Supplemental Online Content

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

eMethods

Study population

We applied clustering per individual, i.e., individuals were included only once, not as counts for all time points. Individual data were extracted from two existing cohorts recruited by the authors: individuals with schizophrenia (SCZ) spectrum disorders (SSD) on treatment with clozapine were selected from our Clozapine International (CLOZIN)[1] and Genetic Risk and Outcome of Psychosis (GROUP) cohorts,[2,3] while individuals with SSD on other antipsychotic medications, individuals' siblings, individuals' parents, and healthy controls were extracted from the GROUP cohort. Participant selection criteria and study methods for each cohort have been previously described.[1,3] A short summary is provided below.

The GROUP cohort consisted of 524 individuals with SSD not on clozapine, 186 individuals with SSD on clozapine, 695 parents, 731 siblings, and 369 controls. It consisted of Dutch speaking participants recruited in Amsterdam, Utrecht, Groningen, and Maastricht between 16 and 50 years of age. Cases had any diagnosis of non-affective psychotic disorder according to the DSM-IV-TR; their unaffected siblings and parents were recruited as well. Controls were recruited from the same geographical area, with no current or previous personal or first-degree family history of non-affective psychosis. The goal of this study was to provide a detailed assessment of vulnerability and resilience factors (environmental and genetic) in individuals with SSD. For individuals with SSD, data on medication status was collected at three distinct time points (cohort entry, three years after cohort entry, and six years after cohort entry). The majority of individuals with SSD were currently on medication, with only a small number of individuals not on medication (n=35) or with an unknown status regarding medication (n=70). Antipsychotic use in GROUP individuals with SSD was verified for up to 6 years at three time points to increase chances that individuals requiring clozapine would be identified. For inclusion in the group of individuals with SSD on other antipsychotics, information about antipsychotic use was required at ≥ 1 time point. We thus excluded 105 individuals with SSD for whom antipsychotic use was missing at all time points. At baseline (time point 0), there were 439 participants with known antipsychotic use data; at time point 1 (3 years after follow-up) 250 participants underwent a visit to record antipsychotic use, while at time point 2 (6 years after follow-up) 221 participants were interviewed. Missingness during follow-up interviews was caused by loss to follow-up.[2,3] All individuals with SSD reported a maximum of 2 psychotic episodes during their lifetime, meaning they were either in an acute episode upon cohort entry or had only had 1 previously. Despite this relatively long-term follow-up, we acknowledge that only a life-long follow-up would confirm a lifetime lack of clozapine prescription. However, our approach is likely to be conservative as potential late-in-life clozapine users would currently be included in the SSD group on other antipsychotics.

The CLOZIN cohort consisted of 687 individuals, who were recruited from inpatient and outpatient settings in the Netherlands, Germany, Austria, Turkey, and Australia. All participants were diagnosed by their treating physician with a primary diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, or psychotic disorder not otherwise specified according to Diagnostic and Statistical Manual of Mental Disorders, Fourth or Fifth Edition (DSM-IV-TR or DSM-5), used clozapine, were aged 18 years or older, were able to speak and read the local language, and were able and willing to provide written informed consent.[1] The goal of CLOZIN is to examine associations between genetic data, side effects, and symptom severity in clozapine users. N=116 clozapine users were genotyped in both cohorts; as CLOZIN participants were genotyped on a more recent genotyping platform these 116 duplicates were removed from the GROUP genotypic data.

Genotyping, genetic data processing, including quality control and imputation

Genotyping procedures were described previously.[1,2] We applied standard participant and single nucleotide polymorphism (SNP) level quality control (QC)[1,2] using PLINK v1.90b3z 64-bit to ensure inclusion of only well performing SNPs in well genotyped individuals. Pre-imputation SNP quality control steps, imputation and post-imputation steps were performed on each individual cohort. The pre-imputation SNP Quality control steps included SNP call rate>98%, HWE P-value >1×10^{-5}, MAF>0.01, and the exclusion of insertions, deletions, ambiguous SNPs, non-autosomal SNPs, and multiallelic SNPs; resulting in 688,618 SNPs for CLOZIN samples and for 267,986 GROUP samples (**eTable 1**). These SNPs for each cohort were imputed separately on the Michigan server[4] using the HRC r1.1 2016 reference panel with European samples after phasing with Eagle v2.3. Post-imputation QC involved removing SNPs with an imputation quality score<0.8, with a MAF<0.01, SNPs that had a discordant MAF more than 0.15 compared to the reference panel, and strand ambiguous AT/CG SNPs and multi-allelic SNPs. In the end, common SNPs in both cohorts were extracted, and the two genotypic datasets were merged, leaving 4,101,456 SNPs. SNPs in a complex linkage disequilibrium (LD) region (**eTable 2**)[5] were

then eliminated. The remaining SNPs were clumped, leaving 146,468 SNPs for the generation of polygenic risk scores (PRSs).

The samples included for the current study (CLOZIN: n=687 and GROUP: n=2505; in total N=3192) underwent standard QC steps outlined in previous studies,[1,2] which involved the following criteria: exclusion of mismatched gender information between phenotypic and genotypic data; exclusion of individuals with excess heterozygosity or homozygosity rates (> 3 standard deviations from the mean); a relatedness check by pairwise identity by descent (IBD) values (unrelated pairs: pihat <0.1, siblings and parent-offspring pairs: pihat>0.35 and pihat<0.65, duplicate pairs: pihat>0.9). We then conducted principal component analyses (PCA) to detect ethnic outliers using genetic PCs after merged best-guess data was generated (**eTable 2**). For PCA, we first selected a set of high-quality SNPs by including Hapmap3 SNPs, SNPs with a call rate>0.99, a minor allele frequency (MAF)>0.1, a Hardy-Weinberg Equilibrium (HWE) p-value (p)>1×10^{-6}, and Linkage Disequilibrium (LD)-pruned with an r^2>0.2, a window size of 50, and window shifting per 5 SNPs, resulting in 229,391 SNPs. The ancestry-informed PCA were then conducted in EIGENSTRAT[6] to generate 20 genetic principal components (PCs). The ethnic outliers of whom the first 2 PCs diverged >10× SD from Utah residents with Northern and Western European ancestry from the CEPH collection (CEU) samples (N=206), and > 3 x SD of our own samples (N=86) were excluded. The 20 genetic PCs were generated again for samples passing all sample QC steps (**eTable 3 and eFigure 1**). Finally, strand ambiguous SNPs and duplicate SNPs were removed. To minimize risk of population stratification incurring bias into the results, PCA was also carried out using Eigensoft v4.2 (2020) against Hapmap Phase 3 individuals. This PCA yielded additional 292 genetic European ancestry outliers that were excluded from further analysis (**eFigure 1**). 2777 individuals passed these abovementioned QC steps. After excluding individuals with SSD whose antipsychotic medication information was not available during 6 years of follow up (n=105), 2672 individuals were left. We then applied several phenotypic QC checks. We ensured the group of other antipsychotics users was not enriched for non-schizophrenia cases relative to the clozapine using group given the possibility that diagnosis (e.g., schizophrenia vs. psychosis not otherwise specified) may be associated with PRS loading. To that end, we removed individuals with any DSM-IV-TR or DSM-5 diagnosis different from schizophrenia (DSM code 295) from the "other antipsychotics" group (n=45) and clozapine users (n=12). Furthermore, we excluded all controls and relatives with any DSM-IV-TR or DSM-5 diagnoses at ≥1 time point(s) from the following groups: controls (n=41), parents (n=134), and siblings (n=96) groups. After this all, our resulting final quality-controlled sample size was n=2344 (**eTable 3**). PRS-SCZ were generated for these n=2344 participants (mean age: 36.95 years; 42.4% female) participants remaining after QC, as outlined below (557 individuals with SSD on clozapine, 350 individuals with SSD on other antipsychotics, 542 parents of individuals with SSD, 574 siblings of individuals with SSD and 321 unrelated healthy controls; **eTable 4**).

Polygenic Risk Score (PRS) generation

PRS-cs-auto (see below) was used for our main analysis, while PRSice (see below) was used for sensitivity analyses, as outlined below. In Figure 1 and eFigures 2 and 3 we show PRS loadings per group. In the legends of these figures, t-test results for group comparisons (PRS-SCZ in each group compared to all other groups) are reported.

PRS-cs-auto

Data analyses were conducted in R version 4.0.5. To prevent possible study population overlap affecting our results, we used the latest (2022) leave-one-out schizophrenia GWAS summary statistics that had excluded the current study populations.[7] Thus, we made sure that all participants (n=2344) we included in the current study had not been used in the GWAS data to train the PRS, allowing for unbiased PRS computation. The odds ratios in the summary statistics were log converted to β-values as effect sizes. We generated PRS-SCZ (genetic liability to schizophrenia) by applying a Bayesian framework method that utilizes continuous shrinkage (cs) on SNP effect sizes, and is robust to varying genetic architectures, provides substantial computational advantages, and enables multivariate modelling of local linkage disequilibrium patterns: PRS-cs-auto.[8] PRS-cs-auto infers posterior SNP weights using GWAS summary statistics combined with an external linkage disequilibrium reference panel, such as the 1000 Genomes Project European sample. We placed a standard half-Cauchy prior on the global shrinkage parameter, which is automatically learnt from data and no validation data set is needed.[8] Scores were calculated by summing the number of risk alleles at each SNP multiplied by the posterior SNP weight inferred using PRS-cs-auto, with a total of 903,007 included SNPs, which were common among the HapMap3 SNP list, the training dataset, and the target dataset. The PRSs were standardized before statistical analyses were conducted.

PRS generation by PRSice

The protocol for PRS generation was described in our previous study.[2] In brief, as quality control for PRS calculation, the SNPs that overlapped between the summary statistics GWASs (training dataset) and our dataset were extracted. To account for complicated linkage disequilibrium (LD) structures in the genome, these SNPs were clumped in two rounds[2,9] with PLINK 1.90: round 1 with the default parameters (physical distance threshold 250 kb and linkage disequilibrium threshold (R2) of 0.5); and round 2 with a physical distance threshold of 5000 kb and linkage disequilibrium threshold (R2) of 0.2. Additionally, we excluded all SNPs in genomic regions with strong or complex linkage disequilibrium structures[5] (e.g., the MHC region on chromosome 6; **eTable 3**). The odds ratios in the summary statistics were log converted to β-values as effect sizes. PRS-SCZ were generated at the p-value threshold $p_t < 0.05$[7] using PRSice-2[10] (default settings) without p_t clumped method (--no-clump, because our dataset has undergone 2 rounds of LD clumping), as this method is both precise and the simplest while maintaining strong prediction performance.[7,11]

Explained variance calculation

The variance explained by genetic risk profiles for binary outcomes is not readily comparable on the observed scale when proportions of cases differ. To facilitate interpretability on the observed scale with varying proportions of ascertained cases, the variance explained was transformed to the 50/50 observed scale.[12] For the case-control comparison, we also calculated variance explained at the liability scale at 13.78% based on a prevalence of 1%, which is in line with previous findings[7] (and corresponds to a variance explained on the 50/50 observed scale of 18.45% from Table 1 model 4). We note that variance explained is often expressed on the liability scale. However, the liability scale has no clear interpretation when comparing subsets of cases to each other.

Sensitivity analyses' methodology

Two sensitivity analyses were conducted to verify the robustness of our findings. As a first sensitivity analysis, we ran all three main analyses listed in the methods section of the main paper (i.e., multinomial regression, logistic regression and PRS quintiles comparisons) with PRS-cs-auto residuals, wherein PRS-cs-auto had been adjusted for the first three genetic ancestry PCs, age, and sex in linear regression. As a second sensitivity analysis, we repeated the same 3 main analyses listed in the methods section of the main paper using PRSice instead of PRS-cs-auto.

eResults

Sensitivity Analyses Results

Both sensitivity analyses confirmed our main results, as outlined below.

Sensitivity analysis 1

In multinomial logistic regression, the adjusted PRS-cs-auto-SCZ still significantly differed between groups, to approximately the same degree and in the same order as for PRS-cs-auto (**eTable 5**). The RRs were highest in clozapine users (RR 3.29 [95% CI 2.71-3.99], p= 1.33×10^{-33}), followed by individuals with SSD on other antipsychotics (RR 2.71 [95% CI 2.19-3.33], p=5.43×10^{-21}), parents (RR 1.46 [95% CI 1.22-1.75], p=5.19×10^{-5}), and siblings (RR 1.38 [95% CI 1.16-1.65], p=4.22×10^{-5}). In the logistic regression analysis of type of antipsychotic medication within individuals with SSD, the adjusted PRS-cs-auto-SCZ were positively associated with clozapine use (**eTable 6**, p=1.41×10^{-5}). The odd ratios of schizophrenia risk in quintile of adjusted PRS-cs-auto groups results were also similar to the PRS-cs-auto results (**eFigure 4**). The odds ratios increased with greater number of schizophrenia risk alleles in each group, with the maximum reached for the fifth quintile in the comparison of clozapine users with unrelated healthy controls: OR 25.51 [95% CI 13.35-48.69].

Sensitivity analysis 2

Similarly, in multinomial logistic regression model, PRSice-SCZ significantly differed between groups, and in the same order as for PRS-cs-auto (**eTable 5**). The RRs were highest in clozapine users (RR 3.08 [95% CI 2.63-3.61], p= 9.67×10^{-44}), followed by individuals with SSD on other antipsychotics (RR 2.19 [95% CI 1.85- 2.59], p=3.49×10^{-20}), parents (RR 1.46 [95% CI 1.26-1.69], p=7.05×10^{-7}), and siblings (RR 1.43 [95% CI 1.23-1.66], p= 1.94×10^{-6}). In the logistic regression analysis of type of antipsychotic medication within individuals with SSD, PRS-ice-SCZ was also positively associated with clozapine use (**eTable 6**, p=2.31×10^{-6}). The odds ratios of schizophrenia risk in quintile PRS groups results were again similar to the PRS-cs-auto results (**eFigure 5**). The odds ratios increased with greater number of schizophrenia risk alleles in each group, with the maximum reached for the fifth quintile in the comparison of clozapine users with unrelated healthy controls: OR 27.58 [95% CI 14.42-52.76].

eAppendix. Discussion of future directions

We believe findings from our study set the stage for personalized interventions in the future. An example of an intervention study is to examine tailoring treatment more specifically to patients with schizophrenia with a high polygenic load as measured by PRS. In a trial setting, said patients could be prescribed clozapine relatively early in their course of illness, i.e., as a second-step monotherapy or add-on therapy and be compared on outcomes, such as quality of life, with patients receiving treatment as usual. Furthermore, an example of a prognostic study is one that assesses whether patients with SCZ and high PRS-SCZ who use clozapine have better prognosis than individuals with SCZ and a high PRS-SCZ who are not prescribed clozapine. Said types of studies should also report on patients' experiences regarding clinical effectiveness, tolerability, quality of life, and functioning, thus allowing clinicians to know whether their patients with SCZ and high PRS-SCZ benefit in the long run from clozapine treatment.

eReferences

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eTable 1. Summary of SNP QC steps for genetic data.				
	CLOZIN		**GROUP**	
Genotyping platform	Illumina Infinium® Global Screening Array (GSA1), version 1 (Illumina, San Diego, CA, USA		Custom Illumina HumanCoreExome-24 BeadChip	
Pre-imputation SNP QC Step	N SNPs before QC	N SNPs after QC	N SNPs before QC	N SNPs after QC
missingness <0.02	725,831	725,506	570,038	565,650
HWE>1x10-5	725,506	725,831	565,650	559140
MAF> 0.01	725,831	706,213	559140	290025
Remove SNPs with insertion or deletion	706,213	703,537	290025	284430
Remove SNPs that are strand ambiguous	703,537	692,458	284430	281794
Only include autosomal SNPs	692,458	69,729	281794	281654
Multiallelic SNPs	769,729	688,618	281654	267,986
Imputation	688,618	39,018,032	267,986	38,346,751
INFO>0.8 and MAF >0.01	39,018,532	5,706,411	38,346,751	5,791,054
Multiallelic SNPs	5,706,411	5,515,767	5,791,054	5,498,846
MAF discontent SNPs	5,515,767	5,506,389	5,498,846	5,211,700
Ambiguous SNPs	5,506,389	5,502,119	5,211,700	5,070,651
Extract common SNPs from 2 cohorts and merge into one best guess data	4,101,456 overlapping SNPs between cohorts			
Clump round 1	535,996			
Clump round 2	146,468			

SNP: single nucleotide polymorphism; QC: quality control.

eTable 2. 20 Complex-LD regions and long-range LD regions which were excluded from PRS analysis.	
Chromosome	Base pair position (start point to end point)
1	48000000-52000000
2	86000000-100500000
2	183000000-190000000
3	47500000-50000000
3	83500000-87000000
5	44500000-50500000
5	129000000-132000000
6	25500000-33500000
6	57000000-64000000
6	140000000-142500000
7	55000000-66000000
8	8000000-12000000
8	43000000-50000000
8	112000000-115000000
10	37000000-43000000
11	87500000-90500000
12	33000000-40000000
20	32000000-34500000
8	8135000-12000000
17	40900000-45000000

LD: linkage disequilibrium; PRS: polygenic risk score

eTable 3. Demographics, characteristics, and data processing of the 5 groups that were compared.

Cohorts (Initial sample size)	GROUP (n=2505)					CLOZIN (n=687)	Total N
Group	controls	siblings	parents	SSD on other AP	CLOZ	CLOZ	
	369	731	695	524	186	687	3192
Remove duplicates	369	731	695	524	757		3076
Mean age (SD)	30.60 (10.74)	27.52 (8.24)	54.59 (6.61)	28.32 (8.69)	38.22 (12.74)		37.02 (14.36)
% female	57.18	56.21	54.46	27.63	26.75		44.72
N of genetic outliers	6	59	19	22	186		292
N samples with missing covariates	1	2	0	2	2		7
Remove individuals with SSD whose information on antipsychotics was not available during 6 years of follow up	0	0	0	105	0		105
Remove individuals based on diagnosis (DSM code)	41	96	134	45	12		328
Final sample	321	574	542	350	557		2344

CLOZ: individuals with SSD using clozapine; SD: standard deviation; SSD: individuals with schizophrenia spectrum disorder; AP: antipsychotic; DSM: Diagnostic and Statistical Manual

eTable 4. Age and sex of the study population after QC per each of the 5 groups.

	Age, mean (SD)	N (male/female)
Individuals with SSD on clozapine	38.9 (12.85)	416/141
Individuals with SSD on other antipsychotics	27.7 (7.59)	260/90
Parents	54.9 (6.69)	257/285
Siblings	27.6 (8.26)	269/305
Controls	30.0 (10.61)	148/173

SD: standard deviation; QC: Quality control; SSD: Schizophrenia spectrum disorders

eTable 5. Multinomial logistic regression results (relative to unrelated healthy controls).

Group	PRS-cs-auto			Residual PRS-cs-auto (sensitivity analysis #1)			PRSice (sensitivity analysis #2)		
	RR	95% CI	P value	RR	95% CI	P value	RR	95% CI	P value
Parents	1.44	1.25-1.68	1.76×10^{-6}	1.46	1.22-1.75	5.19×10^{-5}	1.46	1.26-1.69	7.05×10^{-7}
Siblings	1.40	1.21-1.63	8.22×10^{-6}	1.38	1.16-1.65	4.22×10^{-4}	1.43	1.23-1.66	1.94×10^{-6}
SSD on other AP	2.30	1.95-2.72	3.77×10^{-22}	2.71	2.19-3.33	5.43×10^{-21}	2.19	1.85-2.59	3.49×10^{-20}
Clozapine	3.24	2.76-3.81	2.47×10^{-46}	3.29	2.71-3.99	1.33×10^{-33}	3.08	2.63-3.61	9.67×10^{-44}

SSD: schizophrenia spectrum disorder; AP: antipsychotic.

**eTable 6. Logistic regression results of PRS-SCZ differences between groups.**

Model	Case	Control	PRS-cs-auto residual				PRS-ice			
			$R^2_{obs,50/50}$	OR	95%CI	p	$R^2_{obs,50/50}$	OR	95% CI	p
1	Clozapine (n=557)	Other antipsychotics (n=350)	2.64	1.37	1.19-1.58	1.41×10^{-5}	2.23	1.41	1.23-1.63	2.31×10^{-6}
2	Clozapine (n=557)	Controls (n=321)	20.09	2.81	2.36-3.34	6.34×10^{-32}	20.67	2.83	2.38-3.35	1.02×10^{-32}
3	Other anti-psychotics (n=350)	Controls (n=321)	12.67	2.33	1.92-2.82	5.67×10^{-18}	12.48	2.26	1.88-2.72	7.13×10^{-18}
4	All SSD (n=907)	Controls (n=321)	16.81	2.60	2.23-3.04	1.71×10^{-33}	17.22	2.62	2.25-3.07	4.31×10^{-34}

Note: $R^2_{obs,50/50}$ = variance explained on the observed scale R2 with 50:50 ascertainment (see eMethods above). OR = Odds ratio. 95% CI =95% confidence interval.

**eTable 7. Group comparisons of polygenic risk scores for schizophrenia (PRS-SCZ).**

Group 1	Group 2	T-test p-value
Siblings	Parents	0.66
	Other APs	1.93×10^{-12}
	Clozapine	3.34×10^{-36}
	Control	8.35×10^{-6}
Parents	Other APs	4.03×10^{-11}
	Clozapine	1.57×10^{-33}
	Control	1.62×10^{-6}
Other APs	Clozapine	1.05×10^{-6}
	Control	1.39×10^{-23}
Clozapine	Control	4.01×10^{-47}

eFigure 1. Individuals' first two genetic ancestry principal components after all PCA-based exclusions of genetic outliers. Each dot represents an individual. As can be appreciated from the graph, the participants of our study ('Study Samples', dark dots, left upper part of the graph) are genetically homogenous, minimizing chances that population stratification impacts the results.
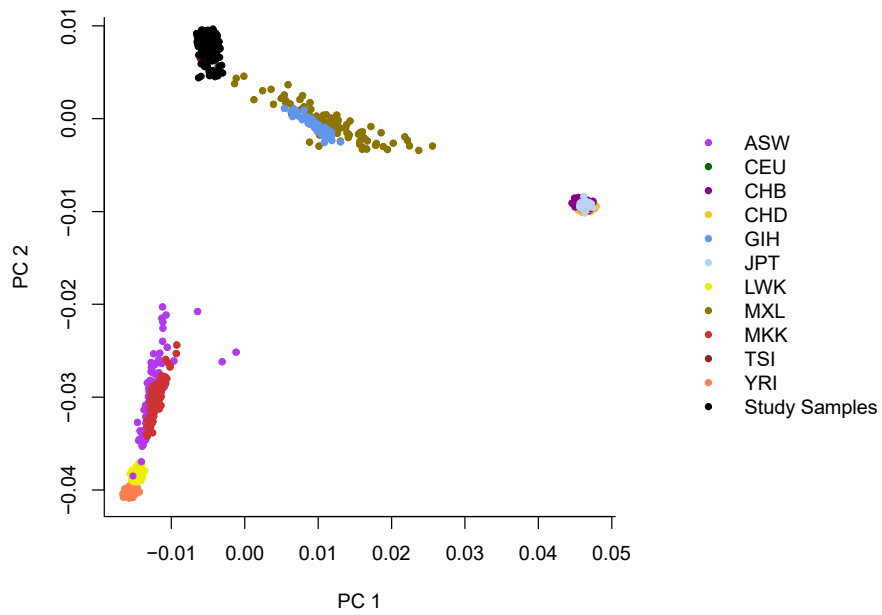

PCA: Principal Component Analysis

eFigure 2. Mean adjusted (residualized) PRS-cs-auto-SCZ loading per group. The thick bar in the middle of the boxplot is the median PRS-cs-auto-SCZ residuals for individuals in each group. The rectangle of the boxplot is delimited by the 25th and 75th percentiles. The widths of the violins reflect the data distributions. Individuals with SSD on clozapine had the highest PRS, followed by individuals with SSD on other antipsychotics, their parents and siblings, and unrelated healthy controls. All one-on-one comparisons were significant (all t-test p-values <0.0001), except for the comparison between siblings and parents of individuals with SSD, which is in line with the main analyses.
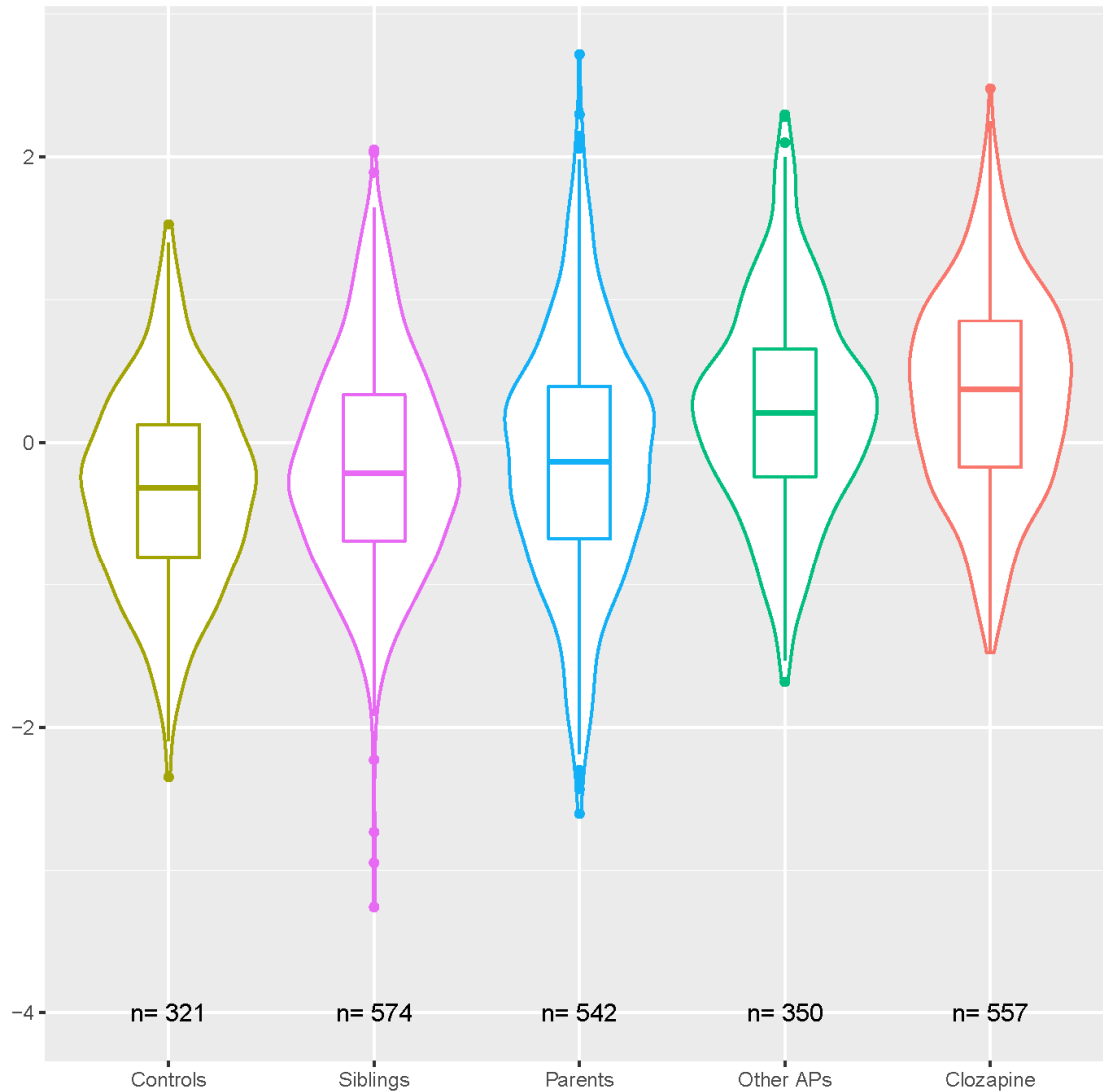
Other APs = Individuals with SSD using other antipsychotic medications.

eFigure 3. Mean PRSice-SCZ loading per group. The thick bar in the middle of the boxplot is the median PRS for individuals in each group. The rectangle of the boxplot is delimited by the 25th and 75th percentiles. The widths of the violins reflect the data distributions. Individuals with SSD on clozapine had the highest PRS, followed by individuals with SSD on other antipsychotics, their parents and siblings, and unrelated healthy controls. All one-on-one comparisons were significant (all t-test p-values <0.0001), except for the comparison between siblings and parents of individuals with SSD, which is in line with the main analyses.
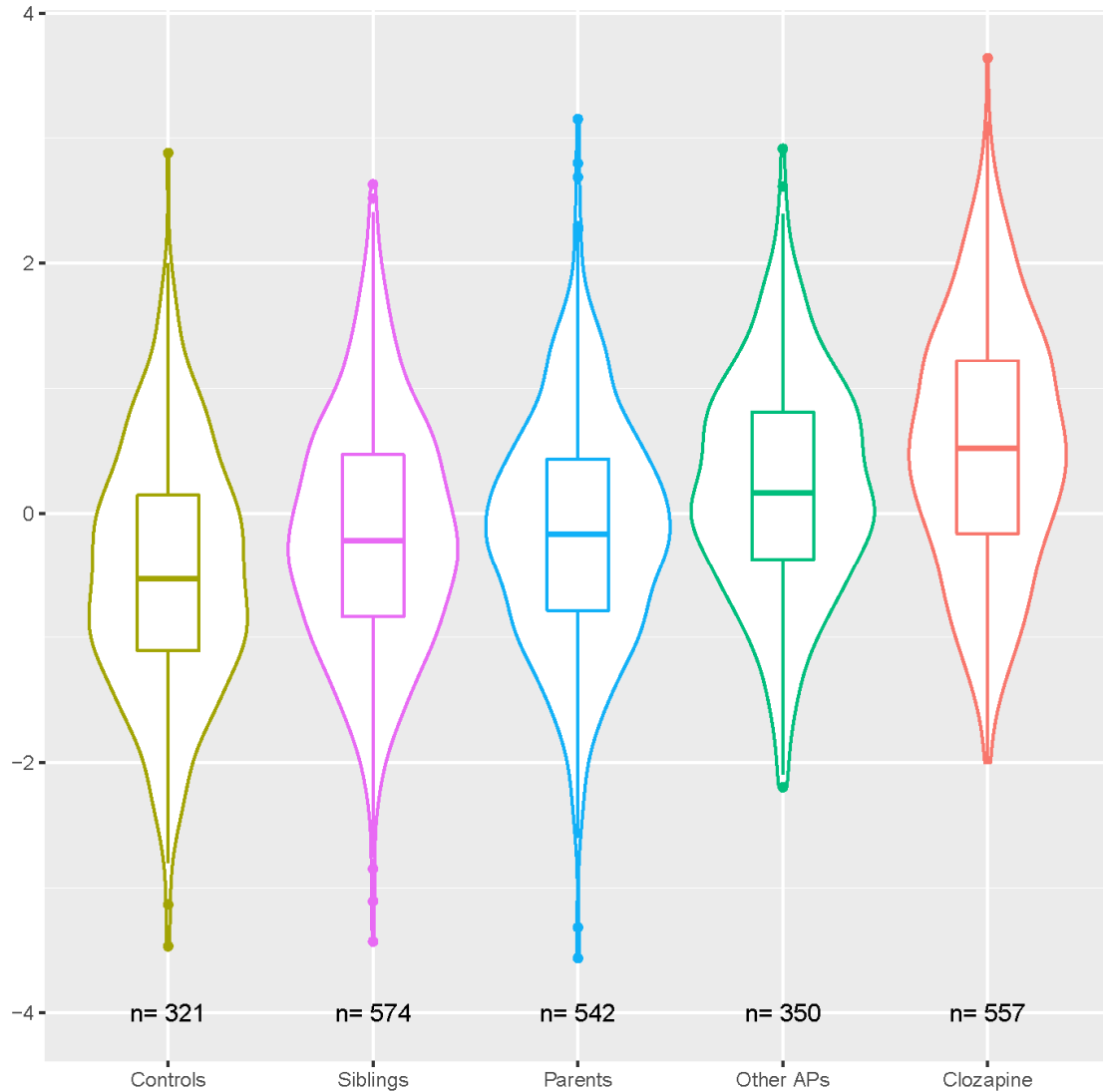
Other APs = Individuals with SSD using other antipsychotic medications.

eFigure 4. Odds ratio by adjusted (residualized) PRS-cs-auto risk score profile.

A. Odds ratio of individuals with SSD on other AP relative to unrelated healthy controls. B. Odds ratio of clozapine users relative to unrelated healthy controls. C. Odds ratio of clozapine use relative to other antipsychotics.

A.

B.

C.
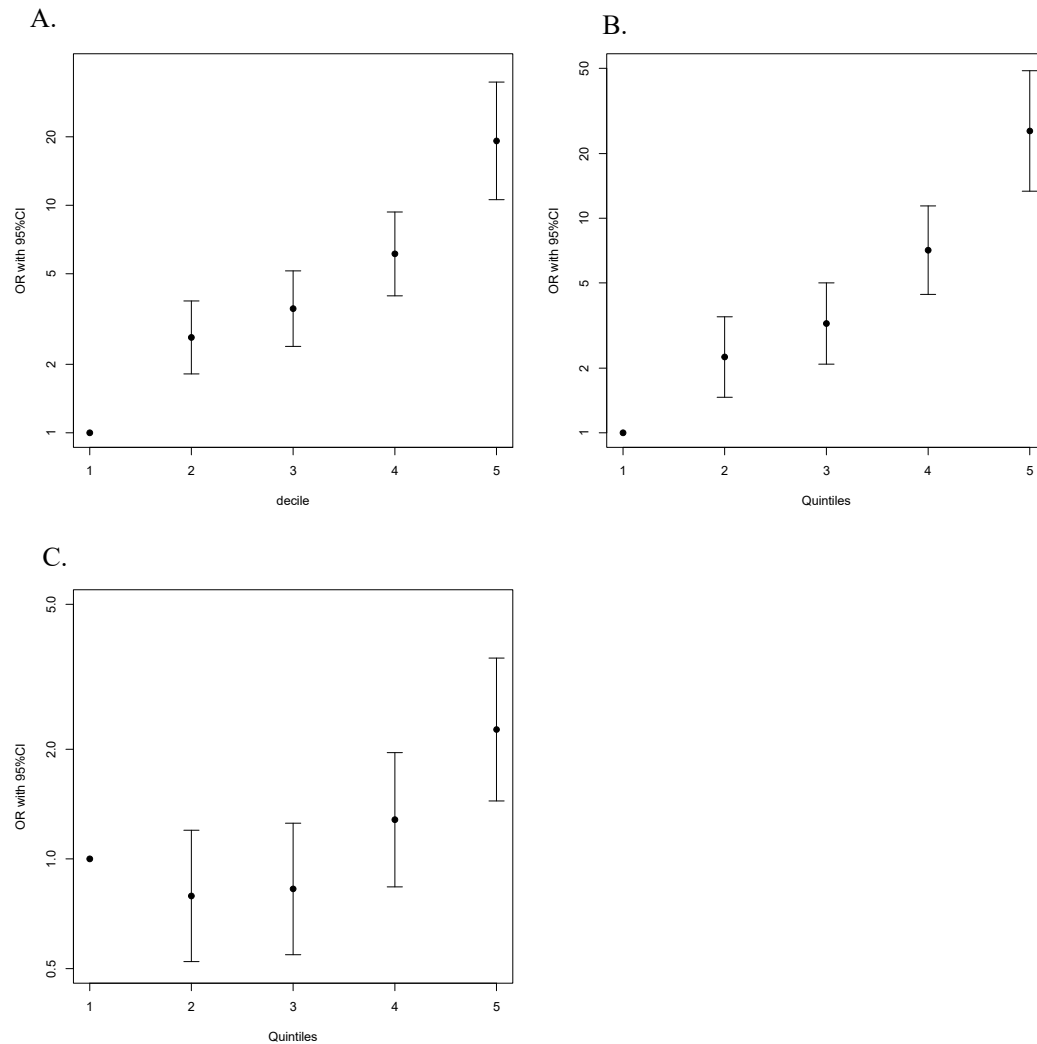
Odds ratio (OR) for schizophrenia by risk score profile (PRS-cs-auto Residual). The PRS were converted to quintile (1 = lowest, 5 = highest PRS), and 4 dummy variables were created to contrast deciles 2-5 to quintile 1 as the reference. Odds ratios and 95% confidence intervals (bars) were estimated using logistic regression. The odds ratios increased with greater number of schizophrenia risk alleles in each group, with the maximum reached for the fourth or fifth quintile in the comparisons of other AP users to unrelated healthy controls: OR= 19.18 [95% CI 10.58-34.78]; of clozapine users to unrelated healthy controls: OR= 25.51 [95% CI 13.35-48.69]; and of clozapine users to users of other antipsychotics: OR= 2.26 [95%CI 1.44-3.56].

eFigure 5. Odds ratio by PRS-ice risk score profile.

A. Odds ratio of other AP users relative to unrelated healthy controls. B. Odds ratio of clozapine users relative to unrelated healthy controls. C. Odds ratio of clozapine use relative to other antipsychotics.

A.

B.

C.
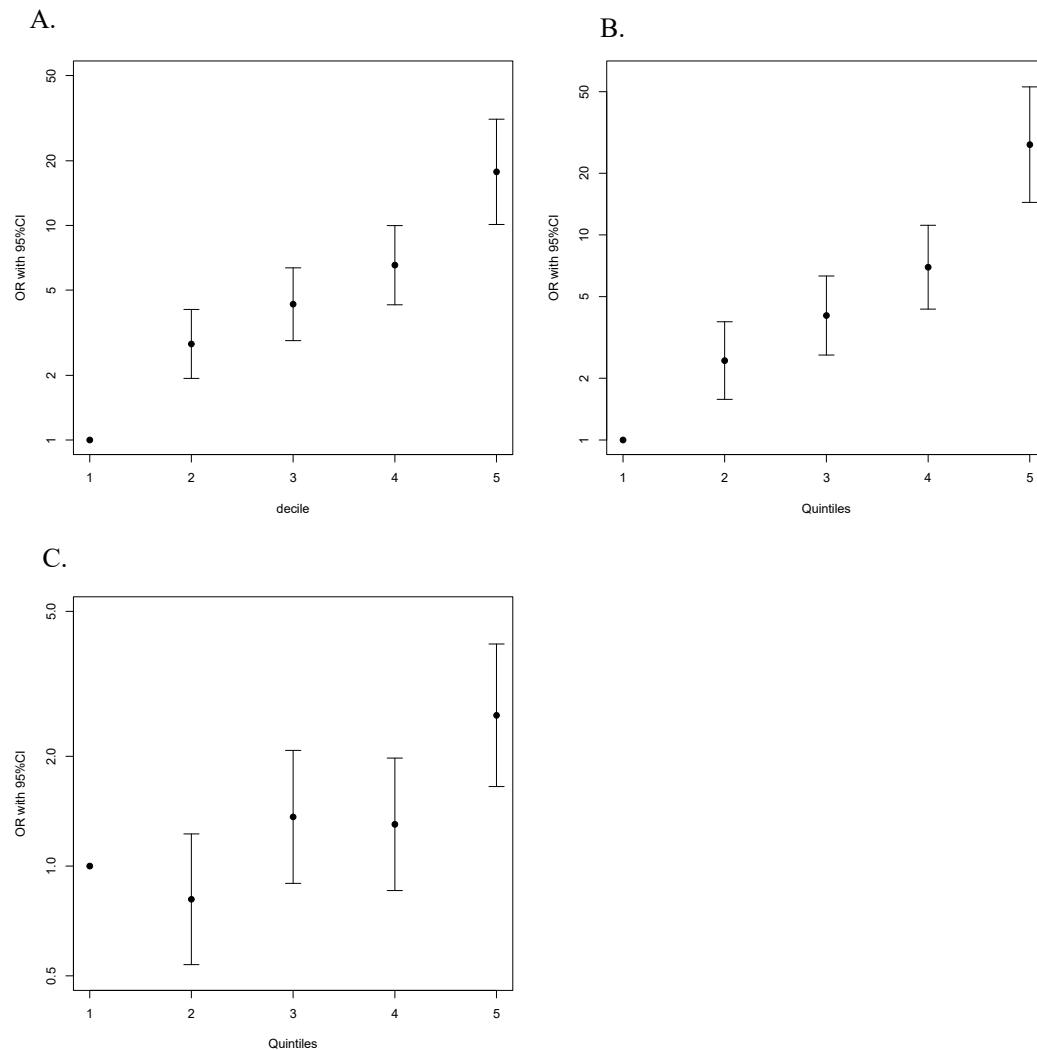
Odds ratio (OR) for schizophrenia by risk score profile (PRS-ice). The PRS were converted to quintile (1 = lowest, 5 = highest PRS), and 4 dummy variables were created to contrast deciles 2-5 to quintile 1 as the reference. Odds ratios and 95% confidence intervals (bars) were estimated using logistic regression. The odds ratios increased with greater number of schizophrenia risk alleles in each group, with the maximum reached for the fifth quintile in the comparisons of other AP users to unrelated healthy controls: OR= 17.77 [95% CI 10.09-31.29]; of clozapine users to unrelated healthy controls: OR= 27.58 [95% CI 14.42-52.76]; and of clozapine users to other AP users: OR= 2.59 [95%CI 1.65-4.06].