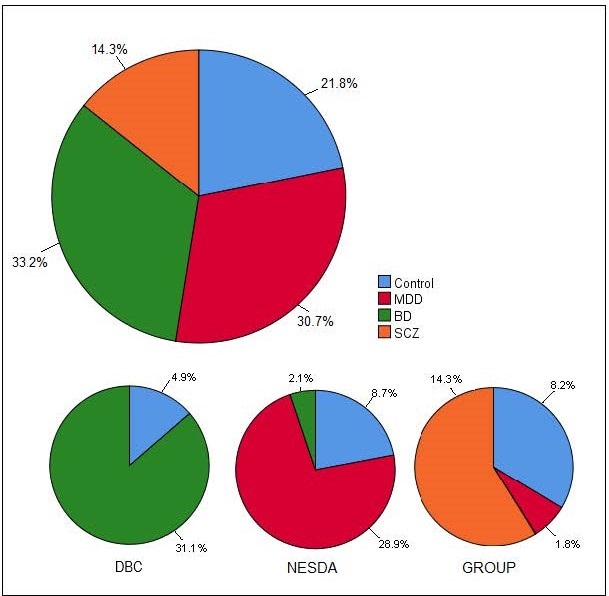
**Supplementary tables and figures**

**Distribution of diagnosis categories per cohort study**



**Figure 1*:***Distribution of cases in percentages (%) of major depressive disorder (MDD), bipolar disorder (BD), schizophrenia (SCZ) and participants without psychiatric diagnosis (controls) in the total dataset (large pie chart) and specified for each cohort study (three smaller pie charts) used for the composite dataset: the Dutch Bipolar Cohort (DBC), the Netherlands Study of Depression and Anxiety (NESDA) and the Genetic Risk and Outcome in Psychosis (GROUP) study.

**Table 1:**Relation of childhood maltreatment type and psychiatric diagnosis in a non-adjusted multivariate regression model, in odds ratio (OR) with 95% confidence interval (OR [95% CI]).

|  |  |  |  |
| --- | --- | --- | --- |
|  | Abuse | Neglect | Combined |
| Major depressive disorder | **1.78 [1.24-2.56]\*** | **2.66 [2.06-3.42]\*** | **4.92 [3.65-6.64]\*** |
| Bipolar disorder | **1.98 [1.39-2.82]\*** | **2.86 [2.23-3.67]\*** | **4.64 [3.44-6.25]\*** |
| Schizophrenia | **3.17 [2.17-4.63]\*** | **1.74 [1.27-2.39]\*** | **3.39 [2.40-4.80]\*** |

\*Significant with α=0.05

**Table 2:** Multivariate logistic regression model using each diagnosis category as reference category, comparing the effects between diagnosis categories per CM type, expressed in p-values.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Abuse | Neglect | Combined |
| *Reference: MDD* |  |  |  |
| BD | 0.375 | 0.268 | 0.864 |
| SCZ | **0.011\*** | 0.108 | 0.566 |
| *Reference: BD* |  |  |  |
| MDD | 0.375 | 0.268 | 0.864 |
| SCZ | **0.048\*** | **0.019\*** | 0.484 |
| *Reference: SCZ* |  |  |  |
| MDD | **0.011\*** | 0.108 | 0.566 |
| BD | **0.048\*** | **0.019\*** | 0.484 |

\*Significant with α=0.05. Abbreviations: CM: childhood maltreatment; MDD: major depressive disorder; BD: bipolar disorder; SCZ: schizophrenia.

**Table 3:** Relation of CM type and psychiatric diagnosis, expressed in odds ratios with 95% confidence intervals (OR [95% CI], in an adjusted multivariate regression model using each CM type as reference category.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Abuse | Neglect | Combined | No CM |
| *Reference: abuse* | | | | |
| MDD | . | 1.35 [0.88-2.08] | **2.61 [1.65-4.13]\*** | **0.6 [0.41-0.87]\*** |
| BD | . | 1.34 [0.89-2.02] | **2.39 [1.53-3.72]\*** | **0.5 [0.35-0.71]\*** |
| SCZ | . | **0.47 [0.26-0.84]\*** | 1.06 [0.58-1.94] | **0.28 [0.18-0.46]\*** |
| *Reference: neglect* | | | | |
| MDD | 0.74 [0.48-1.14] | . | **1.93 [1.33-2.8]\*** | **0.44 [0.34-0.58]\*** |
| BD | 0.75 [0.49-1.12] | . | **1.78 [1.23-2.56]\*** | **0.37 [0.29-0.48]\*** |
| SCZ | **2.15 [1.19-3.88]\*** | . | **2.28 [1.31-3.98]\*** | **0.61 [0.4-0.93]\*** |
| *Reference: combined* | | | | |
| MDD | **0.38 [0.24-0.61]\*** | **0.52 [0.36-0.75]\*** | . | **0.23 [0.17-0.31]\*** |
| BD | **0.42 [0.27-0.65]\*** | **0.56 [0.39-0.81]\*** | . | **0.21 [0.15-0.28]\*** |
| SCZ | 0.94 [0.52-1.71] | **0.44 [0.25-0.76]\*** | . | **0.27 [0.17-0.41]\*** |
| *Reference: no CM* | | | | |
| MDD | **1.66 [1.14-2.42]\*** | **2.25 [1.72-2.93]\*** | **4.34 [3.18-5.92]\*** | . |
| BD | **2 [1.4-2.87]\*** | **2.69 [2.09-3.46]\*** | **4.78 [3.53-6.49]\*** | . |
| SCZ | **3.51 [2.17-5.67]\*** | **1.64 [1.08-2.48]\*** | **3.74 [2.41-5.79]\*** | . |

\*Significant with α=0.05. Abbreviations: CM: childhood maltreatment; MDD: major depressive disorder; BD: bipolar disorder; SCZ: schizophrenia.

**Table 4:** Summary of all statistically significant associations between type of childhood maltreatment and symptoms of depression, mania, and psychosis, with a significance level of α=0.05.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Abuse** | **Neglect** | **Combined** |
| **Depressive symptoms** | Worthlessness/Guilt ↑  Suicide attempt ↑ | Agitation ↑ | Depressive mood ↑  Weight gain/increased appetite ↑  Hypersomnia ↑  Agitation ↑  Retardation ↑  Worthlessness/Guilt ↑  Returning thoughts of death ↑  Suicide attempt ↑ |
| **Manic**  **symptoms** |  | Reduced need for sleep ↑ | Exaggerated confidence ↓  Reduced need for sleep ↑ |
| **Psychotic symptoms** | Delusions ↑  Hallucinations ↑ | Delusions ↓ |  |

**Table 5:**Results of bidirectional MR of abuse, neglect and combined CM (threshold for maltreatment >0) against BD, MDD, and SCZ with p-value threshold: 1e-06 for forward analyses, 5e-08 for backward analyses.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **MR** | **N SNP** | **IVW (95% CI)** | **p-value\*** | **IVW Q (df)** | **Q p-value** | **WM (95% CI)** | **p-value\*** | **MR-Egger (95% CI)** | **p-value\*** | **Egger intercept p-value\*** | **Steiger Test p-value\* b** | **MR-PRESSO a** | **Mean F** |
| Fw: Abuse on BD | 2 | -0.055 (-0.192; 0.082) | 0.430 | 1.71 (1) | 0.191 | NRc | NRc | NRc | NRc | NRc | NRb | NRc | 24.3 |
| Bw: BD on Abuse | 35 | 0.085 (-0.023; 0.193) | 0.123 | 33.9 (34) | 0.473 | 0.074 (-0.084; 0.233) | 0.357 | -0.073 (-0.662; 0.516) | 0.809 | 0.595 | NRb | GT; p=0.445 | 39.4 |
| Fw: Neglect on BD | 2 | -0.136 (-0.269; 0.003) | 0.045 | 3.69 (1) | 0.055 | NRc | NRc | NRc | NRc | NRc | <0.001 | NRc | 25.1 |
| Bw: BD on Neglect | 35 | 0.002 (-0.118; 0.121) | 0.976 | 52.2 (34) | 0.024 | -0.061 (-0.244; 0.123) | 0.517 | -1.04 (-1.76; -0.316) | 0.008 | 0.007 | <0.001 | DT; p=0.673 | 39.4 |
| Fw: Combined on BD | 2 | -0.203 (-0.327; -0.079) | 0.001 | 0.163 (1) | 0.686 | NRc | NRc | NRc | NRc | NRc | <0.001 | NRc | 25.7 |
| Bw: BD on combined | 35 | -0.010 (-0.138; 0.119) | 0.881 | 41.1 (34) | 0.188 | 0.013 (-0.177; 0.202) | 0.896 | -0.772 (-1.50; -0.047) | 0.044 | 0.044 | <0.001 | GT; p=0.184 | 39.4 |
| Fw: Abuse on MDD | 2 | -0.016 (-0.145; 0.113) | 0.808 | 0.365 (1) | 0.546 | NRc | NRc | NRc | NRc | NRc | NRb | NRc | 24.3 |
| Bw: MDD on Abuse | 0 | NRc | NRc | NRc | NRc | NRc | NRc | NRc | NRc | NRc | NRb | NRc | NRc |
| Fw: Neglect on MDD | 2 | -0.057 (-0.184; 0.071) | 0.383 | 0.061 (1) | 0.805 | NRc | NRc | NRc | NRc | NRc | NRb | NRc | 25.1 |
| Bw: MDD on Neglect | 0 | NRc | NRc | NRc | NRc | NRc | NRc | NRc | NRc | NRc | NRb | NRc | NRc |
| Fw: Combined on MDD | 2 | -0.036 (-0.158; 0.086) | 0.562 | 0.004 (1) | 0.949 | NRc | NRc | NRc | NRc | NRc | NRb | NRc | 25.7 |
| Bw: MDD on Combined | 0 | NRc | NRc | NRc | NRc | NRc | NRc | NRc | NRc | NRc | NRb | NRc | NRc |
| Fw: Abuse on SCZ | 2 | 0.125 (0.011; 0.239) | 0.032 | 6.46 (1) | 0.011 | NRc | NRc | NRc | NRc | NRc | <0.001 | NRc | 24.3 |
| Bw: SCZ on Abuse | 176 | 0.105 (0.052; 0.159) | <0.001 | 181 (175) | 0.353 | 0.128 (0.047; 0.210) | 0.002 | 0.251 (0.040; 0.462) | 0.021 | 0.165 | <0.001 | GT; p=0.341 | 45.6 |
| Fw: Neglect on SCZ | 2 | -0.065 (-0.182; 0.052) | 0.279 | 0.374 (1) | 0.541 | NRc | NRc | NRc | NRc | NRc | NRb | NRc | 25.1 |
| Bw: SCZ on Neglect | 176 | 0.086 (0.028; 0.145) | 0.004 | 196 (175) | 0.133 | 0.120 (0.031; 0.209) | 0.008 | 0.121 (-0.123; 0.364) | 0.333 | 0.776 | <0.001 | GT; p=0.127 | 45.6 |
| Fw: Combined on SCZ | 2 | -0.034 (-0.140; 0.073) | 0.537 | 0.002 (1) | 0.963 | NRc | NRc | NRc | NRc | NRc | NRb | NRc | 25.7 |
| Bw: SCZ on combined | 176 | 0.105 (0.042; 0.169) | 0.001 | 156 (175) | 0.844 | 0.116 (0.022; 0.210) | 0.015 | 0.201 (-0.045; 0.448) | 0.111 | 0.431 | <0.001 | GT; p=0.853 | 45.6 |

\*) Significance level α=0.05. Abbreviations: Fw: forward analysis; Bw: backward analysis; BD: bipolar disorder; Combined: Abuse AND Neglect; MDD: major depressive disorder; SCZ: schizophrenia; MR: mendelian randomization; SNP: single nucleotide polymorphism; IVW: inverse variance weighted (fixed effect); 95% CI: 95% confidence interval; Q (df): Cochran’s Q statistic (degrees of freedom); WM: weighted median; NR: not reported, DT: distortion test; GT: global test.   
  
a The Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test identifies possible bias from horizontal pleiotropy, in three parts, (1) the MR-PRESSO global test which detects horizontal pleiotropy, (2) the outlier corrected causal estimate which corrects for the detected horizontal pleiotropy and (3) the MR-PRESSO distortion test which estimates if the causal estimate is significantly different (at p<0.05) after adjustment for outliers. We conduct all three stages (with the argument NbDistribution=1000, namely using1000 simulation from the null distribution to compute empirical p-values) and present the outlier adjusted causal estimates when both global and distortion tests are significant.  
b We did not run Steiger Test if none of the MR analysis resulted significant (NR: not reported in the cell).  
c Not enough SNP to perform this MR (NR: not reported in the cell).

**Table 6:** Results of follow-up analysis on forward MR of abuse, neglect and combined CM against SCZ, BD and MDD with p-value threshold 3e-6.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **MR** | **N SNP** | **IVW (95% CI)** | **p-value\*** | **IVW Q (df)** | **Q p-value** | **WM (95% CI)** | **p-value\*** | **MR-Egger (95% CI)** | **p-value\*** | **Egger intercept p-value\*** | **Steiger Test p-value\* b** | **MR-PRESSO a** | **Mean F** |
| Fw: Abuse on BD | 6 | -0.013 (-0.096; 0.070) | 0.757 | 5.53 (5) | 0.355 | -0.003 (-0.115; 0.109) | 0.963 | -0.077 (-0.638; 0. 483) | 0.800 | 0.764 | NRb | GT; p=0.377 | 23.1 |
| Fw: Neglect on BD | 8 | -0.003 (-0.069; 0.063) | 0.929 | 17.4 (7) | 0.015 | 0.043 (-0.050; 0.135) | 0.366 | 0.178 (0.045; 0.312) | 0.039 | 0.021 | <0.001 | DT; p=0.403 | 23.5 |
| Fw: Combined on BD | 8 | -0.055 (-0.116; 0.005) | 0.074 | 11.5 (7) | 0.117 | -0.028 (-0.112; 0.056) | 0.512 | -0.110 (-0.302; 0.083) | 0.307 | 0.563 | NRb | GT; p=0.119 | 23.5 |
| Fw: Abuse on MDD | 7 | 0.001 (-0.077; 0.076) | 0.993 | 1.44 (6) | 0.963 | 0.024 (-0.068; 0.116) | 0.611 | 0.032 (-0.237; 0.301) | 0.827 | 0.822 | NRb | GT; p=0.967 | 23.2 |
| Fw: Neglect on MDD | 8 | 0.037 (-0.027; 0.100) | 0.256 | 8.58 (7) | 0.284 | 0.037 (-0.054; 0.129) | 0.456 | -0.021 (-0.159; 0.117) | 0.776 | 0.795 | NRb | GT; p=0.320 | 23.4 |
| Fw: Combined on MDD | 9 | -0.058 (-0.112; -0.006) | 0.030 | 3.34 (8) | 0.911 | -0.036 (-0.106; 0.034) | 0.308 | 0.021 (-0.079; 0.122) | 0.689 | 0.418 | <0.001 | GT; p=0.920 | 23.2 |
| Fw: Abuse on SCZ | 6 | 0.112 (0.045; 0.180) | 0.001 | 7.50 (5) | 0.186 | 0.099 (-0.008; 0.191) | 0.132 | 0.174 (-0.321; 0.669) | 0.528 | 0.815 | <0.001 | GT; p=0.196 | 23.1 |
| Fw: Neglect on SCZ | 6 | -0.025 (-0.076; 0.025) | 0.323 | 43.2 (7) | <0.001 | 0.016 (-0.058; 0.090) | 0.667 | 0.150 (-0.050; 0.351) | 0.193 | 0.091 | NRb | DT; p=0.196 | 23.5 |
| Fw: Combined on SCZ |  | 0.017 (-0.035; 0.050) | 0.514 | 8.10 (7) | 0.324 | 0.034 (-0.037; 0.104) | 0.349 | 0.074 (-0.059; 0.206) | 0.317 | 0.391 | NRb | GT; p=0.315 | 23.3 |

\*) Significance level α=0.05. Abbreviations: Fw: forward analysis; BD: bipolar disorder; Combined: Abuse AND Neglect; MDD: major depressive disorder; SCZ: schizophrenia; MR: mendelian randomization; SNP: single nucleotide polymorphism; IVW: inverse variance weighted (fixed effect); 95% CI: 95% confidence interval; Q (df): Cochran’s Q statistic (degrees of freedom); WM: weighted median; DT: distortion test; GT: global test.   
  
a The Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test identifies possible bias from horizontal pleiotropy, in three parts, (1) the MR-PRESSO global test which detects horizontal pleiotropy, (2) the outlier corrected causal estimate which corrects for the detected horizontal pleiotropy and (3) the MR-PRESSO distortion test which estimates if the causal estimate is significantly different (at p<0.05) after adjustment for outliers. We conduct all three stages (with the argument NbDistribution=1000, namely using1000 simulation from the null distribution to compute empirical p-values) and present the outlier adjusted causal estimates when both global and distortion tests are significant.  
b We did not run Steiger Test if none of the MR analysis resulted significant (NR: not reported in the cell).