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Genomic stratification of clozapine prescription patterns using schizophrenia polygenic scores

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Short title: Schizophrenia polygenic risk scores and clozapine dosing
ABSTRACT

BACKGROUND: Treatment-resistant schizophrenia (TRS) affects ~30% of individuals with the disorder. Clozapine is the medication of choice in TRS but optimizing administration and dose titration are complex. The identification of factors influencing clozapine prescription and response, including genetics, is of interest in a precision psychiatry framework.

METHODS: We used linear regression models accounting for demographic, pharmacological, and clinical covariates to determine whether a polygenic risk score (PRS) for schizophrenia is associated with the highest dose recorded during clozapine treatment. Analyses were performed across two independent multi-ancestry samples of individuals from a UK patient monitoring system, CLOZUK2 (n=3133) and CLOZUK3 (n=909); and a European sample from a Norwegian therapeutic drug monitoring service (n=417). In a secondary analysis merging both UK cohorts, logistic regression models were used to estimate the relationship between schizophrenia PRS and clozapine doses classified as low, standard, or high.

RESULTS: After controlling for relevant covariates, schizophrenia PRS was correlated with the highest clozapine dose on record for each individual across all samples: CLOZUK2 (β=12.22, S.E.=3.78, P=0.001), CLOZUK3 (β=12.73, S.E.=5.99, P=0.034) and the Norwegian cohort (β=46.45, S.E.=18.83, P=0.014). In a secondary analysis, the schizophrenia PRS was associated with taking clozapine doses greater than 600 mg/day (OR=1.279, P=0.006).

CONCLUSIONS: Schizophrenia PRS is associated with the highest clozapine dose prescribed to an individual in records from three independent samples, suggesting that the genetic liability to schizophrenia might index factors associated with therapeutic decisions in TRS cohorts.
INTRODUCTION

Approximately one-third of individuals with schizophrenia experience symptoms that do not meaningfully improve after two courses of standard antipsychotics, a presentation often called treatment-resistant schizophrenia (TRS) (1). Clozapine is the evidence-based treatment of choice for TRS, though it also has the potential to cause a range of adverse drug reactions (ADRs). These require careful clinical consideration and are major contributors to treatment discontinuation (3), contributing to the fact that most eligible patients are not offered clozapine as a treatment option (4). Moreover, it is estimated that only about 50% of those treated respond to clozapine (5), and few objective predictors of therapeutic response or adverse effects have been identified to date (6).

Individual differences in response to psychopharmacology are known to be influenced by genetic and environmental factors (7,8). Pharmacogenomics research aims to identify genetic variants that contribute to this variability and is one of the most promising pillars of precision medicine strategies (9). To date, while most known pharmacogenomic variants are associated with ADME processes (absorption, distribution, metabolism, and excretion) influencing drug exposure, markers associated with disease and disorder risk can also be assessed to investigate treatment outcomes (10). In this sense, composite metrics of genetic risk such as polygenic risk scores (PRS), have become widely used in medical genomics research and are also seen as potential predictive markers which could eventually be introduced into patient care (11,12). As an example, hundreds of schizophrenia susceptibility loci have been identified by large-scale genome-wide association studies (GWAS), pointing to neurobiological pathways and mechanisms likely to be disrupted in the disorder (13). Several of these could feasibly play a role in antipsychotic treatment response, such as the dopaminergic signaling pathways indexed by DRD2 (14). Thus, investigating the association between genetic liability to the disorder and response to antipsychotics might be fruitful, with a hypothesis being that a heavier genetic burden could be associated with poorer treatment response.
A key challenge for clinicians is determining the optimal dose of clozapine for a given individual, which requires weighing up the relative likelihoods of therapeutic response versus ADRs. Clinical caution to avoid ADRs, which can be debilitating even if mild, might lead to individuals spending weeks or months on a given dose without apparent benefits before they are escalated to a higher one (15). Additionally, meta-analytic evidence points to the need of taking drug metabolism into account in clinical practice (16). In this sense, therapeutic drug monitoring (TDM) schemes, when available, can facilitate fine-tuning clozapine concentrations (or “levels”) for optimal response, but are particularly suited for the identification of poor or rapid metabolizers (17), a subset of the general population that does not fully account for the rate of clozapine non-responders (18). For these reasons, investigating clinical and demographic characteristics, including genetics, that underlie clozapine prescriptions in real-world settings can help us better understand the clinical decision-making processes behind clozapine dose escalation and provides a pathway towards the inference of predictive factors for treatment outcomes.

The present study analyzes genetic and clozapine pharmacokinetic data in three retrospective cohorts: two from the CLOZUK project in the UK, one of the largest DNA sample collections worldwide of individuals with TRS (19); and another from the therapeutic drug monitoring (TDM) service from Diakonhjemmet Hospital in Oslo (20). The aim is to assess whether the schizophrenia PRS is correlated with the clozapine doses prescribed to those with TRS. We hypothesized that, if associated, schizophrenia PRS could indicate which patients would require higher doses of clozapine, and this information could be a proxy phenotype or indicator for poorer treatment response in the absence of ADRs. Given the underuse of clozapine and the complexities of its clinical management due to dose-dependent and idiosyncratic ADRs, inferring the potential relevance of genomic information in this setting could be informative for the development of future stratification and drug dosing algorithms. Additionally, novel observations supporting that the schizophrenia genetic liability might also index therapeutic decisions and outcomes would be of great interest for precision psychiatry research.
MATERIAL AND METHODS

Samples

The CLOZUK cohort is comprised of individuals taking clozapine in the UK whose DNA samples were collected anonymously. For the present research, we accessed data from a subset of individuals termed CLOZUK2, which were linked to repeated assessments of clozapine pharmacokinetics. Additional descriptions of this cohort, genotyping procedures, and sample/data collection have been previously reported (19,22). A total of 3,439 unrelated individuals over the age of 18 years were available from CLOZUK2 with genotypic data, and more than 12,000 pharmacokinetic assays. This sample was curated to remove individuals taking clozapine for less than 18 weeks to ensure steady-state levels of clozapine in plasma had been reached, and to exclude individuals undergoing the initial titration process (15,23). In contrast to previous studies which have focused on European participants to minimize population stratification, we did not filter our data based on self-reported or genetically-inferred ancestry. Our final curated dataset included a total of 3,133 individuals from CLOZUK2. A summary of demographic and clinical characteristics is given in Supplementary Table 1.

New to this study, we also report another wave of CLOZUK data (CLOZUK3), with more than 900 individuals and 5,000 pharmacokinetic assays. Its collection follows the procedure detailed earlier for CLOZUK2 (19), including the curation protocol for clozapine levels data (22). For our analyses of CLOZUK3, we did not exclude individuals with a clozapine treatment shorter than 18 weeks, as treatment start date information was not available. Nevertheless, to increase compatibility with the curation procedures of CLOZUK2 and reduce the likelihood of analyzing individuals going through clozapine initiation/titration, we removed those in which the highest clozapine dose was less than 100 mg/day. Our final CLOZUK3 dataset included genetic and pharmacokinetic data for 909 individuals (Supplementary Table 1).
Finally, we accessed data from a Norwegian cohort from the TDM database at the Center for Psychopharmacology, Diakonhjemmet Hospital Oslo, with 417 individuals linked to 7963 clozapine pharmacokinetic assays. This cohort included only Norwegian citizens of European ancestry and is fully described elsewhere (20). Phenotype data was extracted from TDM requisition forms filled out by clinicians, including information not explicitly available in CLOZUK, such as smoking habits and co-medication profiles. From this information, we ensured that no Norwegian TDM samples showing concurrent use of clozapine with interacting drugs (e.g., fluvoxamine, a potent inhibitor of clozapine metabolism, or the potent enzyme inducers phenobarbital, phenytoin and carbamazepine) were included in these analyses.

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines (UK National Research Ethics Service approval ref. 10/WSE02/15, following UK Human Tissue Act and Norwegian Regional Committee for Medical and Health Research Ethics approval ref. 2014/1185).

**Study Design**

For the primary analyses, we focused on the highest clozapine daily dose for each of the individuals included in our cohorts. As sample collections, data curation, and genotyping procedures were carried out at different points in time for each dataset, we performed the analysis separately in CLOZUK2, CLOZUK3 and the Norwegian TDM cohort (Figure 1).

In secondary analyses, we merged the two CLOZUK cohorts due to their larger sample size and compatible phenotypic data, and then stratified these individuals by their highest daily clozapine dose into three categories: (1) those taking a low dose (<300 mg/day), (2) those taking standard maintenance doses (300-600 mg/day), and (3) those individuals taking a higher dose than the usual maintenance dose (>600 mg/day)(24). For these analyses, we also included extra curation procedures (Figure 1): First, we
selected only those individuals with at least three assays in the clozapine monitoring system, spanning a period of 6 months or more. This step aimed for the clozapine dose we assessed to more accurately reflect the real highest dose a participant was likely to have taken throughout their treatment. Second, we removed individuals likely not taking their medication (non-adherence) and/or presenting an atypical (rapid/poor) clozapine metabolism, as prescription patterns in these individuals would not likely follow the linear trends of the general population. This last procedure was done by excluding all assays in which the observed clozapine plasma concentrations did not match those expected for the recorded clozapine daily dose, as reflected in Table 5 of Couchman et al., 2010 (25).

Genetics

The genotyping of CLOZUK2 was conducted using Illumina® HumanOmniExpress (Illumina Inc., San Diego, CA, USA) arrays. A detailed description of genotyping, quality control, and imputation procedures for genomic data can be found elsewhere (19). The CLOZUK3 cohort was genotyped using the Illumina® Infinium Global Screening Array-24 and curated using the DRAGON-Data pipeline (26). For PRS analyses, imputed CLOZUK2 and CLOZUK3 dosages were converted to best-guess genotype calls (Genotype probability >90%; INFO >0.9, minor allele frequency [MAF] >10%, HWE mid p-value >10^-4). The genotyping and imputation of the Norwegian cohort are also described in detail elsewhere (20).

For deriving the main predictor of interest, we computed genome-wide PRS profiles from the latest schizophrenia multi-ancestry meta-analysis from the PGC (13). Given the CLOZUK2 and Norwegian cohorts were included in this publication, to avoid sample overlap between training and testing sets, we derived deduplicated schizophrenia summary statistics before calculating the PRS in each sample. We only used summary statistics from the full PGC GWAS as training set to derive PRS in CLOZUK3, as that sample was not included in the PGC meta-analysis. As data within the CLOZUK cohorts does not include known predictors of demographic and lifestyle factors associated with drug metabolism (27), we also computed
proxy PRS for coffee intake, body mass index (BMI), and smoking behavior, using summary statistics from the GIANT consortium (28) and the GeneATLAS UK Biobank GWAS resource (29). PRS were computed using the PRScs method (30), adjusted for LD-structure with default options and a shrinkage parameter of phi=1 for schizophrenia (21) and phi=auto otherwise. Before statistical analysis, PRS were standardized within each sample (mean = 0, SD = 1) to facilitate the results’ interpretability.

STATISTICS

Primary Analyses

To analyze the association between the schizophrenia PRS and the highest daily dose of clozapine, we used linear regression models accounting for relevant demographic, pharmacological, and treatment covariates. In our main analysis, these included sex, age and age², all present in the CLOZUK and Norwegian records, and PRS metrics as proxies of BMI, coffee intake and smoking habits. Since the Norwegian cohort included explicit information on smoking habits, analyses of this cohort also explored the effects of including this data in the regression model, independently and in conjunction with the smoking behavior PRS. All regression models were built in the statistical software R v4.1.0. The change in R² due to the inclusion of each covariate (also known as semi-partial R² or ∆R²) was estimated as an index of the proportion of variance explained by any individual factor in our model using the “rockchalk” package (31).

In further analyses, we also expanded our models by including other predictors which might affect the highest dose outcome, and which could potentially act as mediators of our observed effects. The clozapine plasma concentrations and the clozapine/norclozapine metabolic ratio observed at the point of highest dose were evaluated, as well as the frequency of monitoring assessments (Supplementary Note).

To account for potential confounding from population stratification, we included the probabilities
of pertaining to four of our possible five biogeographical groups in all CLOZUK regression models (Supplementary Note). Additionally, the first ten principal components (PCs) were also used as regression model covariates, both in CLOZUK and in the Norwegian TDM cohort.

Secondary Analyses

We also undertook a series of analyses in the CLOZUK cohorts focusing on a broad but clinically relevant categorization of clozapine dose. We used multinomial and binary logistic regression models to estimate the effects of the schizophrenia PRS in the probability of taking the highest clozapine dose within three different dose groups: low (<300 mg/day), standard (300-600 mg/day) and high (>600 mg/day) (24). We fitted three separate pairwise regression models to assess differences between groups, using the same covariates in these models as in the primary analyses. Also, to ensure compatibility between the CLOZUK2 and CLOZUK3 PRS and PCA variables, we used the deduplicated PGC summary statistics as the PRS training set in this secondary analysis and generated the scores and principal components on strictly overlapping markers passing all quality-control filters in the merged sample. As a sensitivity analysis, we also collapsed individuals taking doses in the low and standard range into one category and compared them with those taking high doses (>600 mg/day), as prescribing a high clozapine daily dose generally requires more complex clinical considerations given the likelihood of ADRs than switches within lower thresholds. In this model, we calculated the area under the curve (AUC) from receiver operating characteristic (ROC) curves using the pROC package (32) in R. This is as a rough estimate of the added utility of our genetic predictor when combined with standard demographic variables used in clinical prediction modelling (33,34).

RESULTS

Primary Analyses: Association of the schizophrenia PRS and the highest clozapine dose
We observed a positive correlation between the schizophrenia PRS and highest clozapine dose in our largest sample, CLOZUK2 (β = 12.217, 95% CI [4.816–19.618], P = 0.001), where the variance explained by the schizophrenia PRS was ΔR² ~ 0.32%. Effect sizes expressed as the change in clozapine dose (mg/day) for one unit increase of the main predictors, accounting for other model covariates, can be seen in Figure 2. These results were essentially unchanged when accounting for possible mediators such as clozapine plasma concentrations, clozapine/norclozapine ratio, the frequency of clozapine monitoring in our dataset, and genetic variants known to affect CYP1A2 metabolism (Supplementary Tables 2-6). Additionally, we explored if the schizophrenia PRS correlated with other features of clozapine metabolism, but no significant associations were found between the PRS and clozapine plasma concentrations or clozapine/norclozapine ratio (Supplementary Table 6).

Exploring our results further via sensitivity analyses, we saw little change in our CLOZUK2 schizophrenia PRS association by restricting the sample to only individuals of European genetic ancestry (n=2577; β = 11.46, 95% CI [3.169-19.75], P = 0.007), and established that this result is specific to schizophrenia genetic liability by assessing a wider range of psychiatric, cognitive and personality PRS, none of which were significantly associated with clozapine doses (Supplementary Figure 2).

To validate our findings, we replicated this analysis in two independent datasets. In CLOZUK3 we found results of similar magnitude and sign (β = 12.730, 95% CI [0.996-24.464], P = 0.033, ΔR² ~ 0.48%; Figure 2B), even after controlling for possible mediators (Supplementary Table 2). In the Norwegian cohort the results showed the same direction of effect with a larger magnitude and confidence interval (β = 46.451, 95% CI [9.424-83.477], P= 0.014, ΔR² ~ 1.33%; Figure 2), consistent with the smaller size of this dataset. In any case, all Norwegian effect sizes were still within the confidence interval range observed in the CLOZUK2 discovery analyses, even when controlling for possible mediators (Supplementary Table 4). Moreover, these results were consistent when replacing the smoking behavior PRS with directly assessed smoking habits (β = 47.759, 95% CI [10.817-84.700], P = 0.011, ΔR² ~ 1.41%; Supplementary Table 5).
Secondary analyses: Genetics-informed classification model of clozapine doses

We next explored to what extent the schizophrenia PRS could reflect broad clozapine prescription patterns in the complete CLOZUK cohort by using a multinomial regression model (Figure 3). For this, in stratified analyses by clozapine dose categories, we observed that the schizophrenia PRS was associated with the probability of taking high doses when compared to those taking either standard doses (OR = 1.277, 95% CI [1.066-1.530], P = 0.008) or low doses (OR = 1.280, 95% CI [1.029-1.593], P = 0.027).

A second stratified analysis specifically examined differences in those taking clozapine doses over 600 mg/day against those below this threshold. In this analysis, we observed an association between the schizophrenia PRS and the probability of taking high doses (OR = 1.279, 95% CI [1.076-1.522], P = 0.005). These results are shown in Table 1 and as a logit probability curve in Figure 4. As an illustration of the detected effects, while the overall prevalence of individuals taking a high dose of clozapine was 15% in the entire CLOZUK sample, it surpassed 20% on those above 2 standard deviations of the schizophrenia PRS, reaching 30% at the upper end of the PRS distribution.

Finally, we assessed the sensitivity and specificity of our prediction models for high clozapine doses by calculating the AUC from ROC statistics, presented in Supplementary Figure 3. AUC from the model including all covariates in the previous analysis (Figure 4, Table 1) was 0.64, while the demographics-only model (not including any genetically derived covariate) was 0.58. We also show that even when accounting for clozapine plasma concentrations, a known target of dose optimization for clozapine and a strong correlate of actual doses, the inclusion of genetic information marginally improves prediction accuracy.

DISCUSSION
This study examines whether the polygenic risk for schizophrenia is associated with the daily dose of clozapine in three independent TRS cohorts, two including individuals from multiple ancestries. Our main result demonstrates an association between genetic liability to schizophrenia, indexed by PRS, and the highest dose of clozapine available in treatment records. Furthermore, this effect is independent of known genetic factors associated to clozapine metabolism (Supplementary Table 6). In the secondary analysis, individuals with high genetic risk of the disorder had a two-fold increased probability of taking high doses (>600 mg/day) compared to those on the lower end of the schizophrenia PRS spectrum (Figure 3). To our knowledge, this is the first study to report these associations. A recent investigation assessed the relationship between schizophrenia PRS and clozapine doses, not finding any significant linear effects, though the sample size (n=44) was very limited compared to ours (23).

Identifying individuals who are more or less likely to respond to different pharmacological treatments has long been one of the hoped-for applications of PRS in precision medicine (11,34). In this study, we leveraged the longitudinal aspect of clozapine monitoring and TDM and examined the highest clozapine daily dose recorded for each individual in these systems. We show that individuals in the high end of the schizophrenia PRS spectrum are more likely to be prescribed higher clozapine doses than the usual maintenance thresholds (300-600 mg/day). Taking this observation at face value implies that these individuals might have needed such high doses to obtain a therapeutic response from the outset of treatment, implying that genetic information could be used to personalize and plan clozapine prescriptions. However, the data available in our samples do not allow us to define the exact role or weight that genetic predictors should have for this potential application, as it cannot be used to formally test the putative causal link between high clozapine doses and response to treatment. It is also uncertain whether individuals requiring high doses of clozapine reflect poorer responders (at low/standard doses) or those who might never respond to the drug, though a combination of both possibilities is likely (16). Indeed, Frank et al. (2015) reported that individuals who were non-responders to clozapine had the highest
schizophrenia PRSs in a TRS cohort. This result would also be consistent with our findings and raises the question as to the utility of clozapine for at least a subset of the individuals at the upper end of the schizophrenia PRS spectrum. Nevertheless, if more consistent and detailed evidence accumulates on the interplay between clozapine prescriptions, genetics and treatment response, interventions might be devised to leverage this information with the goal of improving the overall tolerability and safety of the drug. This might also help address and prevent clozapine resistance, a severe and currently unpredictable outcome with no evidence-based treatment options (35).

Our study findings suggest that although we observe statistically significant associations, the variance explained by the schizophrenia PRS is small, and other genomic and non-genomic factors must contribute to a larger extent to the final phenotype. Indeed, we used several types of genetic predictors in our models (e.g., PCs, genetic ancestry, and PRS for more than one trait), which combined help explain a non-trivial amount of variance in the highest clozapine dose. This is in line with the notion that PRS alone will likely have a relatively small impact in driving clinical practice even once its practical implementation becomes feasible (11). Knowing that a very complex network of factors impacts antipsychotic response, we recommend caution in the interpretation of our findings’ potential clinical relevance, which needs to be further evaluated. Nevertheless, other areas such as cardiovascular disease have shown that combining genetic information with non-genetic predictors and risk factors could be clinically meaningful and may help guide treatment choices (36). Once larger datasets become available, it would be beneficial to evaluate the use of PRS as a predictor for potentially stratified medicine approaches in a clinical trial. This could provide an opportunity to address if individuals that carry a high schizophrenia PRS, and adhere to clozapine therapy in the absence of adverse-side effects, should be offered alternative clozapine prescribing protocols when their response is suboptimal.

Strengths and limitations
The strengths of our present study include its large sample size, as well as taking advantage of some of the largest TRS cohorts in the world with genetic and longitudinal pharmacokinetic information. Additionally, all the individuals with available data were used in our analyses, regardless of ancestry, thus reflecting non-European populations traditionally underrepresented in genomics research. Another distinctive feature is the consistency and replication of the main finding across three different datasets. This included a Norwegian TDM cohort with reliable smoking data, which is a major pharmacokinetic determinant of clozapine and a potential confounder of no apparent relevance for the detected effects.

However, several limitations of the current study need to be considered, and the results should be interpreted in light of those. First, our largest samples (CLOZUK2 and CLOZUK3) are based on electronic health records collected during mandatory clozapine monitoring, which do not include contextual information on clinical management, treatment response, or lifestyle. This impacted our ability to determine factors known to influence clozapine metabolism in our assessed individuals, including smoking status, weight, regular caffeine use, or the use of other medications. However, we attempted to mitigate these issues by using PRS to derive genetically informed proxies of these as in a previous study (22), and these indeed contributed to explaining part of the variance in our dataset and the independent Norwegian TDM cohort (Supplementary Tables 2-5). Second, as in all retrospective analyses, unmeasured confounders might have had an influence on the effects detected, although all models were adjusted for known potential confounders in primary and sensitivity analyses. Third, we acknowledge that even though we present evidence for an association of schizophrenia PRS with clozapine dose in three independent samples, further research will require additional data on treatment response to evaluate mechanisms linking our observations to real-world prescribing practices.

As a final consideration, our main predictor is a schizophrenia PRS built from a mostly cross-sectional case-control analysis, which is not necessarily representative of the diversity of individuals and
symptom profiles encompassed by real-world samples of those with schizophrenia or TRS. Also, although two of our three cohorts are multi-ancestry by design and ascertained through a population-level clozapine monitoring system, they are all primarily composed of European individuals and mainly European GWAS have been used in generating its PRS. For these reasons, it is difficult to evaluate whether potential downstream applications of our research would be translatable or broadly applicable to individuals from worldwide ethnic and genetic backgrounds.

In conclusion, we report that the schizophrenia PRS is associated with the highest clozapine dose on record in patients with TRS in three independent multi-ancestry cohorts, suggesting that genetic susceptibility to schizophrenia is associated with treatment choices in these samples. In the ongoing debate over the clinical utility of PRSs in precision psychiatry, our study adds to the growing body of evidence showing that genomic information can lead to novel answers to topics of interest for clinical care (11,37). More studies are needed to confirm our findings and to benchmark to which extent this or similar data could lead to future improvements in therapeutic decision-making and in the overall clinical management of TRS.

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Disclosures

MH and JJ are full-time employees of Leyden Delta B.V. AK is a full-time employee of Magna Laboratories Ltd. MJO, MCOD and JTRW are supported by a collaborative research grant from Takeda Pharmaceuticals Ltd. for a project unrelated to the work presented here. OAA is a consultant to HealthLytix and has received speaker’s honorarium from Lundbeck and Sunovion. All other authors report no biomedical financial interests or potential conflicts of interests.
References


### Tables

**Table 1:** Effect sizes of each predictor included in the model in relation to probability of taking a high clozapine dose

<table>
<thead>
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<th>Predictor</th>
<th>OR</th>
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<th>97.5% CI</th>
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Figure Legends

**Figure 1.** Sample inclusion flowchart. Curation procedures relevant to each analyses step for CLOZUK2, CLOZUK3 and the Norwegian samples are represented. [CLZ] = clozapine plasma levels * dose-adjusted expected levels extracted from Couchman et al. 2010.

**Figure 2.** Effect size estimates for the main predictors of highest clozapine daily dose. Effects are represented as mean coefficient estimates (±95% confidence intervals) for CLOZUK2 (blue), CLOZUK3 (yellow) and the Norwegian TDM sample (red).

**Figure 3.** Probability estimates for each of highest clozapine dose categories according to schizophrenia PRS. Y-axis represents the probability of belonging to each of the 3 doses groups for individuals along the PRS spectrum.

**Figure 4.** Probability of taking a high clozapine daily dose at different levels of schizophrenia PRS, represented using a logit function (banded area shows 95% confidence interval).
## KEY RESOURCES TABLE

<table>
<thead>
<tr>
<th>Resource Type</th>
<th>Specific Reagent or Resource</th>
<th>Source or Reference</th>
<th>Identifiers</th>
<th>Additional Information</th>
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<tbody>
<tr>
<td>Biological Sample</td>
<td>Cohort of individuals with treatment-resistant schizophrenia</td>
<td><a href="https://doi.org/10.1038/s41588-018-0059-2">https://doi.org/10.1038/s41588-018-0059-2</a></td>
<td>CLOZUK2</td>
<td>12276 individuals; 12267 clozapine assays.</td>
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<td>CLOZUK3</td>
<td>8771 individuals; 8018 clozapine assays.</td>
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<td>Norwegian cohort, Oslo University Hospital</td>
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<td><a href="https://doi.org/10.1038/s41586-022-04434-5">https://doi.org/10.1038/s41586-022-04434-5</a></td>
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<td>417 individuals; 7963 clozapine assays.</td>
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<td><a href="https://doi.org/10.1038/s41398-020-00888-1">https://doi.org/10.1038/s41398-020-00888-1</a></td>
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<td>917 individuals; 5018 clozapine assays.</td>
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<td><a href="https://doi.org/10.1093/hmg/ddy271">https://doi.org/10.1093/hmg/ddy271</a></td>
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### Software; Algorithm

- **PLINK**
  - [https://doi.org/10.1186/s13742-015-0047-8](https://doi.org/10.1186/s13742-015-0047-8)
  - [https://www.cog-genomics.org/plink/2.0/]

- **DRAGON-Data QC pipeline**
  - [https://doi.org/10.1101/2022.01.18.22269463](https://doi.org/10.1101/2022.01.18.22269463)
  - [https://github.com/CardiffMRCPathfinder/GenotypeQCtoHRC]

- **PRScs**
  - [https://doi.org/10.1038/s41467-019-09718-5](https://doi.org/10.1038/s41467-019-09718-5)
  - [https://github.com/getian107/PRScs]

- **Rockchalk R-package**
  - [https://pj.freefaculty.org/R/rockchalk.pdf](https://pj.freefaculty.org/R/rockchalk.pdf)
  - [https://cran.r-project.org/web/packages/rockchalk/index.html]

- **Nnet R-package (multinomial regression module)**
  - [https://www.stats.ox.ac.uk/pub/MASS4/](https://www.stats.ox.ac.uk/pub/MASS4/)
  - [https://cran.r-project.org/web/packages/nnet/index.html]
### Key Resource Table