**Supplementary Material**

This material accompanies the article: "**Attention-deficit/hyperactivity disorder and anxiety disorders as precursors of bipolar disorder onset in adulthood**" by Meier SM, Pavlova B, Dalsgaard S, Nordentoft M, Mors N, Mortensen PB, Uher R, published in the British Journal of Psychiatry.

Correspondence should be addressed to: Dr. Rudolf Uher, Dalhousie University, 5909 Veterans Memorial Drive, Halifax, NS, B3H 2E2, NS, Canada; Email: uher@dal.ca

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# Sample description and stratified analyses

**Table S1**. **Incidence of bipolar disorder stratifies by sample characteristics**. The number of onsets of bipolar disorder, number of person years (PY) of follow-up and incidence rate of bipolar disorder onsets per 10,000 PY are provided for each stratum on each characteristic.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Characteristic |  Stratum | Number of onsets of bipolar disorder | Person Years (PY) of follow up | Rate of bipolar disorder onsets per 10,000 PY |
|  |  |  |  |  |
| Calendar Year of Birth | 1955-1964 | 2869 | 11165832.85 | 2.56945 |
|  | 1965-1974 | 3030 | 13050764.07 | 2.32170 |
|  | 1975-1984 | 2341 | 9634133.55 | 2.42990 |
|  | >1985 | 1010 | 3544134.16 | 2.84978 |
|  |  |  |  |  |
| Gender | Female  | 5240 | 18193423.23 | 2.88016 |
|  | Male | 4010 | 19201441.41 | 2.08838 |
|  |  |  |  |  |
| Maternal Age | <=20 | 1290 | 4721172.95 | 2.73237 |
|  | 21-25 | 3198 | 13581361.15 | 2.35470 |
|  | 25-30 | 2794 | 11502820.50 | 2.42897 |
|  | 31-35 | 1376 | 5400503.62 | 2.54791 |
|  | >35 | 592 | 2189006.40 | 2.70442 |
|  |  |  |  |  |
| Paternal Age | <=20 | 400 | 1366725.27 | 2.92670 |
|  | 21-25 | 2271 | 9161547.79 | 2.47884 |
|  | 25-30 | 2987 | 12816388.03 | 2.33061 |
|  | 31-35 | 2041 | 8120544.17 | 2.51338 |
|  | >35 | 1551 | 5929659.38 | 2.61566 |
|  |  |  |  |  |
| Mother's Psychiatric Diagnosis | Yes | 1970 | 3497874.11 | 5.63199 |
|  | No | 7280 | 33896990.52 | 2.14768 |
|  |  |  |  |  |
| Father's Psychiatric Diagnosis | Yes | 1493 | 2885101.26 | 5.17486 |
|  | No | 7757 | 34509763.38 | 2.24777 |

The incidence of bipolar disorder was higher in females than in males. Family history of mental illness in biological mother and biological father increased the risk of bipolar disorder to a similar degree. The age at study entry (calendar year of birth), maternal and paternal age at birth were not systematically associated with incidence of bipolar disorder in this cohort.

# Analyses adjusted for family history

Adjustment for family history of mental illness was not part of our original analysis plan. However, given the discrepancies between family high-risk studies and studies of general population samples in prior literature, we conducted an additional analysis adjusted for the history of any mental illness in biological mother or biological father. We added this adjustment to the original adjusted analysis reported in Table 1 of the main manuscript. Table S2 compares the incidence rate ratios (IRR) for association between prior diagnoses of ADHD and anxiety and adult onset of bipolar disorder with and without additional adjustment for family history of mental illness.

**Table S2**: Association between prior diagnoses of ADHD and anxiety and later onset of bipolar disorder with and without adjustment for family history of mental illness in parents.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   |   |   |   | Incidence Rate Ratio (IRR) |
|  |  | Original adjustment\* |  | Additional adjustment for family history\* |
|  |  | IRR | 95% CI |  | IRR | 95% CI |
| Single diagnosis Effects |  |  |  |  |  |  |
| ADHD |  | 10.00 | 8.58-11.57 |  | 8.29 | 7.11-9.59 |
| Anxiety Disorders |  | 9.61 | 9.01-10.24 |  | 8.27 | 7.75-8.82 |
|  |  |  |  |  |  |  |
| Joint Effects |  |  |  |  |  |  |
| No ADHD or Anxiety Disorder |  | 1.00 | Reference |  | 1.00 | Reference |
| ADHD only |  | 10.13 | 8.54-11.92 |  | 8.62 | 7.26-10.15 |
| Anxiety Disorders only |  | 9.61 | 9.00-10.25 |  | 8.30 | 7.77-8.87 |
| ADHD and Anxiety Disorders |  | 21.15 | 15.02-28.78 |  | 17.35 | 12.32-23.63 |
|   |   |   |   |   |   |   |

\* Both IRR are corrected for sex, age, interaction of sex and age, calendar year, and parental age.

As expected, the risk ratios were slightly reduced when family history of mental illness was included as an additional covariate. However, the pattern of findings was very similar to the original adjusted analyses and the risk of bipolar disorder associated with the combination of prior ADHD and prior anxiety remained significantly higher than the risk associated with either prior disorder alone. We conclude that the associations between prior childhood diagnoses and later onset of bipolar disorder in adulthood is relatively independent of family history of mental illness.

# Specificity of associations: Predictor specificity

Our primary question was about bipolar disorder and its association with prior prototypical externalizing and internalizing disorders. However, the data in the registers also allow a broader exploration. To probe the specificity of the association between prior ADHD/anxiety and later bipolar disorder, we completed additional analyses replacing ADHD or anxiety with other diagnoses that have a typical onset in childhood or adolescence. We completed analyses for pairs of diagnoses for which there were adequate numbers of individuals for each disorder combination. The results of tests of **predictor specificity** for diagnoses with sufficient numbers of individuals are listed in Table S3.

**Table S3**: **Prediction of bipolar disorder by alternative combinations of child/adolescent disorders**.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   |   | Onset cases |   | Incidence Rate Ratio (IRR) |
|   |  |  |  |  |  |
|  |  | Bipolar |  | Adjusted\* |
|  |  | n |  | IRR | 95% CI |
|  |  |  |  |  |  |
| Original analysis |  |  |  |  |  |
| ADHD only |  | 145 |  | 10.13 | 8.54-11.92 |
| Anxiety Disorders only |  | 1049 |  | 9.61 | 9.00-10.25 |
| Both ADHD and Anxiety Disorders | 37 |  | 21.15 | 15.02-28.78 |
|  |  |  |  |  |  |
| Alternative combination 1 |  |  |  |  |  |
| ODD only |  | 62 |  | 4.21 | 3.25-5.36 |
| ADHD only |  | 164 |  | 9.96 | 8.48-11.60 |
| Both ODD and ADHD |  | 18 |  | 13.33 | 8.07-20.51 |
|  |  |  |  |  |  |
| Alternative combination 2 |  |  |  |  |  |
| ODD only |  | 65 |  | 4.70 | 3.65-5.95 |
| Anxiety disorders only |  | 1071 |  | 9.47 | 8.87-10.10 |
| Both ODD and Anxiety disorder |  | 15 |  | 15.54 | 8.94-24.81 |
|  |  |  |  |  |  |
| Alternative combination 3 |  |  |  |  |  |
| Bulimia nervosa only |  | 42 |  | 7.73 | 5.61-10.33 |
| Anxiety disorders only |  | 1072 |  | 9.47 | 8.87-10.09 |
| Both bulimia and anxiety disorders |  | 14 |  | 17.71 | 9.97-28.72 |
|  |  |  |  |  |  |
| Alternative combination 4 |  |  |  |  |  |
| Anorexia Nervosa only |  | 58 |  | 4.33 | 3.30-5.55 |
| Anxiety disorders only |  | 1066 |  | 9.49 | 8.89-10.12 |
| Both anorexia and anxiety disorders | 20 |  | 12.63 | 7.87-19.03 |
|   |   |   |   |   |   |

\* IRR are corrected for sex, age, interaction of sex and age, calendar year, and parental age.

 Abbreviation: ODD = oppositional-defiant disorder.

These analyses suggest partial specificity - other combinations or prior disorders also predicted bipolar disorder onset, but with smaller effect sizes than ADHD and anxiety disorders. We have seen the relatively strongest effect for the combination of bulimia nervosa and anxiety disorders, but this result comes with a greater degree of uncertainty since bulimia nervosa is not as common as ADHD.

The number of cases with a combination of prior ADHD and anorexia nervosa was too small to allow meaningful analysis.

Like ODD,1,2 bulimia nervosa has components of both internalizing and externalizing psychopathology.3 Therefore, these results are less informative for the general hypothesis that a combination of prior externalizing and internalizing disorders increases the risk of bipolar disorder.

# Specificity of associations: Outcome specificity

To test whether the prediction is specific to bipolar disorder, we repeated the primary analyses for onset of schizophrenia, which is the mental disorder closest to bipolar disorder in terms of age at onset, frequency and severity.

**Table S4**: **Prediction of new onset of bipolar disorder and schizophrenia from prior diagnoses of ADHD and anxiety disorders**.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|   |   |   |   | Onset cases |   | Adjusted Incidence Rate Ratio (IRR) |
|  |  | Bipolar | Schizophrenia |  | Bipolar |  | Schizophrenia |
|  |  | n | n |  | IRR | 95% CI |  | IRR | 95% CI |
| Single diagnosis Effects |  |  |  |  |  |  |  |  |  |
| ADHD |  | 182 | 326 |  | 10.00 | 8.58-11.57 |  | 7.36 | 6.57-8.22 |
| Anxiety Disorders |  | 1086 | 1836 |  | 9.61 | 9.01-10.24 |  | 13.62 | 12.96-14.31 |
|  |  |  |  |  |  |  |  |  |  |
| Joint Effects |  |  |  |  |  |  |  |  |  |
| No ADHD or Anxiety Disorder |  | 8019 | 14310 |  | 1.00 | Reference |  | 1.00 | Reference |
| ADHD only |  | 145 | 250 |  | 10.13 | 8.54-11.92 |  | 6.96 | 6.12-7.89 |
| Anxiety Disorders only |  | 1049 | 1762 |  | 9.61 | 9.00-10.25 |  | 13.60 | 12.92-14.30 |
| ADHD and Anxiety Disorders |  | 37 | 76 |  | 21.15 | 15.02-28.78 |  | 26.88 | 21.24-33.46 |
|   |   |   |   |   |   |   |   |   |   |

The results suggest limited specificity on outcome. Prior ADHD predicts schizophrenia risk less strongly than the risk of bipolar disorder. However, prior anxiety and ADHD-anxiety combination predict the risk of schizophrenia even more strongly than the risk of bipolar disorder. Youth with a combination of ADHD and anxiety disorder may represent a risk group for a range of adult severe mental illnesses, including both bipolar disorder and schizophrenia.

Supplementary References:

 1 Stringaris A, Goodman R. Three dimensions of oppositionality in youth. *J Child Psychol Psychiatry* 2009; **50**: 216-223.

 2 Stringaris A, Maughan B, Goodman R. What's in a disruptive disorder? Temperamental antecedents of oppositional defiant disorder: findings from the Avon longitudinal study. *J Am Acad Child Adolesc Psychiatry* 2010; **49**: 474-483.

 3 Adambegan M, Wagner G, Nader IW, Fernandez-Aranda F, Treasure J, Karwautz A. Internalizing and externalizing behaviour problems in childhood contribute to the development of anorexia and bulimia nervosa-a study comparing sister pairs. *Eur Eat Disord Rev* 2012; **20**: 116-120.