathology may be related in the bipolar spectrum is beyond the focus of this study; however, the literature has suggested that a substantial percentage of depressive patients eventually manifest bipolarity, thus the case ascertainment in our study may be justified (Akiskal *et al.* 2000; Goldberg *et al.* 2001). However, we may still have overlooked subjects with BPD, with a history of major depression and hypomania but without a registered diagnosis of BPD.

In our sample, there were more female cases than female controls. This may be due to clinical referral or admission, since female subjects are suggested to have a lower threshold to clinical referral than males in studies for affective disorders (Weissman & Myers, 1978; Unützer *et al.* 1998).

SES of subjects

Indices suggesting socio-economic disadvantage, such as being single, being at home as a student and homemaker, receipt of pension and social assistance, and unemployment, were significantly associated with increased risk for BPD, and are inconsistent with earlier studies (Eisemann, 1986) but in accord with the recent literature (Weissman *et al.* 1991; Kessler *et al.* 1997). Since our study design allows the true onset of BPD to precede the timing of the measurement of the SES indices in some cases, the observed associations might have been subject to non-specific social decline after the true onset of the illness (Goodwin & Jamison, 1990; Jones *et al.* 1993; Bebbington & Ramana, 1995). The finding regarding sickness payment appears particularly apposite with this consideration, as the association between sickness payment and BPD is obvious. The fact that the ORs for occupation and income decreased after full

Table 2. *Socio-economic status of parents in relation to the risk for bipolar disorder: number of subjects, odds ratios, and 95% confidence interval*

	No. of exposed cases	No. of exposed controls	Crude	First adjustment (by gender and family history)	Full adjustment (by all covariates available)
Lack of link with father in the year prior to first admission					
Yes	169	6103	1.49 (1.25–1.77)	1.27 (1.04–1.55)	1.65 (1.12–2.41)
No*	778	41 247	1	1	1
Lack of link with mother in the year prior to first admission					
Yes	78	2214	1.85 (1.46–2.34)	1.61 (1.26–2.06)	1.20 (0.79–1.82)
No*	869	45 136	1	1	1
Marital status: Father					
Single	132	5684	1.28 (1.06–1.55)	1.00 (0.82–1.21)	0.97 (0.76–1.23)
Cohabiting*	646	35 563	1	1	1
Marital status: Mother					
Single	217	9180	1.31 (1.12–1.53)	1.03 (0.87–1.21)	0.93 (0.75–1.16)
Cohabiting*	652	35 956	1	1	1
Occupation: Father					
Self-employed	155	6616	1.42 (1.17–1.71)	1.42 (1.17–1.72)	1.33 (1.09–1.64)
Student and homemaker	23	616	2.29 (1.49–3.52)	1.96 (1.26–3.04)	1.62 (1.03–2.56)
Social assistance	3	237	0.75 (0.24–2.36)	0.66 (0.21–2.08)	0.53 (0.16–1.73)
Disability pension	44	1701	1.57 (1.14–2.16)	1.05 (0.76–1.46)	1.04 (0.72–1.50)
Age pension	70	3720	1.19 (0.91–1.57)	1.04 (0.79–1.38)	0.82 (0.58–1.16)
Unemployed (0–20%)	42	2388	1.05 (0.76–1.46)	1.04 (0.75–1.44)	1.17 (0.84–1.63)
Unemployed (>20%)	69	3623	1.15 (0.89–1.49)	1.10 (0.84–1.43)	1.11 (0.83–1.48)
Paid worker*	372	22 346	1	1	1
Occupation: Mother					
Self-employed	36	1626	1.18 (0.84–1.66)	1.15 (0.81–1.63)	1.07 (0.75–1.52)
Student and homemaker	75	3591	1.12 (0.87–1.43)	1.02 (0.79–1.32)	0.93 (0.71–1.23)
Social assistance	18	438	2.16 (1.34–3.49)	1.62 (0.99–2.66)	1.36 (0.80–2.33)
Disability pension	72	3677	1.07 (0.83–1.37)	0.70 (0.54–0.90)	0.64 (0.48–0.86)
Age pension	69	2862	1.40 (1.05–1.85)	1.13 (0.85–1.50)	0.92 (0.63–1.34)
Unemployed (0–20%)	38	2659	0.76 (0.54–1.06)	0.72 (0.52–1.01)	0.80 (0.57–1.12)
Unemployed (>20%)	87	5109	0.91 (0.72–1.15)	0.84 (0.66–1.06)	0.89 (0.70–1.14)
Paid worker*	474	25 174	1	1	1
Education: Father					
Longer (Bachelor level and above)	177	6704	1.55 (1.30–1.84)	1.52 (1.27–1.81)	1.24 (1.01–1.52)
Shorter*	510	29 988	1	1	1
Education: Mother					
Longer (Bachelor level and above)	191	6105	1.88 (1.59–2.22)	1.82 (1.53–2.15)	1.59 (1.31–1.94)
Shorter*	607	36 173	1	1	1
Income: Father					
Upper half	414	23 342	0.86 (0.75–1.00)	0.96 (0.83–1.11)	0.89 (0.74–1.07)
Lower half*	364	17 905	1	1	1
Income: Mother					
Upper half	470	25 858	0.87 (0.76–1.00)	0.98 (0.85–1.12)	0.89 (0.75–1.06)
Lower half*	399	19 278	1	1	1
Wealth: Father					
Upper half	437	21 249	1.23 (1.06–1.43)	1.35 (1.16–1.57)	1.29 (1.09–1.52)
Lower half*	341	19 998	1	1	1
Wealth: Mother					
Upper half	400	20 821	1.00 (0.87–1.16)	1.00 (0.87–1.17)	0.96 (0.82–1.12)
Lower half*	469	24 315	1	1	1

* Reference category.

adjustment by all the covariates, including sickness payment, but that the OR for sickness payment did not diminish considerably may also support the suggested association explained

by prodrome prior to first-ever admission or contact. Hence, the observed associations are possible but rather apparent, and they can be explained as a consequence of the illness itself.

SES of parents

Different from the SES of subjects, a longer parental educational history and a higher level of paternal wealth were associated with an elevated risk for BPD. As regards the level of education, our result is consistent with previous studies (Eisemann, 1986; Coryell *et al.* 1989) although it is inconsistent with another study (Lewinsohn *et al.* 1995). To our knowledge, the positive association between the wealth of father and the risk for BPD has not been reported in the literature. In light of our results, socio-economic achievement of parents may be related to an elevated risk for BPD, although some issues of concern remain.

The first issue relates to a referral bias resulting from a low threshold of the educated and wealthy parents to clinical referral. However, in general, subjects with full-blown mania tend to be referred to psychiatric facilities (Angst, 1986; Bebbington & Ramana, 1995). Considering that medical services in Denmark are provided free of charge, it is unlikely that the less-educated or less-wealthy parents would hesitate to refer their children, compared to other parents.

Secondly, the lack of association between parental income and risk for BPD seems inconsistent with the association of parental wealth, because it is logical to assume that the father with a higher level of wealth will also have a higher level of income. Nevertheless, average age of father alive in this data-set is 54.3 years (s.d. 7.9 years), and approximately 9% of them received age pension. In Denmark, anyone aged 67 years or older must receive a pension, the annual amount of which is categorized into the lower level of income. Thus, the lack of association of parental income is unlikely to be a concern.

The third issue is that only the father's wealth index, not the mother's, showed a positive association. This can be explained by the fact that, according to official statistics, wealth in a Danish household where both parents are alive tends to belong to the father rather than the mother (Danmarks Statistik, 2003). It can, therefore, be interpreted that the discrepant findings between father and mother may indicate a higher level of wealth inherent in the family of origin and may also be associated with an increased risk for BPD in the offspring. In this context, a

self-employed father, or a father at home before retirement age, may be connected with socio-economic advantage, e.g. such fathers can be assumed to be wealthy after successful economic achievement in their business or job.

Other explanations for the significant associations we found are also possible, including psychiatric diagnoses of second-degree relatives and other unknown biases.

As for findings regarding the loss of link with parents, parental loss has been implicated as a risk factor for BPD (Tsuchiya *et al.* 2003; Mortensen *et al.* in press). However, a similar interpretation of our result may be limited because one of the reasons for lack of link with the father is lack of a registered link in the data source while for the mother it is not. This requires further investigation.

In conclusion, the present study indicated that, although some low SES indices of subjects seem to be associated with an increased risk for BPD, the associations can be considered as a consequence of the illness. Longer parental educational history and higher level of paternal wealth is associated with increased risk for BPD, and this is unlikely to be explained by known biases. Instead, these associations can be viewed that socio-economic advantage in the family of origin is associated with an increased risk for BPD in the offspring. The causes underlying this association, however, remain unresolved.

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