**Supplementary Table 1:** Univariate and additive models of the influence of polygenic risk score, exposome risk score and family risk score of schizophrenia on poor long-term outcome in FEP patients based on logistic regression models

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | **Row data** | | | |  | **Age-gender adjustedΩ** | | | |
| **Variable** | | **Category** |  | **OR (95%CI)** | **P**  **value** | **R2**  **Nagel** | **Variable**  **importance** |  | **OR (95%CI)** | **P**  **Value** | **R2**  **Nagel** | **Variable**  **importance** |
| **Univariate models** | | |  |  |  |  |  |  |  |  |  |  |
| PRS |  | ≤Sz75 |  | Reference |  |  |  |  | Reference |  |  |  |
|  |  | >Sz75 |  | 1.10[0.54;2.24] | 0.787 | 0.001 | 0.27 |  | 1.17[0.57,2.41] | 0.674 | 0.026 | 0.42 |
| ERS |  | ≤Sz75 |  |  |  |  |  |  | Reference |  |  |  |
|  |  | >Sz75 |  | 1.88[1.04;3.38] | 0.034 | 0.024 | 2.10 |  | 1.98[1.09;3.59] | 0.026 | 0.031 | 2.23 |
| FLS |  | ≤ Sz75 |  | Reference |  |  |  |  | Reference |  |  |  |
|  |  | > Sz75 |  | 2.43[1.34;4.41] | 0.004 | 0.048 | 2.91 |  | 2.50[1.36;4.58] | 0.003 | 0.057 | 2.97 |
| **Additive model PRS & ERS** | | | | |  |  |  |  |  |  |  |  |
| PRS |  | ≤Sz75 |  | Reference |  |  |  |  | Reference |  |  |  |
|  |  | >Sz75 |  | 1.12[0.55;2.29] | 0.759 |  | 0.30 |  | 1.21[0.58;2.52] | 0.610 |  | 0.51 |
| ERS |  | ≤Sz75 |  | Reference |  |  |  |  | Reference |  |  |  |
|  |  | >Sz75 |  | 2.05[0.98;4.30] | 0.057 | 0.030 | 1.90 |  | 2.18[1.01;4.70] | 0.047 | 0.058 | 1.99 |
| **Additive model FLS & ERS** | | | | |  |  |  |  |  |  |  |  |
| FLS |  | ≤Sz75 |  | Reference |  |  |  |  | Reference |  |  |  |
|  |  | >Sz75 |  | 2.31[1.26;4.21] | 0.007 |  | 2.72 |  | 2.39[1.29;4.40] | 0.005 |  | 2.79 |
| ERS |  | ≤Sz75 |  | Reference |  |  |  |  | Reference |  |  |  |
|  |  | >Sz75 |  | 1.72[0.94;3.15] | 0.079 | 0.065 | 1.77 |  | 1.84[0.99;3.40] | 0.053 | 0.078 | 1.94 |
| **Additive model PRS, ERS and FLS** | | | | |  |  |  |  |  |  |  |  |
| PRS |  | ≤Sz75 |  | Reference |  |  |  |  | Reference |  |  |  |
|  |  | >Sz75 |  | 1.20 [0.58;2.48] | 0.620 |  | 0.50 |  | 1.30 [0.62;2.73] | 0.482 |  | 0.70 |
| ERS |  | ≤Sz75 |  | Reference |  |  |  |  | Reference |  |  |  |
|  |  | >Sz75 |  | 1.93 [0.90;4.10] | 0.089 |  | 1.70 |  | 2.06 [0.94;4.50] | 0.070 |  | 1.81 |
| FLS |  | ≤ Sz75 |  | Reference |  |  |  |  | Reference |  |  |  |
|  |  | > Sz75 |  | 1.89 [0.91;3.91] | 0.088 | 0.053 | 1.71 |  | 1.96 [0.93;4.15] | 0.078 | 0.081 | 1.76 |

Ω Adjusted for gender and age, and if PRS was included, adjusted additionally for two PCs

Sz: Schizophrenia. Nagel: Nagelkerke

**Supplementary Table 2:** Polygenic risk score, exposome risk score and family load score of schizophrenia interactions on poor long-term outcome based on logistic regression models without adjustment for age, gender and PC

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **Interaction PRS and ERS** | |  | **Interaction FLS and ERS** | |
|  |  | **PRS ≤ Sz75** | **PRS>Sz75** |  | **FLS≤ Sz75** | **FLS> Sz75** |
|  |  | **OR (95%CI)** | **OR(95%CI)** |  | **OR (95%CI)** | **OR(95%CI)** |
| **ERS ≤ Sz75** |  | 1 | 1.05 [0.47;2.36] |  | 1 | 2.60 [1.27; 5.33] |
| **ERS > Sz75** |  | 1.91 [0.82;4.45] | 2.70 [0.64;11.45] |  | 1.94 [0.95; 3.99] | 3.33 [1.26; 8.81] |
| **RERI** |  | 0.74 [-3.33; 4.81] | |  | -0.21 [-3.89, 3.46] | |
| **R2 Nagelkerke** |  | 0.031 | |  | 0.067 | |
| **Variable Importance** | | | |  |  | |
| **ERS** |  | 1.50 | |  | 1.81 | |
| **PRS or FLS** |  | PRS: 0.12 | |  | FLS: 2.62 | |
| **Interaction** |  | PRS\*ERS: 0.34 | |  | FLS\*ERS: 0.62 | |

CI: Confidence interval; ERS: Exposome risk score; PRS: polygenic risk score; FLS family load score; RERI: Relative excess risk due to interaction. Unadjusted

**Supplementary Table 3:** Polygenic risk score, exposome risk score and family load score of schizophrenia interactions on poor long-term outcome based on logistic regression models using continuous variables

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **OR(95%CI)** | **Variable**  **importance** |  | **Adjusted ORΩ** | **Variable**  **importance** |
| **PRS & ERS** |  |  |  |  |  |
| ***Additive model*** | |  |  |  |  |
| PRS-Sz | 1.22 [0.89,1.67] | 1.22 |  | 1.29 [0.93,1.79] | 1.53 |
| ERS-Sz | 1.29 [0.94,1.77] | 1.60 |  | 1.38 [0.99,.93] | 1.88 |
| R2 Nagelkerke | 0.032 |  |  | 0.068 |  |
| ***With interaction*** | |  |  |  |  |
| PRS-Sz | 1.25 (0.91,1.75) | 1.36 |  | 1.34 (0.96,1.90) | 1.68 |
| ERS-Sz | 1.29 (0.94,1.78) | 1.58 |  | 1.37 (0.98,1.95) | 1.82 |
| PRS-Sz \*ERS-Sz | 1.31(0.92,1.92) | 1.44 |  | 1.38 (0.95,2.07) | 1.65 |
|  |  |  |  |  |  |
| RERI (95%CI BCa) | 0.57 (-0.17, 2.93) |  |  | 0.83 (-0.14,3.83) |  |
| R2 Nagelkerke | 0.049 |  |  | 0.090 |  |
|  |  |  |  |  |  |
| **FLS & ERS** |  |  |  |  |  |
| ***Additive model*** | |  |  |  |  |
| FLS-Sz | 1.21 [0.83,1.77] | 0.99 |  | 1.21 [0.83,1.77] | 0.99 |
| ERS-Sz | 1.25 [0.97,1.62] | 1.73 |  | 1.30 [1.00,1.70] | 1.96 |
| R2 Nagelkerke | 0.025 |  |  | 0.033 |  |
| ***With interaction*** | |  |  |  |  |
| FLS-Sz | 1.31 (0.83,3.24) | 0.82 |  | 1.30 (0.82,3.18) | 0.81 |
| ERS-Sz | 1.35 (1.01,1.96) | 1.87 |  | 1.41 (1.05,2.06) | 2.08 |
| FLS-Sz\*ERS-Sz | 2.44 (0.90,26.83) | 1.05 |  | 2.55 (0.93,27.28) | 1.09 |
|  |  |  |  |  |  |
| RERI (95%CI BCa) | 2.66 (-7834.6, 5608.6) |  |  | 2.97 (-11260.6,3786.0) |  |
| R2 Nagelkerke | 0.040 |  |  | 0.050 |  |

CI: Confidence interval; ERS: Exposome risk score; PRS: polygenic risk score; FLS family load score; RERI: Relative excess risk due to interaction

Ω Adjusted for gender and age, and if PRS was included, adjusted additionally for two PCs

**Supplementary Table 4:** Polygenic risk score, exposome risk score and family load score of schizophrenia interactions using each of the ERS dimensions on poor long-term outcome based on logistic regression models

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | Interaction PRS & ERS dimension | | |  | Interaction FLS & ERS dimension | | |
|  |  |  | PRS ≤ Sz75 | PRS>Sz75 | |  | FLS≤ Sz75 | FLS> Sz75 | |
|  |  |  | OR (95%CI) | OR(95%CI) | |  | OR (95%CI) | OR(95%CI) | |
| **Urbanicity** |  |  |  |  | |  |  |  | |
| Rural |  |  | 1 | 0.52 [0.16;1.71] | |  | 1 | 2.39 [0.93;6.18] | |
| Urban/semi |  |  | 0.62 [0.29; 1.32] | 1.19 [0.43;3.29] | |  | 0.86 [0.45;1.65] | 2.15 [0.89;5.20] | |
| RERI\* |  |  | NCΩ | | |  | NCΩ | | |
| R2 Nagelkerke |  |  | 0.051 | | |  | 0.058 | | |
| Variable Importance | | | | | |  |  | | |
| Urbanicity |  |  | 1.24 | | |  | 0.45 | | |
| PRS or FLS |  |  | PRS: 1.07 | | |  | FLS: 1.80 | | |
| Interaction |  |  | Urbanicity\*PRS: 1.70 | | |  | Urbanicity\*FLS: 0.07 | | |
| **Cannabis use** | | |  | | |  |  | | |
| No |  |  | 1 | | 1.21 [0.51;2.86] |  | 1 | | 3.73 [1.69;8.22] |
| Yes |  |  | 0.86 [0.38;1.98] | | 0.81 [0.20;3.24] |  | 0.82 [0.41;1.63] | | 1.06 [0.41;2.74] |
| RERI\* |  |  | NCΩ | | |  | NCΩ | | |
| R2 Nagelkerke |  |  | 0.030 | | |  | 0.086 | | |
| Variable Importance | | | | | |  |  | | |
| Cannabis |  |  | 0.34 | | |  | 0.57 | | |
| PRS or FLS |  |  | PRS: 0.44 | | |  | FLS: 3.26 | | |
| Interaction |  |  | Cannabis\*PRS: 0.30 | | |  | Cannabis\*FLS: 1.60 | | |
| **Obstetric complications** | | | | | |  |  | | |
| No |  |  | 1 | | 1.08 [0.50;2.35] |  | 1 | | 2.51 [1.27;4.96] |
| Yes |  |  | 2.04 [0.72;5.80] | | 6.22 [0.66;58.80] |  | 3.63 [1.44;9.11] | | 5.49[1.66;18.09] |
| RERI |  |  | 4.10 [-9.86; 18.05] | | |  | 0.35 [-6.78; 7.48] | | |
| R2 Nagelkerke |  |  | 0.063 | | |  | 0.108 | | |
| Variable Importance | | | | | |  |  | | |
| Obstetric complications 1.34 | | | | | |  | 2.74 | | |
| PRS or FLS |  |  | PRS: 0.19 | | |  | FLS: 2.64 | | |
| Interaction |  |  | Obstetric\*PRS: 0.80 | | |  | Obstetric\*FLS: 0.63 | | |
| **Childhood adversity** | | | | | |  |  | | |
| No |  |  | 1 | | 1.42 [0.61;3.32] |  | 1 | | 2.30 [1.06;5.00] |
| Yes |  |  | 3.55 [1.55; 8.14] | | 3.23 [0.81;12.79] |  | 3.07 [1.49;6.31] | | 5.33[2.15;13.20] |
| RERI |  |  | -0.75 [-5.75; 4.26] | | |  | 0.94 [-4.09; 6.02] | | |
| R2 Nagelkerke |  |  | 0.109 | | |  | 0.121 | | |
| Variable Importance | | | | | |  |  | | |
| Childhood adversity 3.00 | | | | | |  | 3.04 | | |
| PRS or FLS |  |  | PRS: 0.81 | | |  | FLS: 2.10 | | |
| Interaction |  |  | Childhood \*PRS: 0.52 | | |  | Childhood\*FLS: 0.42 | | |

\* RERI could not be calculated as at least one of the odds ratios was below 1.

CI: Confidence interval; ERS: Exposome risk score; PRS: polygenic risk score; FLS family load score; RERI: Relative excess risk due to interaction. Adjusted for gender and age, and if PRS was included, adjusted additionally for two PCs

Ω NC: RERI Not Calculable, as at least one of the OR <1