Interaction Testing and Polygenic Risk Scoring to Estimate the Association of Common Genetic Variants With Treatment Resistance in Schizophrenia

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Supplemental Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods.

CLOZUK and PGC data processing and GWAS

Due to the number of different datasets (45) and genotyping arrays (11) jointly involved in this analysis, processing of the TRS and non-TRS GWAS samples was done separately on data generated by the original studies. Imputed genotypes for the TRS analysis were those used by Pardiñas et al. (2018), which were inferred to be predominantly of UK genetic ancestry after principal component analysis (PCA) and ADMIXTURE estimation, and contain no detectable population outliers. Genotypes for the non-TRS analysis were obtained from Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014), following the extensive curation process carried out during this work to discard population outliers and assess stratification.

Both of these imputations used the SHAPEIT/IMPUTE2 pipeline (Howie et al., 2012; Delaneau et al., 2013), though different versions of the 1000 Genomes reference panel were used in CLOZUK and PGC (Phase 3 and Phase 1 respectively). Given that the use of either reference has been found to result in similar imputation accuracies for SNPs with common (>5%) allele frequencies (1000 Genomes Project Consortium, 2015), we restricted to SNPs with a minor allele frequency (MAF) of 5% or higher in both datasets. We also excluded INDELs since their imputation performance tends to be lower than other common variants (Cirulli et al., 2014). Finally, the same post-imputation filters were applied to all remaining SNPs (INFO>0.6, Hardy Weinberg Equilibrium mid p-value > 10^{-6}).

In carrying out the GWAS of these samples, we followed the procedures outlined in the original studies from Pardiñas et al. (2018) and Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014), including controlling for population stratification using covariates derived by PCA (Peloso and Lunetta, 2011). Combined results from the PGC non-TRS GWAS were meta-analysed using the fixed-effects procedure implemented in METAL v2011-03-25 (Willer et al., 2010). Only SNPs called in at least 20,000 combined samples were retained, and any strand-ambiguous markers (A/T, G/C) with MAF≥40% were discarded.

Comparison of the interaction test with the CC-GWAS method

To complement our analytic approach, we also investigated using the recently published CC-GWAS software (Peyrot and Price, 2020), intended for case/case designs similar to ours. However, the high genetic correlation between the TRS and non-TRS GWAS precluded us from using the CC-GWAS$_{OLS}$ or CC-GWAS$_{Exact}$ algorithms due to potential inflation of the false positive rate, with the only alternative being the lesser-powered CC-GWAS$_{Delta}$. Results of a CC-GWAS$_{Delta}$ analysis were closely aligned to our

interaction analysis (rg=0.992), returning the same λ and h^2 estimates to the third decimal place. Thus, for simplicity, we retained the test for interaction as our main genome-wide analysis.

CardiffCOGS genotyping and imputation

Genotypes from the CardiffCOGS samples were collected and curated as described in Pardiñas et al. (2018). Imputation of CardiffCOGS followed the procedure used for the CLOZUK GWAS samples which relied on the 1000 Genomes Phase 3 reference panel, and only SNPs passing a set of post-imputation quality control thresholds were retained (Genotype probability > 90%; INFO >0.8; Missingness < 5%; Hardy Weinberg Equilibrium p-value > 10^{-6}).

STRATA-G sample details

The participants included in STRATA-G are subsamples of participants from the studies listed below. Participants were included in STRATA-G if (1) ethical approval could be obtained to share data with the STRATA consortium, (2) blood, DNA, or genotype data was available to the STRATA-G researchers, and (3) participants had participated in a follow-up study, a minimum of 1 year after baseline. When additional criteria restricted which participants could be included in STRATA-G, we report the details of these below. We used a history of clozapine use to define our primary outcome variable of treatment-resistant schizophrenia.

AESOP (London, UK): The AESOP study (Aetiology and Ethnicity in Schizophrenia and Other Psychoses) is a multi-centre, naturalistic, prospective incidence and case-control study of first-episode psychosis, conducted initially over three years, from September 1997 to August 2000. The study sample comprises: all patients with an International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) diagnosis of F10-F29 or F30-F33, aged 16-65 years, who presented to secondary and tertiary services within tightly defined catchment areas in south-east London, Nottingham, and Bristol (Dazzan et al., 2005; Fearon et al., 2006; Kirkbride et al., 2006; Morgan et al., 2006; Zimbron et al., 2014; Dean et al., 2018). All participants, in centres in southeast London and Nottingham (UK), were invited to take part in a follow-up study, at approximately 10 years after baseline (Morgan et al., 2014; Revier et al., 2015; Demjaha et al., 2017). Treatment resistance/non-resistance and history of clozapine use were determined by Dr Arsime Demjaha (Demjaha et al., 2017) and Dr Sophie Smart.

ESS (Prague, Czech Republic): The Early Stages of Schizophrenia (ESS) study is a hospital-based incidence study of first-episode schizophrenia, conducted initially over an unreported period of time. The study sample comprises: all patients with a ICD-10 diagnosis of F20 or F23, aged 18-35 years, with had less than 2 years of untreated psychosis, who were hospitalised in a large general psychiatry hospital that serves Prague and part of Central Bohemia regions (Melicher et al., 2015; Mikolas et al.,

2016; Spaniel et al., 2016; Kolenic et al., 2018). All participants were invited to take part in follow-up

studies, 1 year after baseline. Treatment resistance/non-resistance was determined by Dr Lina Homman.

EUGEI & BoFEP (Bologna, Italy): The Bologna data is from two studies. EUGEI (European Network of National Schizophrenia Networks Studying Gene-Environment Interactions) is a multi-centre, population-based incidence and case-sibling-control study of first-episode psychosis conducted initially, in Bologna, over a four-year period from January 2011 to December 2014. The study sample comprises: all patients with a ICD-10 diagnosis of F20-F33, aged 18-64 years, who presented to services within the catchment area (Jongsma et al., 2018). All participants, in Bologna, were invited totake part in a follow-up study, in 2016. The BoFEP study (Bologna FEP) is an ongoing, naturalistic, prospective incidence study of first-episode psychosis, conducted initially over an eight-year period from January 2002 and December 2009. The study sample comprises: all patients with a ICD-10 diagnosis of F10–F29 or F30–F33, aged 18-64 years, who presented to services within the defined catchment area in West Bologna. All participants were invited to take part in a follow-up study, 1 yearafter baseline (Tarricone et al., 2012). Treatment resistance/non-resistance, in both samples, was determined by Dr Lina Homman.

EUGEI Istanbul (Turkey): The Istanbul data is from an ongoing, hospital-based incidence study of first-episode schizophrenia, conducted in 1996. This study is sometimes known as the First-Episode Schizophrenia Follow-Up Project and a proportion of this sample was included in EUGEI. The study sample comprises: all patients with a DSM-IV diagnosis of schizophrenia, aged 15-45 years, who were experiencing an acute phase of their first psychotic episode and being treated as an inpatient (Üçok et al., 2004; Üçok et al., 2006; Üçok et al., 2011; Üçok et al., 2016). All participants were invited to takepart in follow up studies, 2+ years after baseline (Üçok et al., 2016). Treatment resistance/non- resistance was determined by Dr Alp Üçok.

EUGEI Paris (France): EUGEI is a multi-centre, population-based incidence and case-sibling-control of first-episode psychosis, conducted initially, in Créteil and Paris, over a two-year period from June 2012 to June 2014. The study sample comprises: all patients with a ICD-10 diagnosis of F20-F33, aged 18-64 years, who presented to services within the catchment area (Jongsma et al., 2018). All participants, in Créteil and Paris, were invited to take part in a follow-up study, in 2017. Treatment resistance/non-resistance was determined by Dr Andrei Szöke and Jean-Romain Richard.

GAP (London, UK): The GAP study (Genetics and Psychosis) is a population-based incidence and case-control study of first-episode psychosis, conducted initially over a three-year period from December 2005 to October 2010. The study sample comprises: all patients with a ICD-10 diagnosis of F20-F29 or

F30-F33, aged 18-65 years, who presented to secondary and tertiary services within tightly defined catchment areas in south-east London (Di Forti et al., 2009; Di Forti et al., 2015). The study exclusion criteria were evidence of 1) psychotic symptoms precipitated by an organic cause; 2) evidence of transient psychotic symptoms resulting from acute intoxication as defined by ICD-10; 3) moderate or severe learning disabilities as defined by ICD-10; or 4) head injury causing clinically significant loss of consciousness. Approximately 5 years after the first contact for psychosis, the follow-up data were extracted retrospectively using the electronic clinical records that are the primary clinical records keeping system within the Trust. This enables searching all clinical information, including correspondence, discharge letters and events, recorded throughout patients' journeys through the Trust (Lally et al., 2016a; Ajnakina et al., 2017). Treatment resistance/non-resistance was determined by Dr Olesya Ajnakina and Dr John Lally (Lally et al., 2016a).

NIFEPS & RGPI (Belfast, UK): The Belfast data is from two studies. The NIFEPS study (Northern Ireland First Episode Psychosis) is a naturalistic, prospective, incidence study, conducted initially over two years from January 2003 and December 2004. The study sample comprises: all patients with an Operational Criteria checklist for Psychotic Illness (OPCRIT) diagnosis of first-episode psychosis, aged 18–64 years, and living in Northern Ireland. All participants were invited to take part in follow-up studies, 1 year after baseline (Turkington et al., 2018) and approximately 13 years after baseline as part of the STRATA consortium. The RGPI study (Resources for Genomics, Ireland) is a multi-centre, population-based, incidence study of first episode of psychosis in 2007. The study sample comprises: all patients with a Diagnostic Statistical Manual IV (DSM-IV) diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder or bipolar affective disorder with psychosis, aged 16+ years, who had Irish born grandparents, and who presented to psychiatric services in the region of the research centres (Casey and Corvin, 2008). All participants, recruited through psychiatric services in the region of Queen's University, Belfast, were invited to take part in a follow-up study, at approximately 9 years after baseline as part of the STRATA consortium. Treatment resistance/non-resistance, in both samples, was determined by Dr Lina Homman.

PAFIP (Santander, Spain): The PAFIP study is an ongoing, naturalistic, prospective incidence study of first-episode psychosis, conducted from February 2001. The study sample comprises: all patients with an DSM-IV diagnosis of non-affective psychosis, aged 15+ years, who were referred from mental health services in the region of Cantabria. All participants were invited to take part in follow-up studies, 3+ years after baseline (Crespo-Facorro et al., 2007; Pelayo-Teran et al., 2008; Ayesa-Arriola et al., 2018; Setien-Suero et al., 2018). Treatment resistance/non-resistance was determined by Dr. Benedicto Crespo-Facorro and Dr. Javier Vázquez-Bourgon.

TIPP (Lausanne, Switzerland): The TIPP study (Treatment and Early Intervention in Psychosis Program) is an ongoing, naturalistic prospective study of early-onset psychosis, conducted from 2004. The study sample comprises: all patients who meet threshold criteria for psychosis (defined by the 'Psychosis threshold' subscale of the Comprehensive Assessment of At Risk Mental States (CAARMS) scale), aged 18-35 years, who reside in the Lausanne catchment area (Baumann et al., 2013a; Golay et al., 2016; Alameda et al., 2017). All participants enrolled in TIPP are invited to take part in follow up studies, lasting 3 years after baseline. A subsample of TIPP patients was included in STRATA-G: those that participated either in a neurobiological research study developed by Prof Kim Do (Baumann et al., 2013b), and/or were part of PsyMetab or Psyclin studies (Choong et al., 2008; Choong et al., 2013; Delacretaz et al., 2015; Quteineh et al., 2015; Vandenberghe et al., 2015). Treatment resistance/non-resistance, in both studies, was determined by Dr Romeo Restellini and Dr Luis Alameda.

TOP (Oslo, Norway): The TOP study (Thematic Organized Psychosis Research) is a naturalistic, prospective incidence and case-control study of first-episode psychosis, conducted initially over a four-year period from May 2003 to July 2007. The study sample comprises: all patients with a DSM-IV diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, psychosis not otherwise specified (NOS), delusional disorder, brief psychosis or major affective disorder with mood incongruent psychotic symptoms, aged 18-65 years, within 1 year of the start of their first adequate treatment with antipsychotic medication, who presented to outpatient and inpatient services within four University Hospitals in Oslo (Faerden et al., 2008; Athanasiu et al., 2010). All participants were invited to take part in a follow-up study, approximately 1 year after baseline (Faerden et al., 2013; Lange et al., 2014; Lyngstad et al., 2018). Treatment resistance/non-resistance was determined by Dr Carmen Simonsen and Professor Ingrid Melle.

West London (London, UK): The West London Longitudinal First-Episode Psychosis Study a naturalistic, prospective incidence study of first-episode psychosis, conducted from 1998 to 2008. The study sample comprises: all patients with an DSM-IV diagnosis of psychosis, aged 16-50 years, who were presenting with a psychotic illness for the first time and had been receiving antipsychotic medication for less than 12 weeks. All participants were invited to take part in follow-up studies, 1+ years after baseline (Huddy et al., 2007; Gutierrez-Galve et al., 2010; Huddy et al., 2013; Gutierrez-Galve et al., 2015). Treatment resistance/non-resistance was determined by Dr Sophie Smart.

STRATA-G genotyping and imputation

All the STRATA-G individuals were genotyped using Illumina platforms as a part of their respective studies; array details are provided in **Supplementary Table 2**. Within each dataset, basic genotypic

quality control (QC) was performed using PLINK v1.9 (Chang et al., 2015) following standard procedures (Anderson et al., 2010), and allowing for 5% of missing data at the marker and individual level. Datasets were then merged into two batches by the similarity of their array content, and all non-overlapping markers were discarded. Relatedness between individuals was assessed in a merged dataset consisting of 203,813 SNPs common between both batches, using the PC-Relate approach (Conomos et al., 2016). A random member of each related pair (ϕ>0.2) was selected for removal in further analyses, prioritising retaining TRS individuals.

Imputation was performed on each batch separately using the Minimac4 algorithm as provided by the Michigan Imputation Server (Das et al., 2016) and HRC reference panel, which has similar accuracy for common variation as the 1000 Genomes Phase 3 panel used in CardiffCOGS (McCarthy et al., 2016). After this process, imputed dosages were converted to best-guess genotype calls for use in polygenic scoring (Genotype probability > 90%; INFO > 0.8, MAF > 1%, HWE mid p-value > 10^{-4}). For their use in association testing, principal components were generated from the post-imputed data using markers in relative linkage equilibrium (r^2<0.2) and the PC-AiR algorithm (Conomos et al., 2015).

Polygenic validation analyses

To avoid the known bias in PRS analysis when samples are present in both training and testing sets, we ensured that no samples from either CardiffCOGS or STRATA-G were included in any discovery GWAS analyses, and that any samples related to either of these cohorts (relatedness coefficient ϕ>0.2) were removed. All summary statistics were curated by retaining only non-ambiguous SNPs outside of long-range LD regions (Price et al., 2008) that had a MAF of 10% or higher and INFO ≥0.9.

In PRSice-2, p-value thresholds for the computed scores were set at 8 different intervals ($p<10^{-5}$, $p<10^{-4}$, p<0.001, p<0.05, p<0.01, p<0.1, p<0.5, p<1). Finally, a score was also generated via the PRS-CS software (Ge et al., 2019), which estimates PRS using all SNPs in a Bayesian framework. The UK-Biobank LD reference provided with PRS-CS was used for all computations. The global shrinkage parameter was set to $\phi=1x10^{-4}$ for the TRS interaction and $\phi=1x10^{-2}$ for the CLOZUK and PGC GWAS, reflecting the differential polygenicity of these analyses, as recommended by the software manual.

Association of the polygenic scores with the TR/non-TRS phenotype was calculated using logistic models with sex and the first 5 genotypic principal components (PCs) as covariates, in order to control for population stratification (Peloso and Lunetta, 2011). Given the presence of multiple ancestries in STRATA-G samples, we employed a previously described model to classify each sample into seven broadly defined biogeographical population groups using ancestry-informative markers (AIMs; Legge et al., 2019). We then used the underlying discriminant functions of this model to compute six

variables reflecting the probability of each sample being classified as “European”, “South West Asian”,“East Asian”, “Subsaharan African” or “North African”; and included these as covariates in all PRS analyses involving STRATA-G. To assess variance explained by the PRS metrics, Nagelkerke’s R^2 valuesfor each PRS logistic regression were calculated on the liability scale (Lee et al., 2012), assuming a 30% population prevalence for TRS in CardiffCOGS (Lally et al., 2016b) and 15% prevalence as a conservative estimate for STRATA-G (Kanahara et al., 2018; Siskind et al., 2021).

Finally, for the STRATA-G analyses, since this cohort was imputed in two independent batches, PRS association tests and their summary statistics were computed separately within each STRATA-G imputation batch (**Supplementary Table 2**), with batch 1 consisting of 466 individuals (46 TRS; 420 non-TRS) and batch 2 consisting of 103 individuals (25 TRS; 72 non-TRS). Effect size statistics reported in **Supplementary Table 3** were derived from the original betas and standard errors using fixed-effect meta-analysis with inverse variance weights. Pooled liability-scale R^2 were computed with the method of Harel (2009). Meta-analytic AUC values were computed with the random-effects method of Debray et al. (2017). All these computations were performed with functions from the R package “*metafor*" (Viechtbauer, 2010). An analogous meta-analysis was also carried out using the association summary statistics from CardiffCOGS and both STRATA-G batches (**Supplementary Figure 3**).

PGC TRS rating system

Cohort	Definition of assessed phenotypes	
	TRS	Non-TRS
aber - Aberdeen, UK	Ever treated with clozapine.	Never treated with clozapine.
asrb - Australia	Treated with clozapine at the time of the diagnostic assessment.	Not treated with clozapine at the time of the diagnostic assessment.
boco - Bonn/Mannheim, Germany	History of clozapine treatment at the time of interview.	No (explicit) disclosure of history of clozapine treatment during interview or in provided patient records.
denm - Denmark	Diagnosed with incident schizophrenia in Danish national registry data (1/Jan/1996 - 31/Dec/2010) and with recorded clozapine initiation.	Diagnosed with incident schizophrenia in Danish national registry data (1/Jan/1996 - 31/Dec/2010) but no recorded clozapine initiation.
dubl - Ireland	Ever treated with clozapine.	Never treated with clozapine.
irwt - Ireland (WTCCC2)	Ever treated with clozapine.	Never treated with clozapine.
munc - Munich, Germany	Ever treated with clozapine.	Never treated with clozapine.
port - Portugal	Negatively rated for OPCRIT item 89 (“psychotic symptoms respond to neuroleptics”; McGuffin et al., 1991).	Positively rated for OPCRIT item 89.
swe[1,5,6]/s234 - Sweden	Redeemed a clozapine prescription between the start of the Swedish drug register and the end of data collection (1/Jul/2005 - 31/Dec/2013)	Did not redeem a clozapine prescription in the same timeframe (1/Jul/2005 - 31/Dec/2013)
top8 - Oslo, Norway	Treated with or considered for clozapine during the follow up period.	Never treated with or considered for clozapine.
uclo - London, UK	Ever treated with clozapine.	Never treated with clozapine.

STRATA-G TRS rating system

Cohort	Definition of assessed phenotypes	
	TRS	Non-TRS
AESOP (London, UK)	Treated with clozapine during the follow up period.	A state, of at least 6 months' duration, in which no symptoms or only symptoms of mild severity, not interfering with daily functioning, were experienced (Andreasen et al., 2005)
ESS (Prague, Czech Republic)	Treated with or considered for clozapine during the follow up period.	Never treated with or considered for clozapine.
EUGEI & BoFEP (Bologna, Italy)	Treated with or considered for clozapine during the follow up period.	Never treated with or considered for clozapine.
EUGEI Istanbul (Turkey)	Treated with or considered for clozapine during the follow up period.	Never treated with or considered for clozapine.
EUGEI Paris (France)	Treated with or considered for clozapine during the follow up period.	Never treated with or considered for clozapine.
GAP (London, UK)	Treated with or considered for clozapine during the follow up period. Excluded those who were intolerant of antipsychotic medications or those who self-discontinued medication.	Never treated with or considered for clozapine.
NIFEPS & RGPI (Belfast, UK)	Treated with or considered for clozapine during the follow up period.	Never treated with or considered for clozapine.
PAFIP (Santander, Spain)	Treated with or considered for clozapine during the follow up period.	Never treated with or considered for clozapine.
TIPP (Switzerland)	Treated with or considered for clozapine during the follow up period. Excluded those with poor compliance and who met criteria for symptom severity.	Never treated with or considered for clozapine.
TOP (Oslo, Norway)	Treated with or considered for clozapine during the follow up period.	Never treated with or considered for clozapine.
West London (London, UK)	Treated with clozapine at the time of a follow up interview.	Never treated with clozapine at the time of a follow up interview.

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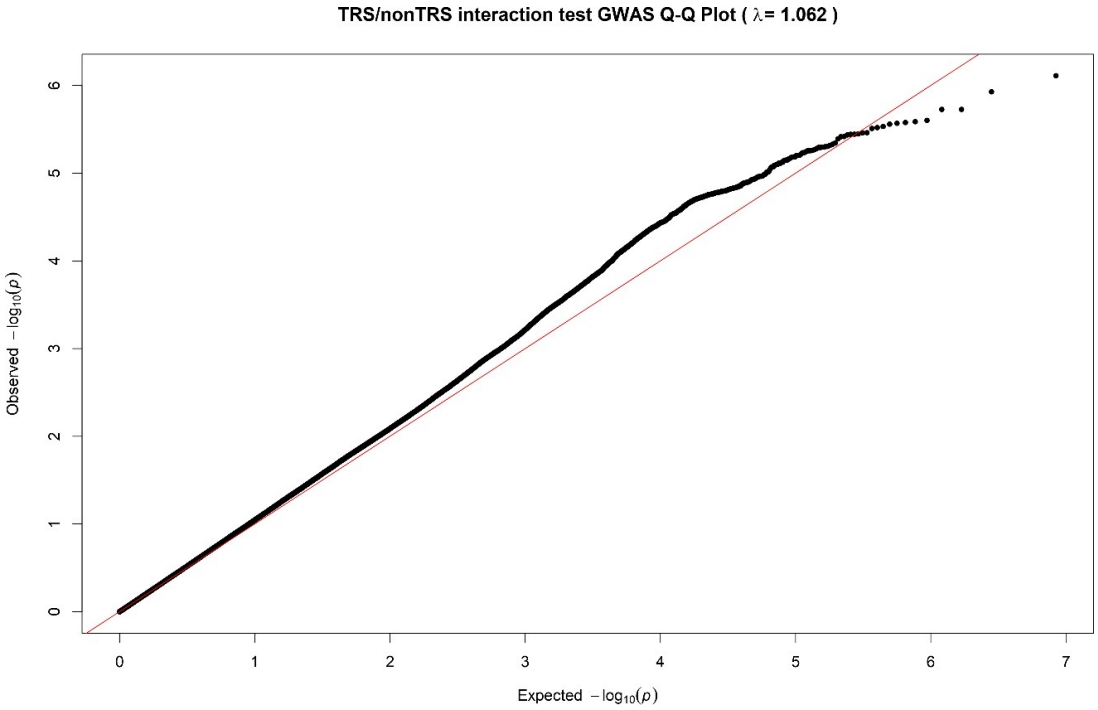
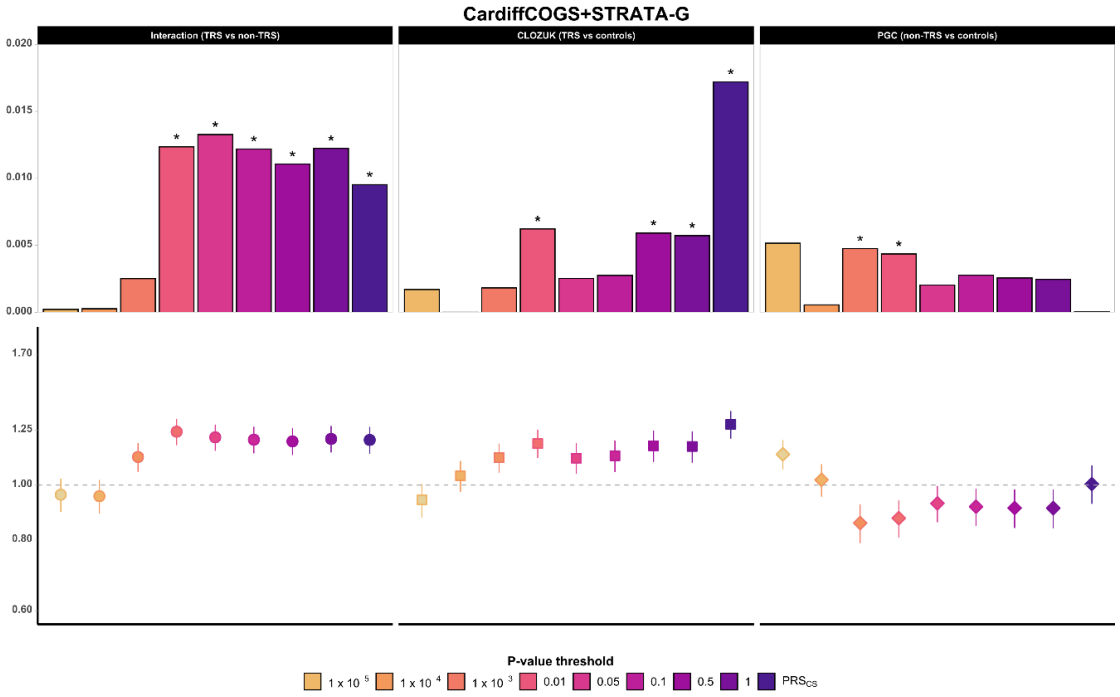
eFigure 1. Mirrored Manhattan plot of the 2 GWAS analysed with the TRS interaction procedure

eFigure 2. Q-Q plot of the TRS interaction GWAS



eFigure 3. PRS meta-analysis of CardiffCOGS and STRATA-G cohorts



PRS meta-analysis of CardiffCOGS (N_{TRS}=315; N_{NONTRS}=502) and STRATA-G (N_{TRS}=71; N_{NONTRS}=492) cohorts, based on the individual cohort results shown in Figure 2 and detailed in the maintext. Explained variances on the liability scale (upper panel) and effect sizes (lower panel) are shown.Asterisks indicate statistically significant ($p<0.05$) associations between PRS and treatment resistancein schizophrenia, defined as a history of taking clozapine in people with a diagnosis of schizophrenia.

eTable 1. Data sets included in the PGC non-TRS GWAS sample

DATASET ID*	TRS CASES (EXCLUDED)**	NON-TRS CASES	UNAFFECTED CONTROLS
ABER	29	691	699
AJSZ	*n/a*	896	1595
ASRB	33	476	310
BOCO	289	1558	2170
BULS	*n/a*	527	608
CATI	*n/a*	409	392
CAWS	*n/a*	476	2936
CIMS	*n/a*	71	69
DENM	105	387	458
DUBL	38	234	860
EDIN	*n/a*	368	284
EGCU	*n/a*	239	1177
ERSW	*n/a*	322	332
GRAS	*n/a*	1086	1232
IRWT	78	1222	1022
LACW	*n/a*	157	466
LIE2	*n/a*	137	269
LIE5	*n/a*	509	389
MGS2	*n/a*	2681	2653
MSAF	*n/a*	327	139
MUNC	166	271	351
PEWB	*n/a*	597	1858
PEWS	*n/a*	82	230
PORT	22	328	212
S234	402	1675	2341
SWE1	60	161	214
SWE5	433	1368	2617
SWE6	228	865	1219
TOP8	25	351	402
UCLA	*n/a*	705	637
UCLO	134	386	494
UMEB	*n/a*	375	584
UMES	*n/a*	197	713
ZHH1	*n/a*	191	190

* For full details see Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014).
** TRS ascertainment could not be carried out in datasets marked with "n/a", as individual-level clinical records were not available.

eTable 2. Data sets included in the STRATA-G sample

DATASET	GEOGRAPHIC AFFILIATION	GENOTYPING CHIP	IMPUTATION BATCH	TRS* CASES	NON-TRS* CASES
AESOP	London, UK	Infinium CoreExome-24	2	3	6
ESS	Prague, Czech Republic	Infinium Omni 2.5-8	1	1	23
EUGEI-BOLOGNA & BOFEP	Bologna, Italy	Human CoreExome-24**	2	0	6
EUGEI-PARIS	Paris, France	Human CoreExome-24**	2	6	15
GAP	London, UK	Infinium CoreExome-24	2	16	45
NIFEPS & RGPI	Belfast, UK	Infinium OmniExpress-24	1	3	8
PAFIP	Santander, Spain	Human OmniExpressExome-8	1	21	206
TIPP	Lausanne, Switzerland	Infinium OmniExpress-24	1	15	89
TOP	Oslo, Norway	Human OmniExpress-12	1	2	72
UCL	London, UK	Infinium OmniExpress-24	1	4	22
TOTAL				**71**	**492**

* Defined as described in the main text and above, restricted to individuals with schizophrenia at thelast time of follow up.

** Custom chip designed for the EUGEI project (van Os et al., 2014; Mihaljevic et al., 2017).

eTable 3. Polygenic risk score analysis results

Training dataset	*Training phenotype*	*Testing dataset*	*Testing phenotype*	*P-value threshold*	*R2 (%)*	*AUC*	*OR**	*s.e***	*p-value*	*p-value (FDR-corrected)****
TRS Interaction analysis	TRS/non-TRS	CardiffCOGS	Clozapine history	0.00001	0.1853%	0.5201	0.9307	0.0725	0.3218	0.3620
TRS Interaction analysis	TRS/non-TRS	CardiffCOGS	Clozapine history	0.0001	0.1289%	0.5168	0.9418	0.0726	0.4089	0.4089
TRS Interaction analysis	TRS/non-TRS	CardiffCOGS	Clozapine history	0.001	1.0666%	0.5483	1.1881	0.0727	0.0177	0.0439
TRS Interaction analysis	TRS/non-TRS	CardiffCOGS	Clozapine history	0.01	2.0328%	0.5667	1.2741	0.0744	0.0011	0.0099
TRS Interaction analysis	TRS/non-TRS	CardiffCOGS	Clozapine history	0.05	1.0352%	0.5476	1.1862	0.0731	0.0195	0.0439
TRS Interaction analysis	TRS/non-TRS	CardiffCOGS	Clozapine history	0.1	0.7265%	0.5398	1.1538	0.0730	0.0502	0.0645
TRS Interaction analysis	TRS/non-TRS	CardiffCOGS	Clozapine history	0.5	0.7991%	0.5418	1.1607	0.0727	0.0404	0.0606
TRS Interaction analysis	TRS/non-TRS	CardiffCOGS	Clozapine history	1	1.2280%	0.5518	1.2087	0.0728	0.0306	0.0551
TRS Interaction analysis	TRS/non-TRS	CardiffCOGS	Clozapine history	PRS-CS	1.1270%	0.5496	1.2013	0.0746	0.0111	0.0439
CLOZUK	TRS/controls	CardiffCOGS	Clozapine history	0.00001	0.1143%	0.5158	0.9453	0.0725	0.4380	0.4380
CLOZUK	TRS/controls	CardiffCOGS	Clozapine history	0.0001	0.1534%	0.5183	1.0677	0.0726	0.3668	0.4127
CLOZUK	TRS/controls	CardiffCOGS	Clozapine history	0.001	0.7109%	0.5394	1.1534	0.0737	0.0528	0.0950
CLOZUK	TRS/controls	CardiffCOGS	Clozapine history	0.01	1.3627%	0.5546	1.2203	0.0744	0.0075	0.0338
CLOZUK	TRS/controls	CardiffCOGS	Clozapine history	0.05	0.5414%	0.5344	1.1361	0.0754	0.0908	0.1279
CLOZUK	TRS/controls	CardiffCOGS	Clozapine history	0.1	0.5137%	0.5335	1.1344	0.0766	0.0995	0.1279
CLOZUK	TRS/controls	CardiffCOGS	Clozapine history	0.5	0.7470%	0.5404	1.1684	0.0784	0.0471	0.0950
CLOZUK	TRS/controls	CardiffCOGS	Clozapine history	1	0.7172%	0.5396	1.1649	0.0785	0.0516	0.0950
CLOZUK	TRS/controls	CardiffCOGS	Clozapine history	PRS-CS	1.6257%	0.5596	1.2513	0.0768	0.0035	0.0315
PGC	non-TRS/controls	CardiffCOGS	Clozapine history	0.00001	0.4249%	0.5305	1.1171	0.0736	0.1327	0.3981
PGC	non-TRS/controls	CardiffCOGS	Clozapine history	0.0001	0.0006%	0.5011	0.9959	0.0729	0.9553	0.9702
PGC	non-TRS/controls	CardiffCOGS	Clozapine history	0.001	1.2123%	0.5515	0.8319	0.0729	0.0116	0.1044
PGC	non-TRS/controls	CardiffCOGS	Clozapine history	0.01	0.6994%	0.5391	0.8694	0.0729	0.0550	0.2475
PGC	non-TRS/controls	CardiffCOGS	Clozapine history	0.05	0.0724%	0.5126	0.9548	0.0747	0.5362	0.6894
PGC	non-TRS/controls	CardiffCOGS	Clozapine history	0.1	0.1722%	0.5194	0.9299	0.0761	0.3399	0.5098
PGC	non-TRS/controls	CardiffCOGS	Clozapine history	0.5	0.2307%	0.5224	0.9188	0.0769	0.2704	0.4867
PGC	non-TRS/controls	CardiffCOGS	Clozapine history	1	0.2467%	0.5232	0.9160	0.0770	0.2544	0.4867
PGC	non-TRS/controls	CardiffCOGS	Clozapine history	PRS-CS	0.0003%	0.5007	0.9969	0.0824	0.9702	0.9702

Training dataset	*Training phenotype*	*Testing dataset*	*Testing phenotype*	*P-value threshold*	*R2 (%)*	*AUC*	*OR**	*s.e***	*p-value*	*p-value (FDR-corrected)****
TRS Interaction analysis	TRS/non-TRS	STRATA-G	Clozapine history	0.00001	0.0066%	0.5200	1.0574	0.1437	0.6978	0.7850
TRS Interaction analysis	TRS/non-TRS	STRATA-G	Clozapine history	0.0001	0.0003%	0.5022	0.9788	0.1495	0.8862	0.8862
TRS Interaction analysis	TRS/non-TRS	STRATA-G	Clozapine history	0.001	0.0228%	0.5388	0.8706	0.1519	0.3617	0.5426
TRS Interaction analysis	TRS/non-TRS	STRATA-G	Clozapine history	0.01	0.1207%	0.5182	1.0768	0.1443	0.6083	0.7821
TRS Interaction analysis	TRS/non-TRS	STRATA-G	Clozapine history	0.05	0.3508%	0.5461	1.2698	0.1426	0.0940	0.2115
TRS Interaction analysis	TRS/non-TRS	STRATA-G	Clozapine history	0.1	1.0916%	0.5649	1.3482	0.1432	0.0370	0.2073
TRS Interaction analysis	TRS/non-TRS	STRATA-G	Clozapine history	0.5	0.0226%	0.5537	1.3029	0.1455	0.0691	0.2073
TRS Interaction analysis	TRS/non-TRS	STRATA-G	Clozapine history	1	0.0443%	0.5558	1.3270	0.1462	0.0530	0.2073
TRS Interaction analysis	TRS/non-TRS	STRATA-G	Clozapine history	PRS-CS	0.4431%	0.5394	1.1451	0.1412	0.3372	0.5426
CLOZUK	TRS/controls	STRATA-G	Clozapine history	0.00001	0.0920%	0.5310	0.8612	0.1458	0.3055	0.7945
CLOZUK	TRS/controls	STRATA-G	Clozapine history	0.0001	0.1887%	0.5233	0.9015	0.1465	0.4794	0.8629
CLOZUK	TRS/controls	STRATA-G	Clozapine history	0.001	0.0409%	0.5148	0.9280	0.1571	0.6341	0.9069
CLOZUK	TRS/controls	STRATA-G	Clozapine history	0.01	0.0085%	0.5035	1.0131	0.1672	0.9380	0.9484
CLOZUK	TRS/controls	STRATA-G	Clozapine history	0.05	0.0064%	0.5031	1.0120	0.1842	0.9484	0.9484
CLOZUK	TRS/controls	STRATA-G	Clozapine history	0.1	0.0204%	0.5126	1.0809	0.2057	0.7054	0.9069
CLOZUK	TRS/controls	STRATA-G	Clozapine history	0.5	0.4219%	0.5350	1.2505	0.2359	0.3434	0.7945
CLOZUK	TRS/controls	STRATA-G	Clozapine history	1	0.4189%	0.5345	1.2468	0.2376	0.3531	0.7945
CLOZUK	TRS/controls	STRATA-G	Clozapine history	PRS-CS	1.5827%	0.5689	1.4033	0.1975	0.0863	0.7767
PGC	non-TRS/controls	STRATA-G	Clozapine history	0.00001	0.6059%	0.5470	1.2234	0.1746	0.2482	0.7885
PGC	non-TRS/controls	STRATA-G	Clozapine history	0.0001	0.4745%	0.5361	1.1863	0.1772	0.3350	0.7885
PGC	non-TRS/controls	STRATA-G	Clozapine history	0.001	0.0096%	0.5143	1.0313	0.1725	0.8581	0.8581
PGC	non-TRS/controls	STRATA-G	Clozapine history	0.01	0.0607%	0.5020	0.9461	0.1630	0.7342	0.8581
PGC	non-TRS/controls	STRATA-G	Clozapine history	0.05	0.6339%	0.5430	0.8307	0.1751	0.2894	0.7885
PGC	non-TRS/controls	STRATA-G	Clozapine history	0.1	0.1871%	0.5102	0.8752	0.1811	0.4619	0.7885
PGC	non-TRS/controls	STRATA-G	Clozapine history	0.5	0.0882%	0.5143	0.8746	0.1912	0.4833	0.7885
PGC	non-TRS/controls	STRATA-G	Clozapine history	1	0.0714%	0.5122	0.8844	0.1937	0.5257	0.7885
PGC	non-TRS/controls	STRATA-G	Clozapine history	PRS-CS	0.0268%	0.5174	1.0632	0.2437	0.8015	0.8581

Training dataset	*Training phenotype*	*Testing dataset*	*Testing phenotype*	*P-value threshold*	*R2 (%)*	*AUC*	*OR**	*s.e***	*p-value*	*p-value (FDR-corrected)****
TRS Interaction analysis	TRS/non-TRS	Meta-analysis	Clozapine history	0.00001	0.0222%	0.5090	0.9615	0.0645	0.5419	0.5419
TRS Interaction analysis	TRS/non-TRS	Meta-analysis	Clozapine history	0.0001	0.0274%	0.5094	0.9559	0.0650	0.4879	0.5419
TRS Interaction analysis	TRS/non-TRS	Meta-analysis	Clozapine history	0.001	0.2520%	0.5045	1.1209	0.0652	0.0801	0.1030
TRS Interaction analysis	TRS/non-TRS	Meta-analysis	Clozapine history	0.01	1.2357%	0.5593	1.2420	0.0660	0.0010	0.0090
TRS Interaction analysis	TRS/non-TRS	Meta-analysis	Clozapine history	0.05	1.3272%	0.5506	1.2140	0.0649	0.0028	0.0093
TRS Interaction analysis	TRS/non-TRS	Meta-analysis	Clozapine history	0.1	1.2194%	0.5494	1.2022	0.0649	0.0046	0.0093
TRS Interaction analysis	TRS/non-TRS	Meta-analysis	Clozapine history	0.5	1.1068%	0.5468	1.1943	0.0648	0.0062	0.0093
TRS Interaction analysis	TRS/non-TRS	Meta-analysis	Clozapine history	1	1.2238%	0.5495	1.2062	0.0649	0.0039	0.0093
TRS Interaction analysis	TRS/non-TRS	Meta-analysis	Clozapine history	PRS-CS	0.9540%	0.5504	1.2011	0.0657	0.0053	0.0093
CLOZUK	TRS/controls	Meta-analysis	Clozapine history	0.00001	0.1706%	0.5145	0.9417	0.0647	0.3538	0.3980
CLOZUK	TRS/controls	Meta-analysis	Clozapine history	0.0001	0.0007%	0.5084	1.0382	0.0648	0.5632	0.5632
CLOZUK	TRS/controls	Meta-analysis	Clozapine history	0.001	0.1829%	0.5261	1.1177	0.0663	0.0933	0.1439
CLOZUK	TRS/controls	Meta-analysis	Clozapine history	0.01	0.6227%	0.5426	1.1835	0.0676	0.0127	0.0572
CLOZUK	TRS/controls	Meta-analysis	Clozapine history	0.05	0.2539%	0.5269	1.1154	0.0694	0.1156	0.1486
CLOZUK	TRS/controls	Meta-analysis	Clozapine history	0.1	0.2762%	0.5286	1.1263	0.0714	0.0959	0.1439
CLOZUK	TRS/controls	Meta-analysis	Clozapine history	0.5	0.5917%	0.5386	1.1731	0.0741	0.0312	0.0779
CLOZUK	TRS/controls	Meta-analysis	Clozapine history	1	0.5730%	0.5379	1.1699	0.0742	0.0346	0.0779
CLOZUK	TRS/controls	Meta-analysis	Clozapine history	PRS-CS	1.7204%	0.5638	1.2794	0.0715	0.0006	0.0054
PGC	non-TRS/controls	Meta-analysis	Clozapine history	0.00001	0.5163%	0.5350	1.1331	0.0677	0.0648	0.1944
PGC	non-TRS/controls	Meta-analysis	Clozapine history	0.0001	0.0557%	0.5081	1.0214	0.0672	0.7531	0.8472
PGC	non-TRS/controls	Meta-analysis	Clozapine history	0.001	0.4760%	0.5303	0.8570	0.0669	0.0211	0.1899
PGC	non-TRS/controls	Meta-analysis	Clozapine history	0.01	0.4364%	0.5335	0.8742	0.0663	0.0426	0.1917
PGC	non-TRS/controls	Meta-analysis	Clozapine history	0.05	0.2042%	0.5176	0.9282	0.0685	0.2768	0.3559
PGC	non-TRS/controls	Meta-analysis	Clozapine history	0.1	0.2771%	0.5230	0.9159	0.0699	0.2089	0.3134
PGC	non-TRS/controls	Meta-analysis	Clozapine history	0.5	0.2571%	0.5233	0.9110	0.0711	0.1901	0.3134
PGC	non-TRS/controls	Meta-analysis	Clozapine history	1	0.2463%	0.5233	0.9105	0.0713	0.1889	0.3134
PGC	non-TRS/controls	Meta-analysis	Clozapine history	PRS-CS	0.0031%	0.5039	1.0041	0.0779	0.9582	0.9582

* Based on standardised polygenic scores.

** Standard error of the regression beta.

*** Correction performed inside each group formed by training dataset and testing phenotype.

eTable 4. LD-Score and LD-Hub analyses of the TRS GWAS summary statistics

Trait	*PMID*	*Category*	*ethnicity*	*rg*	*se*	*z*	*p*	*pFDR*	*h2_obs*	*h2_obs_se*	*h2_int*	*h2_int_se*
TRS GWAS	this study	-	European	-	-	-	-	-	0.013	0.006	1.036	0.007
Years of schooling 2016	27225129	education	European	-0.660	0.157	-4.202	2.64E-05	0.0007	0.125	0.005	0.946	0.013
College completion	23722424	education	European	-0.691	0.180	-3.832	0.0001	0.0009	0.082	0.006	1.021	0.010
Years of schooling (proxy cognitive performance)	25201988	education	European	-0.639	0.165	-3.875	0.0001	0.0009	0.110	0.008	1.025	0.011
Years of schooling 2013	23722424	education	European	-0.643	0.171	-3.751	0.0002	0.0014	0.086	0.007	1.019	0.010
Intelligence	28530673	cognitive	European	-0.562	0.170	-3.314	0.0009	0.0050	0.191	0.011	1.015	0.011
Former vs Current smoker	20418890	smoking_behaviour	European	-0.658	0.286	-2.298	0.0216	0.1008	0.061	0.013	1.002	0.008
Cigarettes smoked per day	20418890	smoking_behaviour	European	0.661	0.309	2.135	0.0327	0.1308	0.057	0.016	1.007	0.008
Ever vs never smoked	20418890	smoking_behaviour	European	0.413	0.203	2.035	0.0419	0.1467	0.070	0.008	1.007	0.008
Childhood IQ	23358156	education	European	-0.361	0.190	-1.898	0.0577	0.1795	0.273	0.049	1.004	0.010
Bipolar disorder	21926972	psychiatric	European	-0.255	0.158	-1.608	0.1077	0.3016	0.440	0.041	1.022	0.009
Attention deficit hyperactivity disorder	20732625	psychiatric	European	-0.413	0.286	-1.444	0.1487	0.3526	0.256	0.104	1.011	0.008
Attention deficit hyperactivity disorder (GC)	27663945	psychiatric	European	0.493	0.353	1.396	0.1627	0.3526	0.068	0.031	0.996	0.009
Attention deficit hyperactivity disorder (No GC)	27663945	psychiatric	European	0.491	0.353	1.393	0.1637	0.3526	0.069	0.031	1.011	0.009
Depressive symptoms	27089181	psychiatric	European	0.183	0.148	1.230	0.2188	0.4376	0.050	0.004	0.999	0.008
Smoking Initiation	30617275	smoking_behaviour	European	0.546	0.499	1.096	0.2730	0.4801	0.007	0.001	1.077	0.010
Subjective well being	27089181	psychiatric	European	-0.164	0.155	-1.057	0.2905	0.4801	0.026	0.002	0.997	0.008
PGC cross-disorder analysis	23453885	psychiatric	European	-0.146	0.140	-1.040	0.2983	0.4801	0.161	0.014	1.034	0.013
Autism spectrum disorder	30804558	psychiatric	European	-0.177	0.180	-0.985	0.3248	0.4801	0.393	0.055	0.984	0.009
Neuroticism	27089181	personality	European	0.117	0.119	0.983	0.3258	0.4801	0.091	0.007	0.988	0.012
Neo-openness to experience	21173776	personality	European	-0.219	0.255	-0.858	0.3909	0.5473	0.110	0.027	0.991	0.008
Smoking Cessation	30617275	smoking_behaviour	European	-0.704	0.871	-0.808	0.4190	0.5587	0.006	0.003	1.006	0.018
Neo-conscientiousness	21173776	personality	European	0.221	0.308	0.717	0.4735	0.5781	0.071	0.032	1.001	0.008
Neuroticism	24828478	personality	European	0.195	0.273	0.715	0.4749	0.5781	0.013	0.004	1.014	0.008
Schizophrenia	25056061	psychiatric	Mixed	0.059	0.092	0.648	0.5172	0.6034	0.456	0.021	1.064	0.015
Major depressive disorder	22472876	psychiatric	European	-0.109	0.208	-0.522	0.6020	0.6742	0.148	0.029	1.017	0.008
Cigarettes Per Day	30617275	smoking_behaviour	European	-0.159	0.338	-0.470	0.6381	0.6872	0.022	0.013	1.000	0.019
Anorexia Nervosa	24514567	psychiatric	European	-0.048	0.142	-0.340	0.7341	0.7613	0.369	0.032	0.974	0.008
Age of smoking initiation	20418890	smoking_behaviour	European	-0.001	0.290	-0.003	0.9973	0.9973	0.060	0.020	0.999	0.008

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