**Clinical Indicators of Treatment-Resistant PSYCHOSIS**

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## Supplementary Methods

### Sample description

Study individuals were from the CardiffCOGS (COGnition in Schizophrenia) sample, which has been previously described1,2. The sample consists of a total of 1302 individuals with schizophrenia (*n*=767), schizoaffective disorder depressed type (*n*=168), schizoaffective disorder bipolar type (*n*=119), related psychotic disorders (*n*=114), and mood disorders (*n*=129). All patient groups were recruited as part of a single study, and all aspects of phenotyping and research diagnosis were equivalent across groups. The study was conducted from Cardiff University and participants were recruited from community, in-patient and voluntary sector mental health services from across the UK, but primarily Cardiff and South Wales. Eligibility criteria included a diagnosis of schizophrenia, psychotic disorder or bipolar disorder and aged between 16 and 65 at the time of recruitment. Participants were excluded if they had a neurological condition (including intellectual disability, dementia, or brain damage) that was likely to affect their ability to participate in the study, or if they had a current substance dependence disorder.

Study individuals completed a comprehensive clinical interview based on the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) instrument3, donated a blood sample for genetic analysis, completed the MATRICS cognitive battery4, and consented for access to their clinical case notes. Trained psychiatrists or psychology graduates conducted these interviews, and regular inter-rater reliability was undertaken. Trained raters reviewed this interview, along with available clinical records, to complete OPCRIT ratings5 and to determine a consensus lifetime DSM-IV and ICD-10 diagnosis[22](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6019354/#b22-43-4-245) (inter-rater reliability κ statistics: schizophrenia = 0.83, schizoaffective depressive = 0.63, schizoaffective bipolar = 0.72, bipolar disorder = 0.85).

### Genotyping and quality control

The CardiffCOGS sample was genotyped on either the Illumina HumanOmniExpressExome-8 array at the Broad Institute (Massachusetts, USA) or the Illumina HumanOmniExpress-12 array at DeCode Genetics (Reykjavik, Iceland) as previously described6,7. After basic QC8, removing all individuals and SNPs with coverage < 2%, the data was imputed using IMPUTE29 and a combination of the 1000 Genomes (phase 3) and UK10K reference panels10. Best-guess genotypes were generated from the imputed data for SNPs with imputation (INFO) score ≥ 0.9, minor allele frequency (MAF) ≥ 1%, and HWE p-value ≤ 1 x 10-10. All genetic analyses were restricted to those of European ancestry, assessed by principal component analysis, and related individuals with 𝜋 > 0.2 were identified and one member removed at random.

### Schizophrenia polygenic risk score (PRS)

Polygenic risk scores were created based on the results from the latest large scale schizophrenia GWAS meta-analysis2 comprised of the Psychiatric Genomics Consortium GWAS (PGC2, excluding individuals from CardiffCOGS)11 and CLOZUK212, totalling 39,915 schizophrenia cases and 64,639 controls. Risk scores were calculated following the method described by Wray et al (2014)13 and using --score function in PLINK v1.0914. High quality SNPs was selected to generate the scores that had a MAF > 10%, INFO score > 0.9, a low linkage disequilibrium to each other and excluding all indels and the extended MHC region. The schizophrenia GWAS results of SNPS associated at nine P-value thresholds (5 x 10-8, 1 x 10-6, 1 x 10-4, 0.001, 0.01, 0.05, 0.1, 0.2, 0.5) were selected to compute the polygenic risk scores in our sample. We regressed a model for each polygenic risk score created from various training p-value thresholds against a base model including the first five principal components and any additional principal components from the first 20 that were nominally associated (P < 0.05) with TRP. To assess the proportion of variance explained we computed the R2 on the liability scale15 based on a lifetime prevalence of 30%, to account for ascertainment bias.

### Copy number variation (CNVs)

The identification and quality control of CNVs in the CardiffCOGS sample has been previously described6,7. Briefly, PennCNV16 was used for CNV detection and CNVs called in the same individual were joined together if the distance separating them was less than 50% of their combined length. CNVs were excluded if they were called using fewer than 10 probes, were less than 10KB in size, overlapped segmental duplications by more than 50% of their length, had a probe density of < 1 probe per 20Kb, had a frequency > 1% or were outliers for the following quality control metrics: log R ratio standard deviation, B-allele frequency drift, wave factor and total number of CNVs. To compare the enrichment of rare, pathogenic CNVs in TRP with non-TRP, we analysed (i) the presence of an intellectual disability (ID) pathogenic CNV, defined as any locus associated with ID in Coe et al (2014)17, and (ii) the presence of a CNV previously associated with schizophrenia, defined as the 16 loci described in Rees et al (2014)6. We also analysed the presence of chromosomal deletions and duplication spanning 500kb or 1Mb in length, irrespective of whether it is considered to be pathogenic. No individual within CardiffCOGS had more than one pathogenic CNV and differences between TRP and non-TRP were analysed using Firth’s logistic regression18 in R.

## Supplementary Table 1: Diagnoses of study individuals

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Diagnosis** | **TRP N (Total=561)** |  | **Non-TRP N (Total=509)** |  | **Total N (Total=1070)** |
| Schizophrenia | 431 (76.83%) |  | 302 (59.33%) |  | 733 (68.50%) |
| Schizoaffective depressed | 66 (11.76%) |  | 83 (16.31%) |  | 149 (13.93%) |
| Schizoaffective bipolar | 45 (8.02%) |  | 49 (9.63%) |  | 94 (8.79%) |
| Other psychotic disorder | 19 (3.39%) |  | 75 (14.73%) |  | 94 (8.79%) |

Supplementary Table 1: DSM-IV or ICD-10 diagnoses of individuals with treatment-resistant schizophrenia (TRP, *n* = 561), treatment-responsive schizophrenia (non-TRP, *n* = 509), and the combined total sample (*n* = 1070). Other psychotic disorder includes: psychotic disorder not otherwise specified, schizophreniform disorder, delusional disorder, and brief psychotic disorder.

## Supplementary Table 2: Definitions of clinical predictive variables

|  |  |  |
| --- | --- | --- |
| **Variable** | **N (1070)** | **Description** |
| ***Demographics and family background*** |
| Male sex | 1069 (99.9%) | Sex: 1 = male, 0 = female |
| Urbanicity | 894 (83.6%) | The main place of upbringing: 1 = city, 0 = a village or town |
| Family Hx of schizophrenia | 923 (86.3%) | Family history of schizophrenia in a first or second degree relative |
| Family Hx of psychosis, affective or suicide | 910 (85.0%) | Family history of a psychotic disorder, affective disorder or suicide in a first or second degree relative |
| Mother’s age at birth | 965 (90.2%) | Mother’s age at birth |
| Father’s age at birth | 916 (85.6%) | Father’s age at birth |
| ***Premorbid factors*** |
| Birth complications | 928 (86.7%) | Complication with the participant’s birth such as low birth weight, hypoxia or assisted delivery |
| Pregnancy complications | 893 (83.5%) | Complication with their mother’s pregnancy such as prematurity, pre-eclampsia or placental problems |
| Developmental problems | 951 (88.9%) | A failure to thrive or meet developmental milestones |
| Childhood abuse | 975 (91.1%) | Childhood physical or sexual abuse reported in the Childhood Life Events Questionnaire (CLEQ) delivered at interview **19** |
| Years in education | 1030 (96.3%) | Total years spent in education |
| Highest level of education | 1040 (97.2%) | Highest educational attainment: 0 = none, 1 = 11+, 2 = CSE, 3 = O-Level or GCSE, 4 = A-level, 5 = Degree, 6 = Post-graduate degree |
| Premorbid IQ (NART) | 953 (89.1%) | Premorbid IQ estimated from the National Adult Reading Test**20** (predicted WAIS-R full scale IQ = 130.6-1.24\*NART error score) |
| Poor premorbid social adjustment | 1016 (95.0%) | Poor premorbid social adjustment defined by OPCRIT item 10: difficulty entering or maintaining social relationships, isolation or social withdrawal prior to onset of psychotic symptoms |
| Poor premorbid work adjustment | 996 (93.1%) | Poor premorbid work adjustment defined by OPCRIT item 9: an inability to maintain a job for more than six months, frequent job changes, only sustaining a job well below that expected by educational level, or failing to keep up with studies before onset of illness |
| ***Illness presentation*** |
| Definite psychosocial stressor within 6m | 1007 (94.1%) | A psychosocial stressor in the six months prior to onset of psychosis defined by OPCRIT item 16: A severely threatening event that occurred prior to onset that was unlikely to have resulted from subject’s own behaviour |
| Age of onset of psychosis | 1027 (96.0%) | Age of onset of psychosis defined by OPCRIT item 4: The age at which treatment was first sought or if earlier when symptoms caused significant impairment |
| Duration of untreated psychosis (years) | 996 (93.1%) | Duration of untreated psychosis defined by the difference in months between age of the first antipsychotic treatment and age of onset of psychosis (as defined above) |
| Cannabis use in year prior to onset | 994 (92.9%) | Regular cannabis use in the year prior to illness onset |
| Cigarette smoking prior to onset | 922 (86.2%) | Regular cigarette smoking in the year prior to illness onset |
| Insidious disease onset (1-6) | 861 (80.5%) | The mode of onset of psychosis defined by OPCRIT item 5: 1 = abrupt onset definable to within hours or up to three days, 2 = acute onset definable to within one week, 3 = moderately acute onset definable within one month, 4 = gradual onset over a period up to six months, 5 = Insidious onset over period greater than six months |

Supplementary Table 2: Definitions of variables tested for TRP prediction. Variables were derived from self-report at interview, clinical case notes and OPCRIT ratings5.

## Supplementary Table 3: Definitions of lifetime clinical variables

|  |  |  |
| --- | --- | --- |
| **Variable** | **N (1070)** | **Description** |
| ***Demographics*** |
| Married or cohabiting | 1043 (97.5%) | Ever been married or lived as married (cohabiting) |
| Have a child | 611 (57.1%) | Ever had a child |
| ***Clinical details*** |
| Schizophrenia diagnosis | 1069 (99.9%) | A schizophrenia diagnosis defined by a DSM-IV or ICD-10 diagnosis of schizophrenia or schizoaffective disorder, depressed type |
| No. of psychiatric hospital admissions | 1054 (98.5%) | Total number of psychiatric hospital admissions, including inpatient, day hospital and intensive home treatment by the crisis team |
| Detained under MHA | 1065 (99.5%) | Ever detained under section 2 or 3 of the Mental Health Act |
| Course of disorder  | 1037 (96.9%) | Course of disorder as defined by OPCRIT item 90 (1 = single episode with good recovery, 2 = multiple episodes with good recovery between, 3 = multiple episodes with partial recovery between, 4 = continuous chronic illness, 5 = continuous chronic illness with deterioration) |
| Deterioration from premorbid level of functioning | 1045 (97.7%) | Deterioration from premorbid level of functioning defined as OPCRIT item 88 (patient does not regain premorbid social, occupational or emotional functioning after an acute episode of illness) |
| Lowest ever GAS  | 1052 (98.3%) | Lifetime worst Global Assessment Scale (GAS)**21** score in a psychotic episode |
| Cognitive functioning  | 1005 (93.9%) | Full scale composite cognition score as measured by the MATRICS Consensus Cognitive Battery**4**, imputed and standardised into z-scores |
| ***Clinical symptoms*** |
| Lifetime depressive episode | 954 (89.2%) | Lifetime depressive episode lasting a minimum of two weeks |
| Lifetime manic episode | 1020 (95.3%) | Lifetime manic episode lasting a minimum of 4 days |
| Severity of negative symptoms | 1034 (96.6%) | Severity of positive symptoms defined as total sum of global lifetime ratings from the scale for the assessment of positive symptoms**22** (SAPS total = global hallucinations + global delusions + global bizarre behaviour + global positive formal thought disorder) |
| Severity of positive symptoms | 1039 (97.1%) | Severity of negative symptoms defined as total sum of global lifetime ratings from the scale for the assessment of negative symptoms**23** (SANS total = global affective flattening + global alogia + global avolition apathy + global anhedonia asociality) |
| ***Substance use*** |
| Lifetime regular smoker | 1045 (97.7%) | Ever been a regular tobacco smoker |
| Lifetime alcohol abuse | 964 (90.1%) | Lifetime alcohol abuse defined by OPCRIT item 78: continued use for at least one month despite knowledge of having a persistent or recurrent social, occupational, psychological or physical problem that is caused or exacerbated by alcohol or recurrent use in situations in which it is physically hazardous; or symptoms definitely indicative of dependence |
| Lifetime regular cannabis use | 1032 (96.4%) | Lifetime regular cannabis use defined as persistent use for one month or repeated use (i.e. one a week) within one year |
| Lifetime regular drug use | 1023 (95.6%) | Lifetime regular unspecified drug use defined as persistent use for one month or repeated use (i.e. one a week) within one year |

Supplementary Table 3: Definitions of variables related to demographics, lifetime clinical characteristics, clinical symptoms and substance use. Variables were derived from self-report at interview, clinical case notes and OPCRIT ratings5.

## Supplementary Table 4: Characteristics of participants with missing data

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Complete data** | **Missing data** | **OR (95% CI)** | **P** |
|  | N (%) or mean (s.d.) | Total N | N (%) ormean (s.d) | Total N |
| Male sex | 206 (61.1%) | 337 | 456 (62.2%) | 733 | 0.96 (0.73-1.25) | 0.735 |
| Age at interview | 42.47 (sd=12.1) | 377 | 43.40 (sd=11.9) | 733 | 0.99 (0.98-1.00) | 0.238 |
| Systematic recruitment | 227 (67.4%) | 337 | 537 (73.4%) | 732 | 0.75 (0.57-0.99) | 0.044 |
| Treatment-resistant schizophrenia | 152 (45.1%) | 337 | 409 (55.8%) | 733 | 0.65 (0.50-0.84) | 1.18x10-3 |

Supplementary Table 4: Characteristics of study participants with missing data. Columns represent characteristics of those with complete data, those with incomplete data (reference group), odds ratio (OR), 95% confidence intervals (CI), and P-value from univariate logistic regression. For binary variables, numbers (N) and percentages (%) are given, and for continuous variables, mean and standard deviation (sd) measures are given.

## Supplementary Table 5: Lifetime characteristics

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **TRP** | **Non-TRP** | **OR (95% CI)** | **P** |
|  | N (%) or mean (s.d.) | Total N | N (%) ormean (s.d) | Total N |
| ***Demographics*** |  |  |  |  |  |  |
| Married or cohabiting | 143 (26.3%) | 544 | 181 (36.3%) | 499 | 0.73 (0.55-0.97) | 0.027 |
| Have a child | 104 (32.7%) | 318 | 127 (43.3%) | 293 | 0.68 (0.48-0.97) | 0.035 |
| ***Clinical details*** |  |  |  |  |  |  |
| Schizophrenia diagnosis | 431 (76.8%) | 561 | 302 (59.4%) | 508 | **2.11 (1.61-2.76)** | **6.64x10-8** |
| No. of psychiatric hospital admissions | 6.32 (sd=7.2) | 551 | 3.79 (sd=4.7) | 503 | **1.12 (1.08-1.15)** | **6.05x10-12** |
| Detained under MHA | 378 (67.9%) | 557 | 288 (56.7%) | 508 | **1.63 (1.26-2.10)** | **2.02x10-4** |
| Course of disorder  | 4.86 (sd=1.2) | 544 | 3.61 (sd=1.3) | 493 | **2.14 (1.91-2.41)** | **7.55x10-38** |
| Deterioration from premorbid level of functioning | 535 (96.1%) | 557 | 416 (85.2%) | 488 | **4.57 (2.75-7.59)** | **4.23x10-9** |
| Lowest ever GAS  | 18.65 (sd=6.8) | 553 | 22.55 (sd=7.9) | 499 | **0.93 (0.92-0.95)** | **1.41x10-13** |
| IQ (MATRICS composite) | -2.58 (sd=1.3) | 538 | -1.93 (sd=1.28) | 467 | **0.62 (0.56-0.70)** | **3.88x10-16** |
| ***Clinical symptoms*** |  |  |  |  |  |  |
| Lifetime depressive episode | 323 (65.3%) | 495 | 335 (73.0%) | 459 | 0.69 (0.52-0.92) | 0.010 |
| Lifetime manic episode | 75 (14.0%) | 536 | 68 (14.0%) | 484 | 1.04 (0.72-1.49) | 0.840 |
| Severity of negative symptoms | 7.91 (sd=4.1) | 536 | 6.47 (sd=4.2) | 498 | **1.09 (1.06-1.12)** | **6.02x10-8** |
| Severity of positive symptoms | 9.78 (sd=3.1) | 540 | 8.67 (sd=2.9) | 499 | **1.13 (1.08-1.18)** | **2.65x10-8** |
| ***Substance use*** |  |  |  |  |  |  |
| Lifetime regular smoker | 434 (79.8%) | 544 | 360 (71.9%) | 501 | 1.56 (1.16-2.09) | 2.96x10-3 |
| Lifetime alcohol abuse | 153 (30.1%) | 508 | 125 (27.4%) | 456 | 1.21 (0.91-1.62) | 0.187 |
| Lifetime regular cannabis use | 243 (45.2%) | 538 | 181 (36.6%) | 494 | 1.35 (1.03-1.77) | 0.031 |
| Lifetime regular drug use | 183 (34.3%) | 533 | 135 (27.6%) | 490 | 1.23 (0.92-1.64) | 0.156 |

Supplementary Table 5: Lifetime characteristics of study participants with treatment-responsive schizophrenia (non-TRP) and treatment-resistant schizophrenia (TRP). Columns represent characteristics of non-TRP (reference group), TRP, odds ratio (OR), 95% confidence intervals (CI), and P-value from univariate logistic regression adjusted for age at interview and method of recruitment. For binary variables, numbers (N) and percentages (%) were given, and for continuous variables, mean and standard deviation (sd) measures were given. P-values in bold survived correction for multiple testing (p < 2.94x10-3).

## Supplementary Table 6: Lifetime clinical characteristics (SZ only)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **TRP** | **Non-TRP** | **OR (95% CI)** | **P** |
|  | N (%) or mean (s.d.) | Total N | N (%) ormean (s.d) | Total N |
| ***Demographics*** |  |  |  |  |  |  |
| Ever married | 121 (25.1%) | 483 | 130 (34.4%) | 378 | 0.75 (0.54-1.03) | 0.073 |
| Having a child | 89 (32.0%) | 278 | 100 (43.5%) | 230 | 0.66 (0.44-0.98) | 0.037 |
| ***Clinical details*** |  |  |  |  |  |  |
| Schizophrenia diagnosis | - | - | - | - | - | - |
| No. psychiatric hospital admissions | 6.11(sd=7.13) | 487 | 4.00 (sd=5.00) | 380 | **1.09 (1.05-1.12)** | **3.62x10-7** |
| Ever sectioned under MHA | 332 (67.2%) | 494 | 225 (58.4%) | 385 | 1.46 (1.10-1.94) | 8.92x10-3 |
| Course of disorder  | 4.90 (sd=1.21) | 487 | 3.79 (sd=1.30) | 375 | **2.03 (1.79-2.31)** | **8.53x10-28** |
| Deterioration from premorbid level of functioning | 479 (97.0%) | 494 | 330 (89.2%) | 370 | **4.25 (2.27-7.96** | **6.00x10-6** |
| Lowest ever GAS  | 18.61 (sd=6.76) | 489 | 21.88 (sd=7.27) | 379 | **0.94 (0.92-0.96)** | **1.06x10-8** |
| IQ (MATRICS composite) | -2.61 (sd=1.34) | 475 | -2.07 (sd=1.30) | 353 | **0.67 (0.59-0.75)** | **1.02x10-10** |
| ***Clinical symptoms*** |  |  |  |  |  |  |
| Lifetime depressive episode | 269 (61.6%) | 437 | 242 (69.5%) | 348 | 0.70 (0.51-0.95) | 0.020 |
| Lifetime manic episode | 35 (7.3%) | 478 | 18 (4.9%) | 368 | 1.45 (0.80-2.63) | 0.225 |
| Severity of negative symptoms | 7.98 (sd=4.15) | 475 | 6.94 (sd=4.16) | 377 | **1.07 (1.03-1.10)** | **2.45x10-4** |
| Severity of positive symptoms | 9.91 (sd=3.06) | 478 | 8.90 (sd=2.86) | 378 | **1.12 (1.07-1.17)** | **6.00x10-6** |
| ***Substance use*** |  |  |  |  |  |  |
| Lifetime regular smoker | 387 (79.8%) | 485 | 279 (73.2%) | 381 | 1.43 (1.03-1.97) | 0.033 |
| Lifetime alcohol abuse | 132 (29.1%) | 453 | 92 (26.7%) | 344 | 1.19 (0.86-1.65) | 0.289 |
| Lifetime regular cannabis use | 125 (39.2%) | 480 | 181 (44.7%) | 372 | 1.18 (0.87-1.59) | 0.287 |
| Lifetime regular drug use | 164 (34.4%) | 477 | 108 (29.3%) | 369 | 1.10 (0.81-1.51) | 0.538 |

Supplementary Table 6: Analyses of lifetime clinical characteristics for participants with treatment-resistant psychosis (TRP) and treatment-responsive psychosis (non-TRP) restricted to those with a schizophrenia or schizoaffective disorder, depressed type diagnosis. Columns represent characteristics of TRP, non-TRP (reference group), odds ratio (OR), 95% confidence intervals (CI), and P-value from univariate logistic regression adjusted for age at interview and method of recruitment. For binary variables, numbers (N) and percentages (%) are given, and for continuous variables, mean and standard deviation (sd) measures are given. P-values in bold survive correction for multiple testing (p < 2.94x10-3).

## Supplementary Table 7: Clinical predictors of TRP (SZ only)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **TRP** |  | **Non-TRP** |  | **Adjusted Univariate (up to N=935)** |  | **Fully Adjusted Multivariate (N=510)** |
|  | N (%) / mean (sd) | Total N |  | N (%) / mean (sd) | Total N |  | OR (95% CI) | P |  | OR (95% CI) | P |
| ***Demographics and family background*** |  |  |  |  |  |  |  |  |  |  |  |
| Male sex | 333 (67.0%) | 497 |  | 247 (64.2%) | 385 |  | 1.12 (0.84-1.50) | 0.428 |  | 0.92 (0.60-1.39) | 0.681 |
| Urbanicity (city birth and upbringing) | 156 (39.4%) | 396 |  | 137 (40.5%) | 338 |  | 1.03 (0.76-1.40) | 0.860 |  |  |  |
| Family Hx of schizophrenia | 114 (26.8%) | 425 |  | 75 (22.5%) | 333 |  | 1.25 (0.88-1.76) | 0.209 |  | 0.90 (0.58-1.41) | 0.654 |
| Family Hx of psychosis, affective or suicide | 220 (52.9%) | 416 |  | 186 (55.9%) | 333 |  | 0.83 (0.61-1.12) | 0.222 |  |  |  |
| Mother’s age at birth | 26.63 (sd=6.3) | 435 |  | 26.87 (sd=6.2) | 357 |  | 1.00 (0.97-1.02) | 0.745 |  |  |  |
| Father’s age at birth | 29.33 (sd=7.3) | 417 |  | 30.02 (sd=7.6) | 336 |  | 0.99 (0.97-1.01) | 0.229 |  | 0.98 (0.95-1.00) | 0.069 |
| ***Premorbid factors*** |  |  |  |  |  |  |  |  |  |  |  |
| Birth complications | 100 (23.8%) | 420 |  | 71 (21.0%) | 338 |  | 1.17 (0.82-1.67) | 0.382 |  |  |  |
| Pregnancy complications | 40 (9.9%) | 405 |  | 27 (8.3%) | 324 |  | 1.22 (0.72-2.07) | 0.463 |  |  |  |
| Developmental problems | 86 (20.0%) | 431 |  | 62 (18.0%) | 344 |  | 1.16 (0.80-1.68) | 0.447 |  |  |  |
| Childhood abuse | 88 (19.4%) | 454 |  | 75 (20.7%) | 362 |  | 0.94 (0.66-1.34) | 0.720 |  |  |  |
| Years in education | 12.70 (sd=3.6) | 479 |  | 13.12 (sd=2.9) | 371 |  | 0.96 (0.91-1.00) | 0.067 |  | 0.98 (0.93-1.04) | 0.582 |
| Highest level of education | 2.53 (sd=1.7) | 481 |  | 2.76 (sd=1.8) | 378 |  | 0.92 (0.85-1.00) | 0.046 |  | 1.07 (0.92-1.25) | 0.383 |
| Premorbid IQ (NART) | 96.78 (sd=13.5) | 456 |  | 99.53 (sd=13.3) | 361 |  | 0.99 (0.98-1.00) | 0.045 |  | 0.98 (0.97-1.00) | 0.070 |
| Poor premorbid social adjustment | 216 (45.5%) | 475 |  | 127 (34.9%) | 364 |  | 1.56 (1.17-2.10) | 2.44x10-3 |  | **1.74 (1.14-2.65)** | **0.010** |
| Poor premorbid work adjustment | 108 (23.7%) | 455 |  | 57 (15.7%) | 362 |  | 1.56 (1.09-2.25) | 0.017 |  | 1.32 (0.78-2.24) | 0.301 |
| ***Illness presentation*** |  |  |  |  |  |  |  |  |  |  |  |
| Definite psychosocial stressor within 6 m | 33 (7.1%) | 465 |  | 37 (10.1%) | 365 |  | 0.70 (0.42-1.16) | 0.162 |  | 0.74 (0.36-1.51) | 0.401 |
| Age of onset of psychosis | 22.92 (sd=8.0) | 480 |  | 27.10 (sd=9.9) | 366 |  | **0.95 (0.93-0.97)** | **3.08x10-8** |  | **0.96 (0.93-0.98)** | **1.84x10-3** |
| Duration of untreated psychosis (years) | 2.14 (sd=4.6) | 467 |  | 2.03 (sd=4.2) | 357 |  | 1.01 (0.98-1.04) | 0.487 |  |  |  |
| Cannabis use in year prior to onset | 172 (37.1%) | 463 |  | 96 (26.7%) | 359 |  | 1.46 (1.06-2.03) | 0.022 |  | **1.60 (1.02-2.52)** | **0.041** |
| Cigarette smoking prior to onset | 273 (65.6%) | 416 |  | 219 (62.9%) | 348 |  | 1.12 (0.83-1.52) | 0.453 |  |  |  |
| Insidious disease onset (1-6) | 3.66 (sd=1.4) | 384 |  | 3.61 (sd=1.4) | 321 |  | 0.97 (0.87-1.09) | 0.624 |  |  |  |

Supplementary Table 7: Association of clinical predictors with treatment-resistant psychosis (TRP) restricted to individuals with a schizophrenia or schizoaffective disorder, depressed type diagnosis. Columns represent clinical variables, TRP, non-TRP (reference group), odds ratio (OR), 95% confidence intervals (CI) and P-value from univariate logistic regression adjusted for age at interview and method of recruitment, and adjusted multivariate logistic regression. For binary variables, numbers (N) and percentages (%) are provided, and for continuous variables, mean and standard deviation (sd) are provided. P-values in bold survived correction for multiple testing (p < 2.38x10-3).

## Supplementary Table 8: Multivariate model (N=337)

|  |  |
| --- | --- |
|  | **Fully Adjusted Multivariate (N=337)** |
|  | OR (95% CI) | P |
| ***Demographics and family background*** |  |  |
| Male sex | 1.14 (0.66-1.97) | 0.645 |
| Urbanicity (city birth and upbringing) | 1.13 (0.68-1.90) | 0.631 |
| Family Hx of schizophrenia | 1.22 (0.63-2.39) | 0.557 |
| Family Hx of psychosis, affective or suicide | 0.45 (0.25-0.79) | 5.19x10-3 |
| Mother’s age at birth | 1.07 (1.00-1.15) | 0.066 |
| Father’s age at birth | 0.93 (0.87-0.99) | 0.015 |
| ***Premorbid factors*** |  |  |
| Birth complications | 1.08 (0.57-2.06) | 0.808 |
| Pregnancy complications | 1.17 (0.44-3.12) | 0.759 |
| Developmental problems | 0.42 (0.20-0.90) | 0.026 |
| Childhood abuse | 1.45 (0.71-2.93) | 0.298 |
| Years in education | 1.00 (0.88-1.13) | 0.941 |
| Highest level of education | 1.02 (0.81-1.28) | 0.867 |
| Premorbid IQ (NART) | 0.98 (0.96-1.01) | 0.141 |
| Poor premorbid social adjustment | 3.02 (1.66-5.49) | 2.91x10-4 |
| Poor premorbid work adjustment | 1.45 (0.67-3.12) | 0.349 |
| ***Illness presentation*** |  |  |
| Definite psychosocial stressor within 6 m | 0.97 (0.39-2.39) | 0.947 |
| Age of onset of psychosis | 0.93 (0.89-0.97) | 2.70x10-4 |
| Duration of untreated psychosis (years) | 0.96 (0.89-1.03) | 0.222 |
| Cannabis use in year prior to onset | 1.46 (0.79-2.67) | 0.227 |
| Cigarette smoking prior to onset | 1.07 (0.59-1.96) | 0.819 |
| Insidious disease onset (1-6) | 0.95 (0.79-1.15) | 0.614 |

Supplementary Table 8: Association of clinical predictors with TRP restricted to individuals with no missing data (n=377) for direct comparison with machine-learning analyses.

## Supplementary Table 9: Schizophrenia PRS and TRP (SZ only)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Score P-value Threshold** | **OR (95% CI)** | **R2** | **AUC** | **SE** | **P-value**  |
| P < 1 x 10-8 | 1.07 (0.92-1.24) | 0.0011 | 0.516 | 0.0028 | 0.387 |
| P < 1 x 10-6 | 1.06 (0.91-1.23) | 0.0009 | 0.514 | 0.0025 | 0.447 |
| P < 1 x 10-4 | 1.04 (0.89-1.21) | 0.0004 | 0.509 | 0.0017 | 0.647 |
| P < 1 x 10-3 | 1.15 (0.97-1.35) | 0.0050 | 0.533 | 0.0059 | 0.099 |
| P < 0.01 | 1.12 (0.94-1.34) | 0.0031 | 0.526 | 0.0046 | 0.212 |
| P < 0.05 | 1.13 (0.93-1.37) | 0.0030 | 0.526 | 0.0046 | 0.214 |
| P < 0.1 | 1.11 (0.91-1.36) | 0.0024 | 0.523 | 0.0040 | 0.283 |
| P < 0.2 | 1.18 (0.96-1.45) | 0.0046 | 0.532 | 0.0056 | 0.124 |
| P < 0.5 | 1.13 (0.91-1.40) | 0.0025 | 0.523 | 0.0042 | 0.272 |

Supplementary Table 9: Analysis of association of schizophrenia polygenic risk score (PRS) with TRP only including individuals with a schizophrenia or schizoaffective disorder, depressed type diagnosis (*n*=694 total). Columns represent the p-value threshold used in discovery cohort to derive scores, odds ratio (OR) and 95% confidence intervals, R2 calculated on the liability scale**15** , area under the curve (AUC), standard error (SE), and P-value of association of each score of with TRP.

## Supplementary Table 10: CNVs and TRP (SZ only)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **TRP N (%)**Total = 380 | **Non-TRP N (%)** Total = 307 | **OR (95% CI)** | **P** |
| Intellectual disability pathogenic CNV | 9 (2.4%) | 11 (3.6%) | 0.66 (0.27-1.58) | 0.348 |
| Schizophrenia pathogenic CNV | 7 (1.8%) | 11 (3.6%) | 0.52 (0.19-1.30) | 0.161 |
| >500kb deletion | 10 (2.6%) | 9 (2.9%) | 0.89 (0.36-2.21) | 0.799 |
| >1Mb deletion | 4 (1.1%) | 0 (0.0%) | 2.78 (0.78-975.5) | 0.088 |
| >500kb duplication | 31 (8.2%) | 25 (8.1%) | 1.00 (0.58-1.73) | 0.996 |
| >1Mb duplication | 8 (2.1%) | 13 (4.2%) | 0.50 (0.20-1.17) | 0.111 |

Supplementary Table 10: Association analysis of CNVs with TRP restricted to study individuals with a schizophrenia or schizoaffective disorder, depressed type diagnosis (*n*=634 total). Columns represent CNVs assessed (intellectual disability (ID) pathogenic CNV17, previously associated pathogenic schizophrenia CNV6, robustly associated schizophrenia pathogenic CNV24, deletions spanning 500kb or 1Mb in length, and duplications spanning 500kb or 1Mb in lengths), frequencies of each CNV in non-TRP (reference group), TRP, odds ratio (OR), 95% confidence intervals (CI) and P-value from Firth’s logistic regression.

## Supplementary Table 11: Proportion of TRP by age of onset of psychosis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Age of onset** | **TRP** | **Non-TRP** | **Total** | **Proportion TRP** |
| <=12 | 18 | 5 | 23 | 0.78 |
| 14 | 21 | 8 | 29 | 0.72 |
| 15 | 15 | 9 | 24 | 0.63 |
| 16 | 28 | 18 | 46 | 0.61 |
| 17 | 29 | 19 | 48 | 0.60 |
| 18 | 32 | 19 | 51 | 0.63 |
| 19 | 31 | 11 | 42 | 0.74 |
| 20 | 35 | 22 | 57 | 0.61 |
| 21 | 41 | 21 | 62 | 0.66 |
| 22 | 40 | 24 | 64 | 0.63 |
| 23 | 33 | 16 | 49 | 0.67 |
| 24 | 18 | 17 | 35 | 0.51 |
| 25 | 19 | 36 | 55 | 0.35 |
| 26 | 15 | 19 | 34 | 0.44 |
| 27 | 24 | 16 | 40 | 0.60 |
| 28 | 18 | 22 | 40 | 0.45 |
| 29 | 17 | 20 | 37 | 0.46 |
| 30 | 14 | 16 | 30 | 0.47 |
| 32 | 21 | 20 | 41 | 0.51 |
| 34 | 20 | 25 | 45 | 0.44 |
| 36 | 17 | 27 | 44 | 0.39 |
| 38 | 13 | 19 | 32 | 0.41 |
| 40 | 7 | 19 | 26 | 0.27 |
| 45 | 7 | 30 | 37 | 0.19 |
| 60 | 5 | 25 | 30 | 0.17 |
| **Total** | **538** | **483** | **1021** | **0.53** |

Supplementary Table 11: Proportion of study individuals with TRP by age of onset of psychosis (data used for Figure 2). Columns represent age of onset of psychosis, the number with TRP, number with non-TRP, total sample size, and the proportion with TRP (TRP/Total) for each age of onset group.

## Supplementary Table 12: Predictive analysis of age of onset of psychosis

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Age** | **Sensitivity** | **Specificity** | **PPV** | **NPV** | **Adjusted PPV** | **Adjusted NPV** |
| < 16 | 0.90 | 0.05 | 0.29 | 0.51 | 0.51 | 0.29 |
| 16 – 20 | 0.71 | 0.18 | 0.36 | 0.49 | 0.60 | 0.27 |
| 21 – 25 | 0.72 | 0.24 | 0.43 | 0.51 | 0.66 | 0.29 |
| 26 – 30 | 0.84 | 0.19 | 0.51 | 0.54 | 0.73 | 0.31 |
| 31 – 40 | 0.86 | 0.23 | 0.59 | 0.55 | 0.79 | 0.32 |
| 41 + | 0.98 | 0.11 | 0.82 | 0.55 | 0.92 | 0.32 |

Supplementary Table 12: Predictive analysis for age of onset of psychosis and **non-TRP (total n=1021)**. Columns represent age of onset of psychosis, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), PPV adjusted for prevalence rate of TRP in schizophrenia (30%), and NPV adjusted for prevalence rate of TRP in schizophrenia (30%).

## Supplementary Table 13: Schizophrenia PRS and age of onset

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Score P-value Threshold** | **Beta (95% CI)** | **R2** | **SE** | **P-value**  |
| P < 1 x 10-8 | -0.32 (-0.96-0.32) | 0.0012 | 0.326 | 0.333 |
| P < 1 x 10-6 | -0.73 (-1.37--0.85) | 0.0061 | 0.328 | 0.027 |
| P < 1 x 10-4 | -0.69 (-1.35--0.04) | 0.0053 | 0.333 | 0.037 |
| P < 1 x 10-3 | -0.59 (-1.28-0.09) | 0.0035 | 0.349 | 0.090 |
| P < 0.01 | -0.86 (-1.62-0.10) | 0.0060 | 0.389 | 0.027 |
| P < 0.05 | -0.74 (-1.56-0.09) | 0.0037 | 0.421 | 0.080 |
| P < 0.1 | -0.73 (-1.58-0.12) | 0.0035 | 0.432 | 0.091 |
| P < 0.2 | -0.87 (-1.75-0.01) | 0.0046 | 0.448 | 0.052 |
| P < 0.5 | -0.74 (-1.65-0.16) | 0.0032 | 0.462 | 0.108 |

Supplementary Table 13: Analysis of association of schizophrenia polygenic risk score (PRS) with age of onset of psychosis (total *n*=814). Columns represent the p-value threshold used in discovery cohort to derive scores, odds ratio (OR) and 95% confidence intervals, R2, area under the curve (AUC), standard error (SE), and P-value of association of each score of with age of onset of psychosis.

## Supplementary Table 14: Schizophrenia PRS and age of onset (SZ only)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Score P-value Threshold** | **Beta (95% CI)** | **R2** | **SE** | **P-value**  |
| P < 1 x 10-8 | -0.21 (-0.87-0.45) | 0.0006 | 0.338 | 0.534 |
| P < 1 x 10-6 | -0.55 (-1.22-0.12) | 0.0039 | 0.341 | 0.107 |
| P < 1 x 10-4 | -0.51 (-1.18-0.17) | 0.0032 | 0.346 | 0.145 |
| P < 1 x 10-3 | -0.34 (-1.05-0.36) | 0.0014 | 0.360 | 0.340 |
| P < 0.01 | -0.82 (-1.61--0.04) | 0.0064 | 0.400 | 0.040 |
| P < 0.05 | -0.87 (-1.71--0.03) | 0.0063 | 0.428 | 0.042 |
| P < 0.1 | -0.92 (-1.78--0.06) | 0.0066 | 0.439 | 0.037 |
| P < 0.2 | -1.01 (-1.90--0.12) | 0.0075 | 0.455 | 0.026 |
| P < 0.5 | -0.90 (-1.81-0.02) | 0.0055 | 0.468 | 0.056 |

Supplementary Table 14: Analysis of association of schizophrenia polygenic risk score (PRS) with age of onset of psychosis restricted to study individuals with a schizophrenia or schizoaffective disorder, depressed type diagnosis (total *n*=663). Columns represent the p-value threshold used in discovery cohort to derive scores, odds ratio (OR) and 95% confidence intervals, R2, area under the curve (AUC), standard error (SE), and P-value of association of each score of with age of onset of psychosis.

## Supplementary Figure 1: Correlation matrix of clinical predictive variables



Supplementary Figure 1: Correlation matrix of 21 clinical predictive variables produced by the ‘corrplot’ R package. Positive correlations are displayed in blue and negative correlations in red. Colour intensity and the size of the circle are proportional to the correlation coefficients.

## Supplementary Figure 2: Conditional inference forests model (SZ only)



Supplementary Figure 2: Variable importance plots from conditional inference forests models predicting TRP restricted to those with a schizophrenia or schizoaffective disorder, depressed type diagnosis.

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