

# Polygenic risk and progression to bipolar or psychotic disorders among individuals diagnosed with unipolar depression in early life

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## Supplemental Materials

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## Abbreviations

BD = Bipolar disorder

SZ = Schizophrenia

MD = Major depression

UD = Unipolar depression

HR = Hazard ratio

LCL = Lower confidence limit

UCL = Upper confidence limit

## Supplemental Tables

Table S1. Breakdown of specific diagnoses within each main and secondary outcome category

| Outcome category                     | ICD-10 | Description   | N (%)        |
|--------------------------------------|--------|---|--------------|
| <b>Main Outcomes</b>                 |        |   |              |
| Bipolar disorder                     | F30    | Manic episode   | 33 (5%)      |
|                                      | F31    | Bipolar disorder  | 679 (95%)    |
|                                      | Total: |   | 712 (100%)   |
| Psychotic disorders                  | F20    | Schizophrenia   | 545 (33%)    |
|                                      | F21    | Schizotypal disorder  | 424 (26%)    |
|                                      | F22    | Persistent delusional disorders   | 109 (7%)     |
|                                      | F23    | Acute and transient psychotic disorders                                     | 230 (14%)    |
|                                      | F25    | Schizoaffective disorder  | 86 (5%)      |
|                                      | F28    | Other psychotic disorder  | 75 (5%)      |
|                                      | F29    | Unspecified psychotic disorder  | 171 (10%)    |
|                                      | Total: |   | 1,640 (100%) |
| <b>Secondary Outcomes</b>            |        |   |              |
| Schizophrenia                        | F20    | Schizophrenia   | 814 (100%)   |
|                                      | Total: |   | 814 (100%)   |
| Psychotic depression                 | F32.3  | Single depressive episode, severe with psychotic symptoms                   | 180 (58%)    |
|                                      | F33.3  | Recurrent depression, current episode severe with psychotic symptoms        | 128 (42%)    |
|                                      | Total: |   | 308 (100%)   |
| Any Affective psychotic disorder     | F30.2  | Mania with psychotic symptoms   | 7 (2%)       |
|                                      | F31.2  | Bipolar disorder, current episode manic with psychotic symptoms             | 23 (6%)      |
|                                      | F31.5  | Bipolar disorder, current episode severe depression with psychotic features | 30 (8%)      |
|                                      | F32.3  | Single depressive episode, severe with psychotic symptoms                   | 179 (49%)    |
|                                      | F33.3  | Recurrent depression, current episode severe with psychotic symptoms        | 127 (35%)    |
|                                      | Total: |   | 366 (100%)   |
| Any disorder with psychotic features | F20    | Schizophrenia   | 460 (26%)    |
|                                      | F21    | Schizotypal disorder  | 400 (23%)    |
|                                      | F22    | Persistent delusional disorders   | 97 (6%)      |
|                                      | F23    | Acute and transient psychotic disorders                                     | 202 (12%)    |
|                                      | F25    | Schizoaffective disorder  | 64 (4%)      |
|                                      | F28    | Other psychotic disorder  | 61 (3%)      |
|                                      | F29    | Unspecified psychotic disorder  | 151 (9%)     |
|                                      | F30.2  | Mania with psychotic symptoms   | 7 (<1%)      |
|                                      | F31.2  | Bipolar disorder, current episode manic with psychotic symptoms             | 19 (1%)      |
|                                      | F31.5  | Bipolar disorder, current episode severe depression with psychotic features | 26 (1%)      |
|                                      | F32.3  | Single depressive episode, severe with psychotic symptoms                   | 159 (9%)     |
|                                      | F33.3  | Recurrent depression, current episode severe with psychotic symptoms        | 99 (6%)      |
|                                      | Total: |   | 1,745 (100%) |

These numbers reflect each individuals *first* diagnosis within that outcome category, and do not preclude individuals receiving multiple diagnoses either within the same category over time, or within different categories.

Note also that while the primary outcomes are defined based on mutually exclusive sets of diagnostic codes, the secondary outcomes are not – thus, individuals diagnosed with psychotic depression were included in the analyses for ‘psychotic depression’, ‘affective psychotic disorder’ and ‘any disorder with psychotic features’ on the basis of that psychotic depression diagnosis alone.

Table S2. Mean PRS variables among individuals who progressed to primary and secondary outcome categories (Overall sample mean = 0, SD = 1)

|                                  |          | <b>PRS-BD</b> | <b>PRS-SZ</b> | <b>PRS-MD</b> |
|----------------------------------|----------|---------------|---------------|---------------|
| <b>Outcome</b>                   | <b>N</b> | <b>M (SD)</b> | <b>M (SD)</b> | <b>M (SD)</b> |
| <i>Primary outcomes</i>          |          |               |               |               |
| Bipolar disorder                 | 712      | 0.15 (1.05)   | 0.13 (1.01)   | 0.02 (1.05)   |
| Psychotic disorder               | 1,640    | 0.05 (1.01)   | 0.10 (1.03)   | 0.05 (1.00)   |
| <i>Secondary outcomes</i>        |          |               |               |               |
| Schizophrenia                    | 814      | 0.02 (0.99)   | 0.08 (1.02)   | 0.09 (1.01)   |
| Psychotic depression             | 308      | 0.06 (1.05)   | -0.01 (1.05)  | 0.08 (1.07)   |
| Any affective psychotic disorder | 366      | 0.15 (1.08)   | 0.08 (1.07)   | 0.07 (1.06)   |
| Any psychotic disorder           | 1,745    | 0.06 (1.03)   | 0.09 (1.03)   | 0.05 (1.02)   |

Table S3. Hazard ratios and 95% confidence intervals for the associations between polygenic risk scores for bipolar disorder, major depression and schizophrenia and progression to bipolar disorder, psychotic disorders, schizophrenia, psychotic depression, any affective psychotic disorder and any disorder with psychotic features among individuals diagnosed with unipolar depression in Danish psychiatric hospitals

|   |        | Adjusted vs. Unadjusted |      |      |        |                   |      |      |        |
|---|--------|-------------------------|------|------|--------|-------------------|------|------|--------|
|   |        | Not mutually adjusted   |      |      |        | Mutually adjusted |      |      |        |
| Outcome   | PRS    | HR                      | LCL  | UCL  | p*     | HR                | LCL  | UCL  | p*     |
| Bipolar disorder<br>(n = 712)                       | PRS-BD | 1.14                    | 1.06 | 1.23 | 0.0004 | 1.11              | 1.03 | 1.21 | 0.009  |
|   | PRS-MD | 1.03                    | 0.96 | 1.11 | 0.44   | 1.01              | 0.94 | 1.09 | 0.83   |
|   | PRS-SZ | 1.11                    | 1.03 | 1.20 | 0.004  | 1.07              | 0.98 | 1.16 | 0.12   |
| Psychotic disorders<br>(n = 1,640)                  | PRS-BD | 1.06                    | 1.01 | 1.11 | 0.03   | 1.01              | 0.96 | 1.07 | 0.66   |
|   | PRS-MD | 1.04                    | 0.99 | 1.09 | 0.10   | 1.03              | 0.98 | 1.08 | 0.29   |
|   | PRS-SZ | 1.11                    | 1.06 | 1.17 | <.0001 | 1.10              | 1.04 | 1.16 | 0.0004 |
| Schizophrenia<br>(n = 814)                          | PRS-BD | 1.02                    | 0.95 | 1.09 | 0.65   | 0.98              | 0.90 | 1.05 | 0.53   |
|   | PRS-MD | 1.08                    | 1.00 | 1.15 | 0.04   | 1.07              | 1.00 | 1.15 | 0.07   |
|   | PRS-SZ | 1.08                    | 1.01 | 1.16 | 0.03   | 1.08              | 1.00 | 1.17 | 0.04   |
| Psychotic depression<br>(n = 308)                   | PRS-BD | 1.08                    | 0.96 | 1.20 | 0.20   | 1.09              | 0.96 | 1.23 | 0.17   |
|   | PRS-MD | 1.07                    | 0.96 | 1.20 | 0.22   | 1.07              | 0.95 | 1.20 | 0.25   |
|   | PRS-SZ | 0.99                    | 0.88 | 1.11 | 0.84   | 0.95              | 0.84 | 1.07 | 0.37   |
| Any affective psychotic disorder<br>(n = 366)       | PRS-BD | 1.17                    | 1.06 | 1.30 | 0.002  | 1.16              | 1.04 | 1.30 | 0.009  |
|   | PRS-MD | 1.07                    | 0.96 | 1.18 | 0.22   | 1.04              | 0.94 | 1.16 | 0.42   |
|   | PRS-SZ | 1.08                    | 0.97 | 1.19 | 0.16   | 1.01              | 0.90 | 1.13 | 0.88   |
| Any disorder with psychotic features<br>(n = 1,745) | PRS-BD | 1.06                    | 1.01 | 1.11 | 0.01   | 1.03              | 0.98 | 1.08 | 0.29   |
|   | PRS-MD | 1.04                    | 0.99 | 1.09 | 0.12   | 1.02              | 0.98 | 1.07 | 0.32   |
|   | PRS-SZ | 1.09                    | 1.04 | 1.15 | 0.0002 | 1.08              | 1.02 | 1.14 | 0.005  |

\*Pink: Significant at the  $p < .017$  level; Blue: Significant at the  $p < .05$  level

Table S4. Overall absolute risk of progression to main and secondary outcomes over 21 years among individuals diagnosed with unipolar depression in Danish psychiatric hospitals

| <b>Outcome</b>                       | <b>All patients with depression<br/>(N = 16,949)</b> | <b>F32<br/>(n = 13,655)</b>           | <b>F33<br/>(n = 3,294)</b>            |
|--------------------------------------|--|---------------------------------------|---------------------------------------|
|                                      | <b>Cumulative Hazard<br/>(95% CI)</b>                | <b>Cumulative Hazard<br/>(95% CI)</b> | <b>Cumulative Hazard<br/>(95% CI)</b> |
| <i>Primary outcomes:</i>             |  |                                       |                                       |
| Bipolar disorder                     | 7.3% (6.4-8.3%)                                      | 6.7% (5.8-7.7%)                       | 10.3% (8.5-12.3%)                     |
| Psychotic disorders                  | 13.8% (12.2-15.5%)                                   | 14.1% (12.5-15.9%)                    | 12.3% (10.4-14.4%)                    |
| <i>Secondary outcomes:</i>           |  |                                       |                                       |
| Schizophrenia                        | 6.5% (5.9-7.1%)                                      | 6.6% (6.0-7.3%)                       | 5.8% (4.8-7.0%)                       |
| Psychotic depression                 | 2.2% (1.9-2.4%)                                      | 2.3% (2.0-2.6%)                       | 1.7% (1.3-2.3%)                       |
| Any affective psychotic disorders    | 2.8% (2.5-3.3%)                                      | 2.9% (2.5-3.4%)                       | 2.4% (1.8-3.2%)                       |
| Any disorder with psychotic features | 15.0% (13.4-16.8%)                                   | 15.4% (13.7-17.2%)                    | 13.3% (11.4-15.5%)                    |



Table S5. Absolute risk of progression to bipolar disorder and psychotic disorders by PRS quartile

| <b>Outcome</b>      | <b>PRS quartile</b> | <b>Cumulative Hazard</b> | <b>LCL</b> | <b>UCL</b> |
|---------------------|---------------------|--------------------------|------------|------------|
| Bipolar disorder    | 1                   | 6.1%                     | 5.2%       | 7.3%       |
|                     | 2                   | 6.8%                     | 6.0%       | 7.8%       |
|                     | 3                   | 7.6%                     | 6.6%       | 8.7%       |
|                     | 4                   | 8.4%                     | 7.2%       | 9.9%       |
| Psychotic disorders | 1                   | 12.4%                    | 10.8%      | 14.2%      |
|                     | 2                   | 13.3%                    | 11.7%      | 15.0%      |
|                     | 3                   | 14.2%                    | 12.6%      | 16.1%      |
|                     | 4                   | 15.3%                    | 13.4%      | 17.5%      |

Table S6. Sensitivity analysis 1: Inpatient and outpatient treatment settings only

|   |        | Adjusted vs. Unadjusted |      |      |        |                   |      |      |        |
|---|--------|-------------------------|------|------|--------|-------------------|------|------|--------|
|   |        | Not mutually adjusted   |      |      |        | Mutually adjusted |      |      |        |
| Outcome   | PRS    | HR                      | LCL  | UCL  | p*     | HR                | LCL  | UCL  | p*     |
| Bipolar disorder<br>(n = 712)                       | PRS-BD | 1.17                    | 1.07 | 1.27 | 0.0003 | 1.14              | 1.04 | 1.25 | 0.004  |
|   | PRS-MD | 1.01                    | 0.93 | 1.10 | 0.77   | 0.99              | 0.91 | 1.07 | 0.76   |
|   | PRS-SZ | 1.12                    | 1.03 | 1.21 | 0.009  | 1.06              | 0.97 | 1.16 | 0.20   |
| Psychotic disorders<br>(n = 1,640)                  | PRS-BD | 1.05                    | 0.99 | 1.11 | 0.09   | 1.00              | 0.94 | 1.06 | 0.97   |
|   | PRS-MD | 1.04                    | 0.98 | 1.10 | 0.19   | 1.02              | 0.97 | 1.08 | 0.41   |
|   | PRS-SZ | 1.12                    | 1.06 | 1.18 | 0.0001 | 1.11              | 1.05 | 1.18 | 0.0007 |
| Schizophrenia<br>(n = 814)                          | PRS-BD | 1.00                    | 0.92 | 1.07 | 0.93   | 0.95              | 0.88 | 1.04 | 0.26   |
|   | PRS-MD | 1.08                    | 1.00 | 1.17 | 0.04   | 1.08              | 1.00 | 1.17 | 0.06   |
|   | PRS-SZ | 1.08                    | 1.00 | 1.16 | 0.06   | 1.09              | 1.00 | 1.18 | 0.049  |
| Psychotic depression<br>(n = 308)                   | PRS-BD | 1.05                    | 0.92 | 1.20 | 0.49   | 1.09              | 0.94 | 1.26 | 0.24   |
|   | PRS-MD | 1.07                    | 0.94 | 1.23 | 0.29   | 1.08              | 0.94 | 1.23 | 0.28   |
|   | PRS-SZ | 0.92                    | 0.80 | 1.05 | 0.21   | 0.88              | 0.76 | 1.02 | 0.08   |
| Any affective psychotic disorder<br>(n = 366)       | PRS-BD | 1.17                    | 1.03 | 1.32 | 0.01   | 1.18              | 1.04 | 1.35 | 0.01   |
|   | PRS-MD | 1.08                    | 0.95 | 1.22 | 0.23   | 1.06              | 0.94 | 1.20 | 0.36   |
|   | PRS-SZ | 1.02                    | 0.90 | 1.15 | 0.75   | 0.95              | 0.83 | 1.08 | 0.41   |
| Any disorder with psychotic features<br>(n = 1,745) | PRS-BD | 1.06                    | 1.00 | 1.11 | 0.045  | 1.02              | 0.96 | 1.08 | 0.48   |
|   | PRS-MD | 1.04                    | 0.99 | 1.10 | 0.13   | 1.03              | 0.97 | 1.09 | 0.29   |
|   | PRS-SZ | 1.09                    | 1.03 | 1.15 | 0.002  | 1.07              | 1.01 | 1.14 | 0.02   |

In these analyses, all diagnoses used in sample selection and effect estimation were received in inpatient or outpatient settings. Full sample: N = 14,427. Excluding patients with psychotic depression at first diagnosis: N = 13,984.

\*Pink: Significant at the  $p < .017$  level; Blue: Significant at the  $p < .05$  level

Table S7. Sensitivity analysis 2: Main diagnoses only

|   |        | Adjusted vs. Unadjusted |      |      |         |                   |      |      |         |
|---|--------|-------------------------|------|------|---------|-------------------|------|------|---------|
|   |        | Not mutually adjusted   |      |      |         | Mutually adjusted |      |      |         |
| Outcome   | PRS    | HR                      | LCL  | UCL  | p value | HR                | LCL  | UCL  | p value |
| Bipolar disorder<br>(n = 712)                       | PRS-BD | 1.17                    | 1.08 | 1.27 | 0.0001  | 1.14              | 1.04 | 1.24 | 0.005   |
|   | PRS-MD | 1.02                    | 0.94 | 1.11 | 0.61    | 1.00              | 0.92 | 1.08 | 0.93    |
|   | PRS-SZ | 1.13                    | 1.05 | 1.23 | 0.0021  | 1.08              | 0.99 | 1.18 | 0.10    |
| Psychotic disorders<br>(n = 1,640)                  | PRS-BD | 1.04                    | 0.99 | 1.10 | 0.12    | 0.99              | 0.93 | 1.05 | 0.73    |
|   | PRS-MD | 1.05                    | 1.00 | 1.11 | 0.06    | 1.04              | 0.98 | 1.09 | 0.193   |
|   | PRS-SZ | 1.13                    | 1.07 | 1.19 | <.0001  | 1.12              | 1.06 | 1.19 | <.0001  |
| Schizophrenia<br>(n = 814)                          | PRS-BD | 1.00                    | 0.93 | 1.08 | 0.93    | 0.97              | 0.89 | 1.05 | 0.43    |
|   | PRS-MD | 1.08                    | 1.00 | 1.16 | 0.04    | 1.08              | 1.00 | 1.16 | 0.06    |
|   | PRS-SZ | 1.06                    | 0.99 | 1.14 | 0.11    | 1.07              | 0.98 | 1.16 | 0.12    |
| Psychotic depression<br>(n = 308)                   | PRS-BD | 1.13                    | 1.00 | 1.28 | 0.046   | 1.15              | 1.01 | 1.31 | 0.043   |
|   | PRS-MD | 1.06                    | 0.94 | 1.20 | 0.34    | 1.05              | 0.93 | 1.19 | 0.45    |
|   | PRS-SZ | 1.01                    | 0.89 | 1.14 | 0.90    | 0.95              | 0.83 | 1.08 | 0.42    |
| Any affective psychotic disorder<br>(n = 366)       | PRS-BD | 1.22                    | 1.09 | 1.36 | 0.0006  | 1.21              | 1.07 | 1.37 | 0.002   |
|   | PRS-MD | 1.06                    | 0.95 | 1.19 | 0.30    | 1.03              | 0.92 | 1.16 | 0.56    |
|   | PRS-SZ | 1.09                    | 0.98 | 1.22 | 0.13    | 1.01              | 0.89 | 1.14 | 0.92    |
| Any disorder with psychotic features<br>(n = 1,745) | PRS-BD | 1.06                    | 1.01 | 1.11 | 0.03    | 1.02              | 0.96 | 1.08 | 0.50    |
|   | PRS-MD | 1.05                    | 0.99 | 1.10 | 0.08    | 1.03              | 0.98 | 1.09 | 0.23    |
|   | PRS-SZ | 1.10                    | 1.04 | 1.16 | 0.0003  | 1.09              | 1.03 | 1.15 | 0.004   |

In these analyses, only main diagnoses in the DCPRR were used in sample selection and effect estimation. Full sample: N = 14,743. Excluding patients with psychotic depression at first diagnosis: N = 14,304.

\*Pink: Significant at the  $p < .017$  level; Blue: Significant at the  $p < .05$  level

Table S8. Sensitivity analysis 3: Including related individuals

|   |        | Adjusted vs. Unadjusted |      |      |         |                   |      |      |         |
|---|--------|-------------------------|------|------|---------|-------------------|------|------|---------|
|   |        | Not mutually adjusted   |      |      |         | Mutually adjusted |      |      |         |
| Outcome   | PRS    | HR                      | LCL  | UCL  | p value | HR                | LCL  | UCL  | p value |
| Bipolar disorder<br>(n = 712)                       | PRS-BD | 1.15                    | 1.07 | 1.23 | 0.0002  | 1.12              | 1.03 | 1.21 | 0.005   |
|   | PRS-MD | 1.03                    | 0.95 | 1.10 | 0.47    | 1.00              | 0.93 | 1.08 | 0.90    |
|   | PRS-SZ | 1.11                    | 1.03 | 1.19 | 0.005   | 1.06              | 0.98 | 1.15 | 0.15    |
| Psychotic disorders<br>(n = 1,640)                  | PRS-BD | 1.05                    | 1.00 | 1.10 | 0.047   | 1.01              | 0.95 | 1.06 | 0.84    |
|   | PRS-MD | 1.04                    | 0.99 | 1.09 | 0.09    | 1.03              | 0.98 | 1.08 | 0.26    |
|   | PRS-SZ | 1.11                    | 1.06 | 1.16 | <.0001  | 1.10              | 1.05 | 1.16 | 0.0003  |
| Schizophrenia<br>(n = 814)                          | PRS-BD | 1.01                    | 0.94 | 1.08 | 0.78    | 0.97              | 0.90 | 1.04 | 0.40    |
|   | PRS-MD | 1.07                    | 1.00 | 1.15 | 0.044   | 1.07              | 0.99 | 1.14 | 0.07    |
|   | PRS-SZ | 1.08                    | 1.01 | 1.16 | 0.03    | 1.09              | 1.01 | 1.17 | 0.03    |
| Psychotic depression<br>(n = 308)                   | PRS-BD | 1.10                    | 0.99 | 1.23 | 0.08    | 1.11              | 0.99 | 1.26 | 0.08    |
|   | PRS-MD | 1.09                    | 0.98 | 1.22 | 0.11    | 1.09              | 0.97 | 1.21 | 0.15    |
|   | PRS-SZ | 1.00                    | 0.89 | 1.12 | 0.98    | 0.95              | 0.84 | 1.07 | 0.37    |
| Any affective psychotic disorder<br>(n = 366)       | PRS-BD | 1.19                    | 1.08 | 1.32 | 0.0006  | 1.18              | 1.06 | 1.32 | 0.003   |
|   | PRS-MD | 1.08                    | 0.98 | 1.20 | 0.13    | 1.06              | 0.95 | 1.17 | 0.29    |
|   | PRS-SZ | 1.08                    | 0.98 | 1.20 | 0.12    | 1.01              | 0.90 | 1.12 | 0.92    |
| Any disorder with psychotic features<br>(n = 1,745) | PRS-BD | 1.06                    | 1.01 | 1.11 | 0.01    | 1.03              | 0.97 | 1.08 | 0.33    |
|   | PRS-MD | 1.04                    | 1.00 | 1.09 | 0.07    | 1.03              | 0.98 | 1.08 | 0.21    |
|   | PRS-SZ | 1.09                    | 1.04 | 1.14 | 0.0002  | 1.08              | 1.02 | 1.13 | 0.005   |

Full sample: N = 17,458. Excluding patients with psychotic depression at first diagnosis: N = 16,985.

\*Pink: Significant at the  $p < .017$  level; Blue: Significant at the  $p < .05$  level

Table S9. Sensitivity analysis 4: Including individuals with non-European ancestry

|   |        | Adjusted vs. Unadjusted |      |      |         |                   |      |      |         |
|---|--------|-------------------------|------|------|---------|-------------------|------|------|---------|
|   |        | Not mutually adjusted   |      |      |         | Mutually adjusted |      |      |         |
| Outcome   | PRS    | HR                      | LCL  | UCL  | p value | HR                | LCL  | UCL  | p value |
| Bipolar disorder<br>(n = 712)                       | PRS-BD | 1.16                    | 1.08 | 1.25 | <.0001  | 1.14              | 1.05 | 1.23 | 0.002   |
|   | PRS-MD | 1.02                    | 0.95 | 1.10 | 0.56    | 1.00              | 0.93 | 1.07 | 0.94    |
|   | PRS-SZ | 1.13                    | 1.04 | 1.23 | 0.003   | 1.07              | 0.98 | 1.17 | 0.14    |
| Psychotic disorders<br>(n = 1,640)                  | PRS-BD | 1.05                    | 1.00 | 1.10 | 0.049   | 1.00              | 0.95 | 1.05 | 0.99    |
|   | PRS-MD | 1.05                    | 1.01 | 1.10 | 0.03    | 1.04              | 0.99 | 1.09 | 0.11    |
|   | PRS-SZ | 1.13                    | 1.08 | 1.20 | <.0001  | 1.13              | 1.06 | 1.20 | <.0001  |
| Schizophrenia<br>(n = 814)                          | PRS-BD | 1.01                    | 0.94 | 1.08 | 0.78    | 0.97              | 0.90 | 1.04 | 0.40    |
|   | PRS-MD | 1.07                    | 1.00 | 1.15 | 0.045   | 1.07              | 0.99 | 1.14 | 0.07    |
|   | PRS-SZ | 1.08                    | 1.01 | 1.16 | 0.03    | 1.09              | 1.01 | 1.17 | 0.03    |
| Psychotic depression<br>(n = 308)                   | PRS-BD | 1.10                    | 0.98 | 1.23 | 0.11    | 1.09              | 0.97 | 1.24 | 0.15    |
|   | PRS-MD | 1.08                    | 0.97 | 1.21 | 0.14    | 1.07              | 0.96 | 1.20 | 0.20    |
|   | PRS-SZ | 1.03                    | 0.90 | 1.16 | 0.70    | 0.97              | 0.85 | 1.12 | 0.71    |
| Any affective psychotic disorder<br>(n = 366)       | PRS-BD | 1.20                    | 1.08 | 1.33 | 0.0006  | 1.17              | 1.05 | 1.31 | 0.006   |
|   | PRS-MD | 1.06                    | 0.96 | 1.17 | 0.23    | 1.04              | 0.94 | 1.14 | 0.49    |
|   | PRS-SZ | 1.13                    | 1.01 | 1.27 | 0.03    | 1.05              | 0.93 | 1.19 | 0.45    |
| Any disorder with psychotic features<br>(n = 1,745) | PRS-BD | 1.06                    | 1.01 | 1.11 | 0.02    | 1.02              | 0.97 | 1.07 | 0.52    |
|   | PRS-MD | 1.05                    | 1.01 | 1.10 | 0.03    | 1.04              | 0.99 | 1.09 | 0.11    |
|   | PRS-SZ | 1.12                    | 1.06 | 1.17 | <.0001  | 1.10              | 1.04 | 1.17 | 0.0009  |

Full sample: N = 19454. Excluding patients with psychotic depression at first diagnosis: N = 18,916.

\*Pink: Significant at the p < .017 level; Blue: Significant at the p < .05 level

Table S10. Comparison of main effects of PRS-BD and PRS-SZ on hazard of progression to bipolar disorder or psychotic disorders from the main analyses, competing risk models and multi-state models

| PRS variable | Model                  | Progression to bipolar disorder |       | Progression to Psychotic disorders |        |
|--------------|------------------------|---------------------------------|-------|------------------------------------|--------|
|              |                        | HR                              | p     | HR                                 | p      |
| PRS-BP       | Main analysis*         | 1.14                            | .0004 | 1.06                               | .03    |
|              | Competing risk model** | 1.14                            | .0008 | 1.06                               | .03    |
|              | Multi-state model****  | 1.15                            | .0006 | 1.04                               | .11    |
| PRS-SZ       | Main analysis*         | 1.11                            | .004  | 1.11                               | <.0001 |
|              | Competing risk model** | 1.11                            | .005  | 1.11                               | <.0001 |
|              | Multi-state model ***  | 1.11                            | .02   | 1.09                               | .002   |

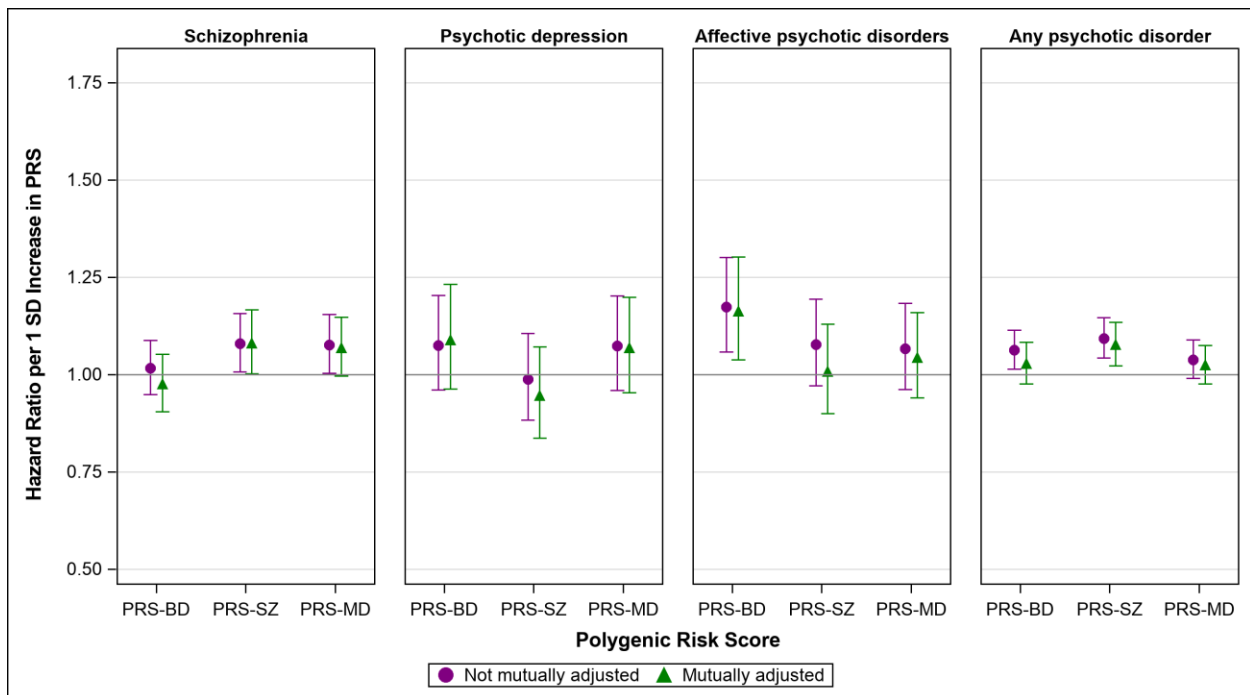
\*Estimates from the unadjusted main models (i.e., adjusted for birth year, gender, and the first 5 principal components but not adjusted for other PRS variables).

\*\*Competing risk model estimated using Fine & Gray's extension of the Cox model, see Fine JP & Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc.* 1999;94:496-509. Analyses conducted in SAS 9.4.

\*\*\*Multi-state models computed using the 'mstate' package in R. The following states were included in the multi-state model: unipolar depression, bipolar disorder, psychotic disorders, bipolar disorder + psychotic disorders, and death. These analyses are based on a cohort of 17,460 iPSYCH2012 participants (69% female) with a unipolar depression diagnosis. Of these, 719 subsequently received a bipolar disorder and 1,669 received a subsequent psychotic disorder diagnosis. Analyses were adjusted for gender and birthdate.

## Supplemental Figures

Figure S1. Associations between polygenic risk scores for bipolar disorder, schizophrenia and major depression and hazard of progression to schizophrenia, psychotic depression, affective psychosis and any disorder with psychotic features in individuals diagnosed with non-psychotic unipolar depression in Danish psychiatric hospitals (N = 16,491)



Numbers of individuals who progressed to a secondary outcomes: schizophrenia = 814, psychotic depression = 308, Any affective psychotic disorder = 366, any psychotic disorder = 1,745.

Figure S2. Interaction between PRS-BD and PRS-SZ on hazard of progression to psychotic depression and any affective psychotic disorder

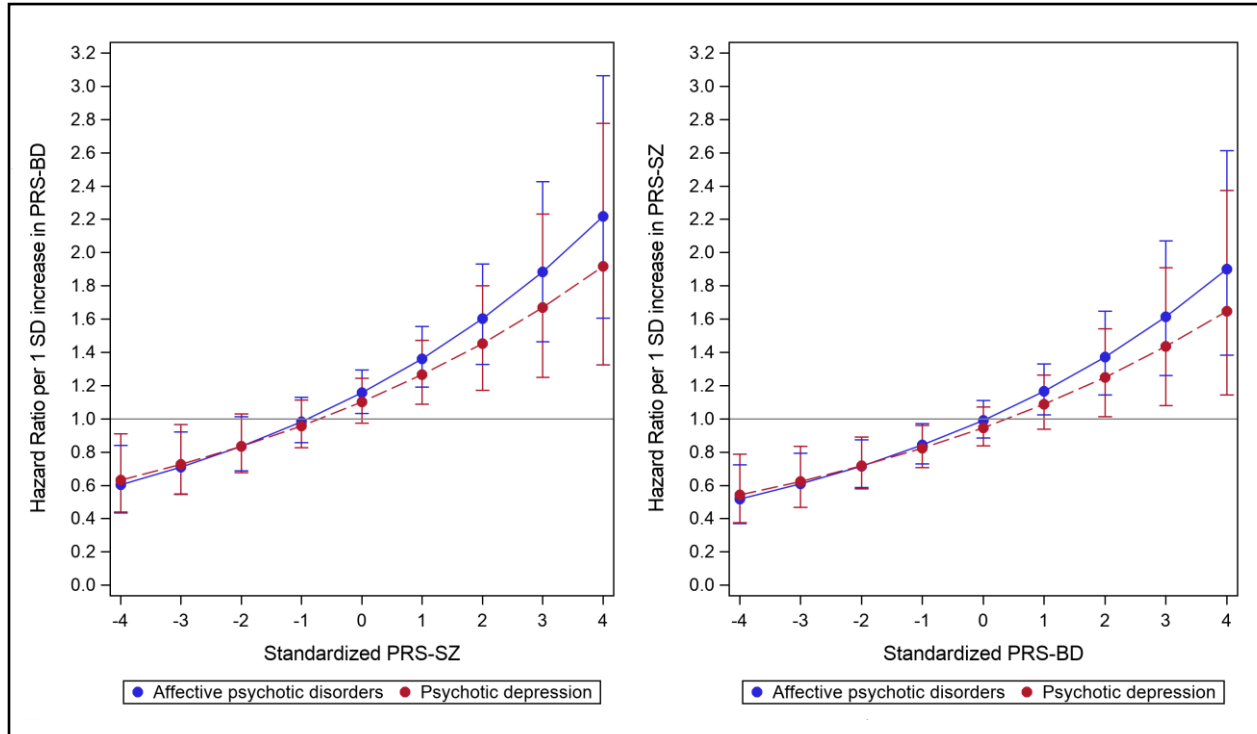
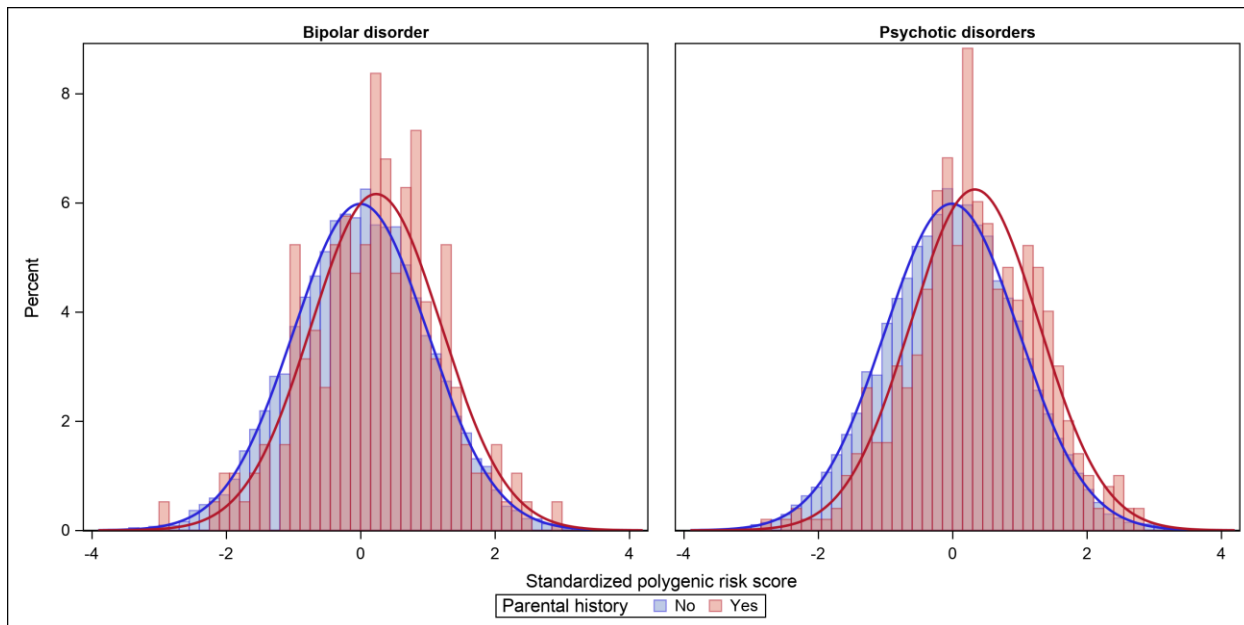


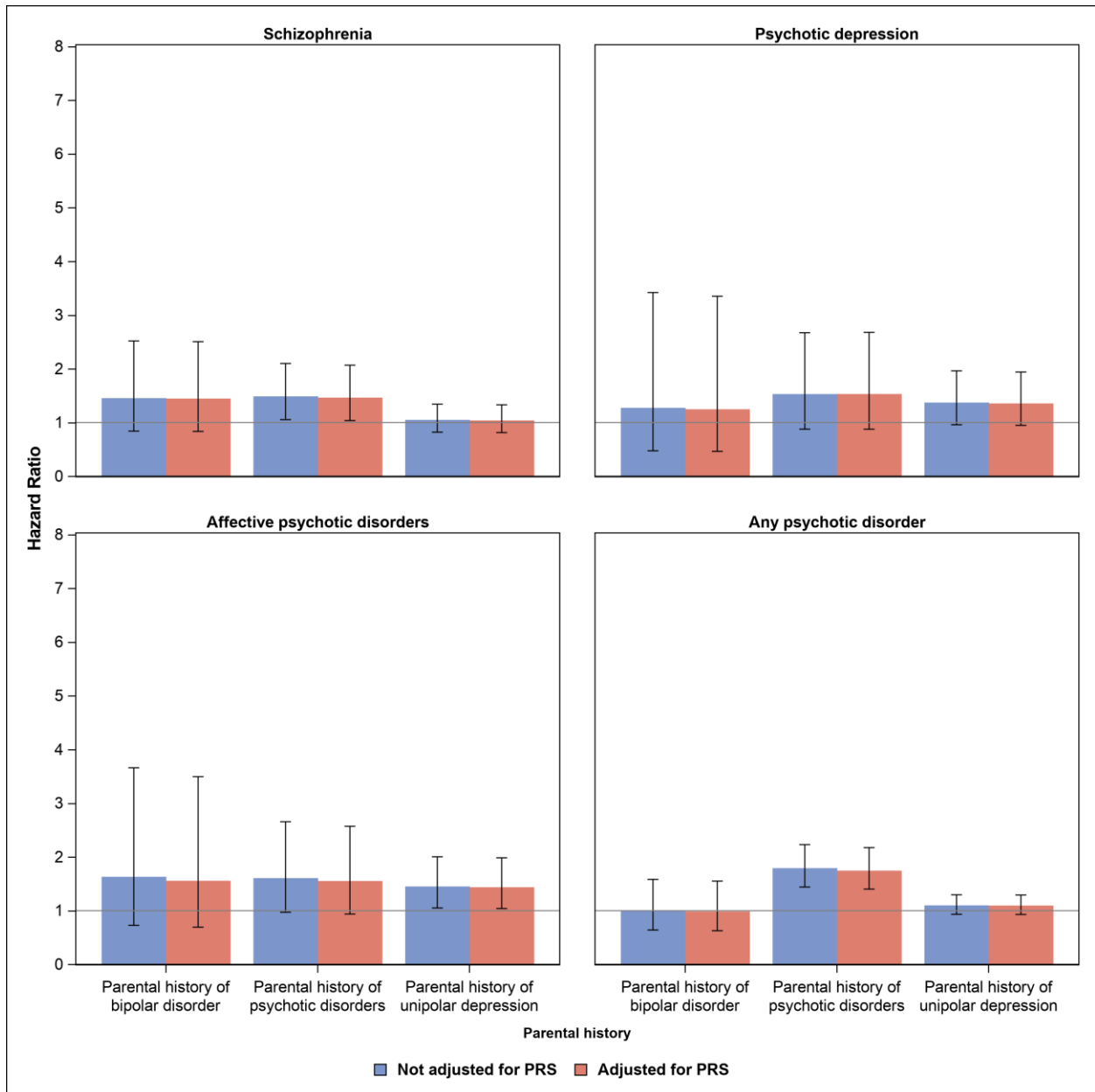


Figure S3. Distribution of polygenic risk for bipolar disorder and schizophrenia, stratified by parental history



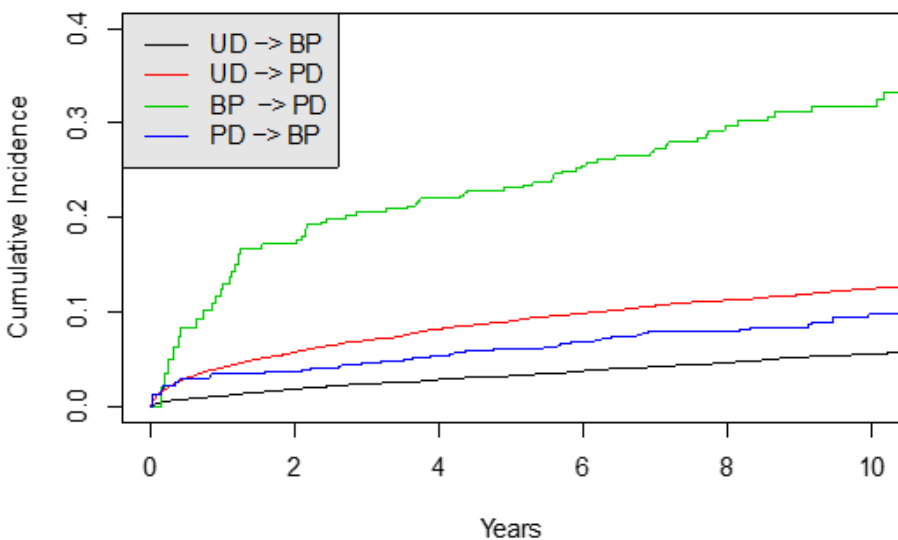
Parental history and polygenic risk score refer to parental history or PRS of that specific outcome (bipolar disorder or psychotic disorders/schizophrenia).

Figure S4. Effects of parental history on hazard of progression from depression to schizophrenia, psychotic depression, Any affective psychotic disorder and any disorder with psychotic features, adjusted and unadjusted for polygenic risk.



Numbers of individuals who progressed to a secondary outcomes: schizophrenia = 712, psychotic depression = 308, Any affective psychotic disorder = 366, any psychotic disorder = 1,745.

Figure S5. Cumulative incidence estimates from multi-state model of progression from depression to bipolar disorder or psychotic disorders



Cumulative incidence calculated using the 'mstate' package in R. These analyses are based on a cohort of 17,460 iPSYCH2012 participants (69% female) with a unipolar depression diagnosis. Of these, 719 subsequently received a bipolar disorder and 1,669 received a subsequent psychotic disorder diagnosis. Analyses were adjusted for gender and birthdate.

- Black line (UD -> BP): cumulative incidence of progression from unipolar depression to bipolar disorder
- Red line (UD -> PD): cumulative incidence of progression from unipolar depression to psychotic disorders
- Green line (BP -> PD): cumulative incidence of progression to psychotic disorders among unipolar depression patients who have already progressed to bipolar disorder
- Blue line (PD -> BP): cumulative incidence of progression to bipolar disorder among unipolar depression patients who have already progressed to psychotic disorders