Polygenic Liability for Antipsychotic Dosage and Polypharmacy - A Real-World Registry and Biobank Study

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Article

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Abstract

Genomic prediction of antipsychotic dose and polypharmacy has been difficult, mainly due to limited access to large cohorts with genetic and drug prescription data. In this proof of principle study, we investigated if genetic liability for schizophrenia is associated with high dose requirements of antipsychotics and antipsychotic polypharmacy, using real-world registry and biobank data from five independent Nordic cohorts of a total of N = 20,805 individuals with psychotic disorders (schizophrenia, bipolar disorder, and other psychosis). Within linear regression models, a polygenic risk score (PRS) for schizophrenia was studied in relation to standardized antipsychotic dose as well as antipsychotic polypharmacy, defined based on longitudinal prescription registry data as well as health records and self-reported data. Meta-analyses across the five cohorts showed that PRS for schizophrenia was significantly positively associated with prescribed (standardized) antipsychotic dose (OR = 1.05, CI = 1.03–1.09, p = 0.0008) and antipsychotic polypharmacy defined as taking ≥ 3 antipsychotics (OR = 1.30, CI = 1.00-1.74, p = 0.048). The direction of effect was similar in all five independent cohorts. These findings indicate that genotypes may aid clinically relevant decisions on individual patients´ antipsychotic treatment. Further, the findings illustrate how real-world data have the potential to generate results needed for future precision medicine approaches in psychiatry.

Introduction

In mental disorders, psychopharmacological treatment often involves a trial-and-error approach, balancing between treatment effects and adverse effects[1]. Precision psychiatry aims to predict clinical outcomes and treatment effects, to improve psychological treatments[2]. Access to large cohorts with longitudinal treatment data that are representative of real-world clinical practice is essential for the development of stratification and prediction algorithms, but such data are difficult to obtain homogeneously at a large scale, which makes it difficult to investigate predictors of psychopharmacological treatment outcomes in psychiatry[2, 3]. Recent initiatives have started to utilize large-scale data obtained from real-world health care settings[4], facilitated by electronic health records and hospital biobanks. In the Nordic countries, nationwide medical registries with health and prescription information together with genotypes from biobanks, dramatically increase the sample size and form the basis for developing precision medicine approaches[3]. Although there are clear limitations to phenotype quality, registry data can provide valuable information about drug use patterns and treatment outcomes. This can be deduced from e.g., the duration and changes in the type and dosage of medication[5]. Combining real-world data from biobanks, hospital records, registries, and questionnaires could entail the potential to develop precision psychiatry approaches, and advance the clinical management and pharmacological treatment of mental disorders[3].

Antipsychotics, the most common medications used to treat psychotic disorders, can have serious adverse effects[6–9] often resulting in comorbidities as well as treatment discontinuation leading to relapse and increased risk for suicide[10, 11]. Moreover, currently available antipsychotics are not effective in all patients even with good compliance and acceptable side effects[12]. Individuals who

experience symptoms that do not meaningfully improve after ≥ 2 trials of antipsychotics are defined as being treatment resistant, which occurs in over 30% of patients with psychosis[13]. These individuals are often treated with Clozapine, which has superior efficacy, but also more severe side effects compared to most other antipsychotics[14]. Other strategies to overcome antipsychotic treatment resistance include antipsychotic polypharmacy (concurrent use of several antipsychotic medications) and/or to increase the antipsychotic dosage[15, 16]. It remains a key challenge to choose the optimal antipsychotic drug regime[1, 16]. While clinical caution is required to avoid adverse drug reactions[1, 16], individuals may spend too long time on a given dose without sufficient effect before they are prescribed a higher dose[1] or addition of another antipsychotic drug[16]. Considering this trial-and-error approach, there is a need to identify patients who are likely to not respond adequately to antipsychotics or who are more likely to develop antipsychotic treatment resistance. However, a major challenge in the identification of useful predictors of antipsychotic treatment response is the clinical heterogeneity among treatment resistant individuals[17].

Recent evidence suggests that treatment response to antipsychotic drugs may be heritable[18, 19], and disease genetics have been utilized to investigate treatment outcomes[20, 21]. Polygenic risk scores (PRS) represent the cumulative effect of susceptibility to a disorder, and can be used to study the association with treatment-related outcomes[21–23]. We have recently shown that schizophrenia PRS is associated with high Clozapine dose requirements in three cohorts of treatment resistant schizophrenia[21]. In this proof of principle study, we investigated if real-world registry and biobank data can be used to assess treatment trajectories that can be used to address clinically useful research questions on treatment outcomes. We analyzed schizophrenia PRS in relation to antipsychotic dosage as well as antipsychotic polypharmacy in five independent Nordic cohorts of a total of N = 20,805 individuals with psychosis. Investigating genetic factors that are associated with antipsychotic prescription patterns can help to predict dose requirements, antipsychotic polypharmacy, and treatment resistance. These predictions are of great interest for precision psychiatry, but large-scale data is needed to train the PRS to obtain the necessary accuracy. If successful, such clinically relevant predictions can lead to precision medicine opportunities and aid in drug prescription.

Methods

Samples

Five independent cohorts with a total of 20,805 individuals were included in the present study. These included two Norwegian samples, a Finnish sample, an Estonian sample, and an Icelandic sample (**Figure 1**). The inclusion criteria were schizophrenia, bipolar disorder, or other psychosis, from ICD10[24]. Diagnoses were obtained from clinical routine and registries in the Finnish, Estonian, Icelandic, and one Norwegian (TDM) sample, and systematic clinical interview (SCID) in the Norwegian TOP sample. The quality of the registry data was found acceptable[25].

In all five samples, antipsychotic drugs were defined according to the anatomical therapeutic chemical (ATC) classification system, defining antipsychotics as all drugs within the ATC code N05A excluding lithium (N05AN01), as its mechanism of action differs from other antipsychotics[26]. A list of all included antipsychotic drugs with corresponding number of individuals in the five cohorts can be found in **Supplementary Table 1**. In four out of the five samples, antipsychotic drug use was defined based on longitudinal data on use of psychopharmacological agents. All individuals in the five cohort are of European ancestry. Because of GDPR and Ethics requirements, we performed the harmonized analyses separately in the individual cohorts, followed by meta-analyses.

Norway:

TDM: From the therapeutic drug monitoring (TDM) system at the Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway, during the period January 2010 and August 2022, a total of 1,369 individuals with schizophrenia (611 females and 758 males) aged between 15-93 years were included.

TOP: From the Thematically Organized Psychosis (TOP) study, a total of 1,162 participants (517 females and 645 males) aged between 15-86 years were included in the current study. Of the 1,162 participants, 687 fulfilled diagnostic criteria for a schizophrenia spectrum disorder, 249 for a bipolar disorder, and 226 for other psychosis. In the TDM and TOP samples, the use of antipsychotic drugs was verified by detectable serum concentrations.

Iceland:

deCODE: From the deCODE genetics Icelandic population, antipsychotic use was determined based on purchases at pharmacies. A total of 19,132 participants born between 1905 and 2000, had purchased one or more antipsychotics between 2003 and 2021. Of these, 780 had been diagnosed with schizophrenia, 1,441 had been diagnosed with bipolar disorder, and 1,735 had been diagnosed with either schizophrenia or bipolar disorder and 243 were diagnosed with both, comprising a total of 1,978 individuals (1,175 females and 803 males) included in the current study.

Finland:

FinnGen: From the FinnGen study[27], antipsychotic dosage was calculated by using the Social Insurance Institution of Finland's national medical drug purchase registry, with data for all drug purchases in Finland from 1995 and forward. The PRE2DUP algorithm[28] was used to infer dosage for each antipsychotic drug during the time-period it was purchased. We focused on antipsychotic drug purchases in all individuals with a psychotic diagnosis (ICD10 equivalents: F20-F29, F30.2, F31, F32.3, and F33.3), totaling 15,210 individuals (55.5% females), of which 5,837 individuals had a schizophrenia diagnosis.

Estonia:

EstBB: From the Estonian Biobank (EstBB)[29], antipsychotic use was determined based on electronic drug dispensing data in Estonia from year 2000. Of 20,259 individuals who had purchased one or more

antipsychotics, individuals who carried a psychosis diagnosis (F20-F31; first report at the age of 15-50 years) and had at least three antipsychotic purchases during their last available treatment year were included in the current study, comprising a total of 1,086 genotyped individuals (672 females and 414 males). For each individual, the daily antipsychotic dose was calculated for the antipsychotic drugs purchased at least three times in their last available treatment year based on purchase data across all available purchases. Specifically, for each purchase, the package content was multiplied by the number of purchased packages. Next, the calculated dose per purchase was divided by the number of days until the next purchase and the daily antipsychotic dose was derived by taking the median across the derived daily doses per purchased time periods.

Ethics:

All procedures contributing to this work were carried out in accordance with relevant guidelines and regulations, and all participants gave written informed consent. The Norwegian TDM and TOP studies were approved by the Norwegian Regional Committe for Medical Research Ethics and the Norwegian Data Inspectorate. The overall study protocol of FinnGen was approved by the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS) (HUS/990/2017). Approval for the deCODE study was obtained from the National Bioethics Committee of Iceland and the Icelandic Data Protection Authority. The Estonian Biobank study was approved by the Estonian Committee on Bioethics and Human Research (1.1-12/624) and carried out under data release S28.

Detailed information about the five samples, including information on genotyping and imputation, can be found in the **Supplementary Methods**.

Polygenic risk scoring

In all five samples, the schizophrenia PRS was calculated based on the latest schizophrenia genome-wide association study (GWAS) performed by the PGC[30] using the meta-analysis of European samples comprising 53,386 cases and 77,258 controls excluding the respective target sample. In the deCODE sample, the PRS was calculated with LDPred[31], using the weight that best predicted schizophrenia in the population. In all other samples, PRS were calculated using the PRS continuous shrinkage (PRS-cs) approach[32], adjusting for linkage disequilibrium (LD) based on the LD structure of the European sample of the 1000 Genomes Phase III[33] with default options and a shrinkage parameter of phi=1[32]. To facilitate the interpretability of the results, PRS were standardized within each sample (mean=0, SD=1) before statistical analysis.

Antipsychotics variables

We applied the following procedure to estimate standardized antipsychotic doses, daily doses of different antipsychotics, antipsychotic polypharmacy, and dose-adjusted antipsychotic serum concentrations. For each antipsychotic drug, standardized dose was defined according to the defined daily dose (DDD) method[34]. The formula to derive standardized doses across antipsychotics is: Daily dose of drug/DDD

of drug, where DDD refers to the defined daily dose presented by the World Health Organisation's Collaborative Center for Drug Statistics Methodology[35]. For individuals using several antipsychotic drugs simultaneously, the standardized doses of all concurrently used antipsychotics were added together. In samples where longitudinal data was used, standardized antipsychotic dose was calculated as the mean from the longitudinal data. Antipsychotic polypharmacy was calculated as the maximum number of antipsychotics used concurrently from longitudinal data, and defined as concurrent use of ≥3 antipsychotics. In the deCODE sample, polypharmacy was estimated based on number of antipsychotics purchased during the last three months. In EstBB, polypharmacy was determined in case an individual had purchased each distinct antipsychotic drug at least three times during their latest treatment year. In FinnGen, antipsychotic polypharmacy was calculated as the maximum number of antipsychotics taken for at least 90 days for any time-period, and the number of individuals having purchased ≥3 antipsychotics for any 90-day period were identified. Dose-adjusted antipsychotic serum concentrations were calculated by dividing the measured serum concentrations in nmol/L by the prescribed daily antipsychotic dose (mg/day).

Statistical analyses

To investigate if a PRS for schizophrenia is associated with standardized antipsychotic doses, linear regression analyses including the antipsychotic dose as the dependent variable were performed. These models included the PRS and the following covariates for adjustment: age, age^2, sex, diagnosis (in samples including individuals with various psychotic disorders), genotyping batch, and the first 5 principal components for genetic ancestry. In addition, we ran analyses for daily doses of various antipsychotics separately to see whether a possible relationship between PRS and antipsychotic dose differs between distinct antipsychotic drugs. These analyses were performed for antipsychotics used by at least 50 individuals in all samples, comprising the following antipsychotics: Aripiprazole, Clozapine, Olanzapine, Quetiapine, and Risperidone. These analyses also included number of antipsychotics used per individual as an additional covariate. In samples with longitudinal data, number of antipsychotics used per individual was calculated as the average number of antipsychotics used. In further analyses, we also expanded our models by including smoking (yes or no) and BMI in cohorts where these data were available, as these might affect antipsychotic dosing. Furthermore, we investigated if PRS for schizophrenia is associated with antipsychotic polypharmacy. This was done in logistic regression analyses using a dichotomized variable for polypharmacy (defined as taking ≥3 antipsychotics), adjusted for age, age^2, sex, diagnosis, genotyping batch, and the first 5 principal components for genetic ancestry. As additional analyses, we also investigated if PRS for schizophrenia is associated with concurrent use of ≥2 antipsychotics as well as total number of antipsychotics (linear regression). To address potential residual diagnostic bias, we also performed analyses in the FinnGen sample restricted to individuals with schizophrenia (N=5,837), as this sample is of sufficient sample size. Meta-analyses of results from the five cohorts were performed using the R-package metaplus[36] with standard normal random effect. In addition, we explored whether the schizophrenia PRS was associated with serum concentrations of individual antipsychotics, within the Norwegian TDM and TOP sample. These analyses

included antipsychotic serum concentrations or dose-adjusted antipsychotic serum concentrations as the dependent variable, the schizophrenia PRS, and the following covariates for adjustment: age, age^2, sex, diagnosis, smoking, number of antipsychotics used, genotyping batch, and the first 5 principal components. All regression analyses were performed in R v4.1.2.

Results

Antipsychotic prescription patterns from real-world registries and biobanks

An overview of the five independent Nordic samples, from which we extracted data on antipsychotic use, is shown in **Figure 1**. Whereas antipsychotic use in the two Norwegian samples was based on health records and questionnaires, antipsychotic use was estimated based on data from drug purchases in the EstBB, FinnGen, and deCODE samples. In the EstBB, FinnGen, and TDM samples, the standardized antipsychotic dose as well as the dose from individual antipsychotics was calculated as the mean dose from the longitudinal data, whereas the most recent dose was used in the deCODE sample. We also calculated the number of concurrently used antipsychotics. In the TDM sample, 794 individuals (58%) had concurrently used ≥2 antipsychotic drugs during their longitudinal TDM. Within the FinnGen cohort, 9,188 individuals (60%) had concurrently used ≥2 antipsychotic drugs during the study period. From the data of the last three months of the deCODE sample, 763 individuals (39%) had concurrently used ≥2 antipsychotics, and from the data of the last available treatment year of the EstBB sample, 228 individuals (21%) had concurrently used ≥2 antipsychotics. In the TOP sample, 244 individuals (21%) had concurrently used ≥2 antipsychotics at their baseline examination.

Association between schizophrenia PRS and antipsychotic dosage

Our meta-analysis showed that the PRS for schizophrenia was significantly positively associated with standardized antipsychotic dose across the five cohorts (OR=1.05, CI=1.03-1.09, p=0.0008), shown in **Figure 2**. Results for the individual samples are presented in **Table 1**, showing that this association was significant in four out of the five samples. In the TOP sample, the results showed the same direction of effect, but did not reach significance (**Table 1, Figure 2, Figure S1**).

Table 1: Association between polygenic risk for schizophrenia and standardized antipsychotic dose across antipsychotic drugs

Sample (N)	Beta (SE)	t-value	p-value
FinnGen (15,210)	0.0417 (0.0067)	6.257	4.04e-10*
deCODE (1,978)	0.0710 (0.0264)	2.685	0.0070*
EstBB (1,086)	0.0617 (0.0297)	2.081	0.0376*
TOP (1,162)	0.0669 (0.0495)	1.349	0.1775
TDM (1,369)	0.1132 (0.0441)	2.566	0.0104*

* p<0.05. Antipsychotic doses have been normalized with z-transformation.

The results were consistent when BMI was added as an additional covariate in the deCODE and TOP samples (**Supplementary Table 2**). In the TDM and TOP samples, we also added smoking as additional covariate. Although smoking was significantly positively associated with standardized antipsychotic doses in the TDM (beta(SE)=0.2603(0.081), t=3.229, p=0.0013) and TOP samples (beta(SE)=0.177(0.055), t=3.216, p=0.0013), the observed association between schizophrenia PRS and standardized antipsychotic dose in the TDM sample was still significant when adjusting for smoking behavior, and remained non-significant in the TOP sample (**Supplementary Table 3**). As additional sensitivity analysis, we restricted our analysis to schizophrenia patients in the FinnGen sample (N=5,837), and observed that the association between schizophrenia PRS and standardized antipsychotic dose was still significant (beta(SE)=0.0577(0.0128), t=4.502, p=6.87e-6).

To investigate whether the relationship between schizophrenia PRS and higher antipsychotic dose requirements differs between antipsychotic drugs, we also investigated the association between schizophrenia PRS and the daily doses of individual antipsychotics. Meta-analyses across the five cohorts showed that the direction of effect was similar for the different antipsychotics, i.e., higher PRS was related to higher doses (**Figure S2**). Results for the individual samples are shown in **Supplementary Table 4**. In addition, we explored whether the schizophrenia PRS was correlated with plasma drug concentrations of different antipsychotic drugs, within the Norwegian TDM and TOP sample. Higher schizophrenia PRS was associated with higher Clozapine concentrations in the TDM sample (p=0.0043) (**Supplementary Table 5**), but not with dose-adjusted Clozapine concentrations (**Supplementary Table 6**). Moreover, higher schizophrenia PRS was associated with lower Olanzapine concentrations in the TOP sample (p=0.0116) (**Supplementary Table 5**), and lower dose-adjusted serum concentrations of Olanzapine in both the TDM (p=0.0118) and the TOP samples (p=0.0211) (**Supplementary Table 6**). No other associations were found between schizophrenia PRS and either antipsychotic serum concentrations (**Supplementary Table 5**) or dose-adjusted antipsychotic serum concentrations (**Supplementary Table 6**).

Association between schizophrenia PRS and antipsychotic polypharmacy

Meta-analyses showed a significant association between schizophrenia PRS and antipsychotic polypharmacy defined as taking ≥3 antipsychotics (OR=1.30, CI=1.00-1.74, p=0.048). This association was significant in the FinnGen and TDM samples, and a similar direction of effect was observed in the deCODE, EstBB, and TOP samples (**Table 2, Figure 3**).

Table 2: Association between polygenic risk for schizophrenia and antipsychotic polypharmacy

Sample (N)	Beta (SE)	t-value	p-value
FinnGen (3,295)	0.0644 (0.0228)	2.826	0.0047*
deCODE (148)	0.094 (0.1033)	0.910	0.3630
EstBB (23)	0.2858 (0.2346)	1.218	0.2230
TOP (37)	0.3623 (0.3110)	1.165	0.2440
TDM (175)	0.670 (0.1350)	4.966	6.84e-7*

* p<0.05

Meta-analyses did not show a significant association between schizophrenia PRS and concurrent use of ≥2 antipsychotics (OR=1.08, CI=0.98-1.21, p=0.105) or total number of concurrently used antipsychotics (OR=1.04, CI=0.99-1.10, p=0.085), although a significant association with both concurrent use of ≥2 antipsychotics and total number of concurrently used antipsychotics was seen in both the FinnGen and the TDM sample (**Supplementary Table 7**)**.** In the FinnGen sample, these associations remained significant when the analyses were restricted to individuals with a schizophrenia diagnosis (**Supplementary Table 8**). Accounting for smoking behavior in the Norwegian TDM and TOP cohorts did not essentially change the results (**Supplementary Table 9**), although smoking was significantly associated with number of antipsychotics (beta(SE)=0.2152(0.047), t=4.600, p=4.76e-6), taking ≥2 antipsychotics (beta(SE)=0.4393(0.134), t=3.276, p=0.0011), and taking ≥3 antipsychotics (beta(SE)=0.7704(0.194), t=3.967, p=7.28e-5) in the TDM sample, but not in the TOP sample (p>0.05).

Discussion

In this proof of principle study of Nordic registry and biobank data, we investigated whether polygenic risk for schizophrenia is associated with antipsychotic dose and polypharmacy in five independent cohorts of psychotic disorders, using a combination of clinical and real-world registry and biobank data. This study demonstrates that real-world data can be used to address clinically useful research questions on treatment outcomes, and thus form the foundations for future precision medicine approaches in psychiatry.

In five independent cohorts, we examined whether schizophrenia PRS is associated with standardized daily antipsychotic doses across antipsychotics. Higher genetic liability for schizophrenia was significantly associated with a higher standardized antipsychotic dose in four cohorts (FinnGen, deCODE,

TDM, EstBB), with a similar direction of effect in the TOP cohort. Of note, the standardized antipsychotic dose in the TOP cohort was derived from cross-sectional data, which may be biased from multiple factors, such as individuals being in a phase of cross-titration and receiving a low dose before switching to another antipsychotic. In addition, antipsychotic dosage may differ during the course of illness, and individuals starting antipsychotic treatment usually receive lower doses to reduce the risk of side effects[1]. Therefore, an average dose derived from longitudinal data may reflect a better measure of dosage than dose derived from cross-sectional data. However, in the deCODE sample, a significant association between schizophrenia PRS and antipsychotic dosage was observed even though only the latest dose was used. It should also be noted that antipsychotic dosage in the deCODE, EstBB, and FinnGen samples was estimated based on pharmacy purchases, which may not always reflect the exact dose taken and does not allow for inclusion of doses from injections given in hospitals. In the TDM and TOP samples, we were able to confirm antipsychotic use by detectable serum concentrations. TDM is used as a tool for clinical follow-up in psychiatry, making this sample more likely to include individuals with higher disease burden and drug-related problems, which may favor the ability to detect associations between genetic disease liability and antipsychotic dose requirements. Additional analyses showed that the observed association between genetic liability for schizophrenia and higher antipsychotic dosage remained significant after accounting for BMI and smoking behavior, indicating that the association is independent of the effects of BMI or smoking. Moreover, we observed that the direction of effect was similar across different antipsychotics. In a previous study[37] investigating whether schizophrenia PRS is associated with standardized antipsychotic dose, such an association was not found. However, these results were based on a single sample of limited size, and the dosage was derived from cross-sectional data[37].

To our knowledge, this is the first study investigating the association of schizophrenia PRS with both antipsychotic dosage and antipsychotic polypharmacy. Due to increased risk for side effects, antipsychotic combination therapy is not recommended by treatment guidelines[16]. However, in clinical practice, antipsychotic combination therapy is frequently observed in individuals with inadequate response to antipsychotic monotherapy[15, 16]. Here, we found that a higher genetic liability of schizophrenia was significantly associated with antipsychotic polypharmacy defined as the concurrent use of ≥ 3 antipsychotics. However, in three cohorts (EstBB, deCODE, TOP), no significant association between schizophrenia PRS and antipsychotic polypharmacy was found. In these three samples, polypharmacy was defined based on either cross-sectional data (TOP), individuals' last treatment year (EstBB), or individuals' last three months of treatment only (deCODE), likely making these data underpowered for the polypharmacy analyses. These results encourage follow-up studies on the potential of schizophrenia PRS in aiding to plan antipsychotic monotherapy or polypharmacy approaches.

The application of PRS in precision medicine has long been discussed, and it is expected that PRS will become part of clinical psychiatry in the future[38, 39]. Currently, the predictive ability of psychiatric PRS remains insufficient for clinical utility, which largely depends on the power of the GWAS the PRS is derived from[39, 40]. With larger GWASs, improved phenotyping, technological refinement, and the inclusion of rare high impact variants, the predictive performance of PRS is likely to improve in the

coming years[39–41]. In addition, large-scale, genotyped prescription registries such as FinnGen[27] and the Estonian Biobank[29] will offer new opportunities to investigate the genetics of treatment outcomes[23, 42]. Here, we demonstrate that individuals with a high genetic burden of schizophrenia are more likely to receive higher antipsychotic doses and antipsychotic polypharmacy, which might reflect poor antipsychotic treatment response. In fact, it has been shown that higher schizophrenia PRS is associated with worse antipsychotic treatment response[43, 44]. Assuming that individuals with a high genetic liability for schizophrenia may need higher antipsychotic doses and/or antipsychotic polypharmacy to obtain sufficient therapeutic response, genetic information could potentially be useful for therapeutic decision making on antipsychotic prescription. Taken together, our results suggest that genetic liability for schizophrenia is associated with worse antipsychotic treatment outcomes, indicating potential utility of schizophrenia PRS in predicting antipsychotic treatment outcomes once larger, deeply-phenotyped datasets become available.

Some limitations of the present study should be acknowledged. Our results may be influenced by unmeasured factors known to influence antipsychotic metabolism such as regular use of caffeine, alcohol use, and other substance use. However, we used available data on smoking as well as BMI, and showed that the observed association between high schizophrenia PRS and antipsychotic dose as well as antipsychotic polypharmacy were independent of these covariates. Our results could also be affected by the different diagnostic groups of psychotic disorders in the cohorts. To address potential diagnostic bias, we accounted for diagnosis in all models and performed sensitivity analyses in FinnGen restricted to individuals with a schizophrenia diagnosis, showing similar results. Moreover, data on treatment response were not available in any of the samples, thus we were not able to verify if higher dose requirements or antipsychotic polypharmacy reflect poor treatment response. It should also be noted that the individuals in our samples are of European ancestry, and our results may therefore not be directly translatable to other ethnicities. Finally, the schizophrenia PRS is built from a case-control GWAS including a considerable portion of severe schizophrenia cases, which is not necessarily representative of the diversity of psychotic disorders in our samples. Although we show evidence for an association between schizophrenia genetics and high antipsychotic dose requirements and antipsychotic polypharmacy in multiple independent cohorts of psychotic disorders as well as in two schizophrenia cohorts, these findings have yet to be replicated in other independent cohorts to investigate if such findings could finally aid in therapeutic decision making on antipsychotic treatment.

Conclusion

Using real-world data from Nordic registries and biobanks, we show that genetic liability for schizophrenia is associated with both higher antipsychotic doses and antipsychotic polypharmacy. This study demonstrates the potential for real-world registry and biobank data in building precision psychiatry approaches, which may become clinically useful in the future. However, large-scale data with genomic and longitudinal treatment information is still needed to train the PRS to obtain the necessary accuracy for clinically relevant predictions. In conclusion, this study supports that the use of real-world data can generate information with the potential to aid in therapeutic decision making on antipsychotic treatment.

Declarations

Author contributions

OA, KO, and EK conceived the study and were involved in study design. EK, SS, AK, MA, GE, and JP conducted analyses. EK drafted the initial manuscript. All authors (including banner authors of the Estonian Biobank Research team and FinnGen) contributed to data interpretation and editing of the manuscript.

Data Availability

The GWAS summary statistics included in this study are publicly available. Data from the five cohorts can be made available upon request and with appropriate data transfer agreements. Due to national personal data protection regulations, raw data cannot be shared.

Conflict of Interest

Dr. Andreassen reported grants from Stiftelsen Kristian Gerhard Jebsen, South-East Regional Health Authority, Research Council of Norway, and European Union's Horizon 2020 during the conduct of the study; personal fees from cortechs.ai (stock options), Lundbeck (speaker's honorarium), and Sunovion (speaker's honorarium) and Janssen (speaker's honorarium) outside the submitted work. Dr. Taipale reports personal fees from Gedeon Richter, Janssen, Lundbeck and Otsuka, and grants from Eli Lilly and Janssen, outside of the submitted work. No other disclosures were reported.

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(https://www.ppshp.fi/Tutkimus-ja-opetus/Biopankki/Pages/Biobank-Borealis-briefly-in-English.aspx), Finnish Clinical Biobank Tampere (www.tays.fi/en-US/Research_and_development/Finnish_Clinical_Biobank_Tampere), Biobank of Eastern Finland (www.ita-suomenbiopankki.fi/en), Central Finland Biobank (www.ksshp.fi/fi-FI/Potilaalle/Biopankki), Finnish Red Cross Blood Service Biobank (www.veripalvelu.fi/verenluovutus/biopankkitoiminta), Terveystalo Biobank (www.terveystalo.com/fi/Yritystietoa/Terveystalo-Biopankki/Biopankki/) and Arctic Biobank (https://www.oulu.fi/en/university/faculties-and-units/faculty-medicine/northern-finland-birth-cohorts-and-arctic-biobank). All Finnish Biobanks are members of BBMRI.fi infrastructure (www.bbmri.fi). Finnish Biobank Cooperative -FINBB (https://finbb.fi/) is the coordinator of BBMRI-ERIC operations in Finland. The Finnish biobank data can be accessed through the Fingenious® services (https://site.fingenious.fi/en/) managed by FINBB.

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Figures

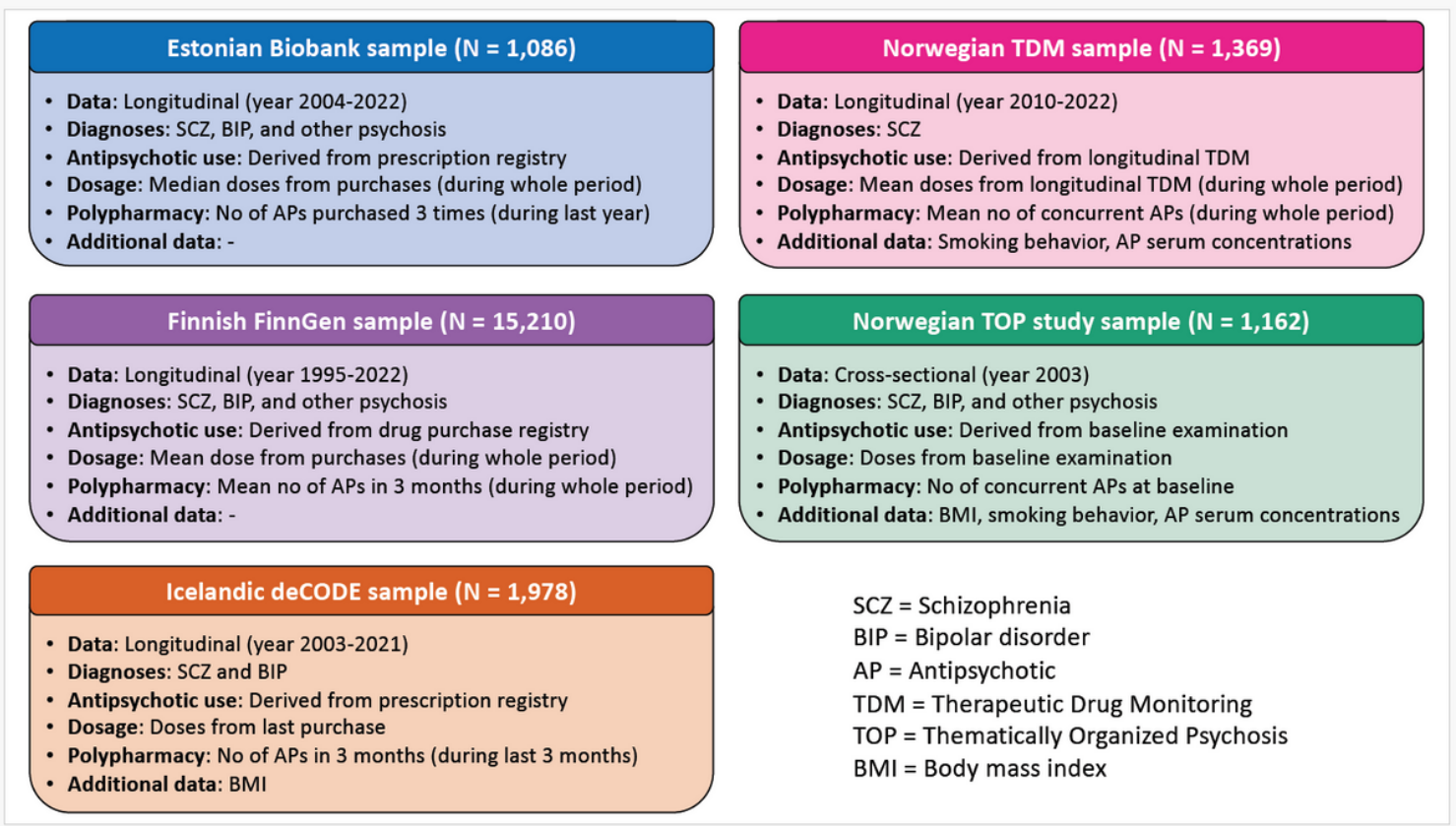

Figure 1

Sample overview with description of available data and derivation of antipsychotic dosage and antipsychotic polypharmacy.

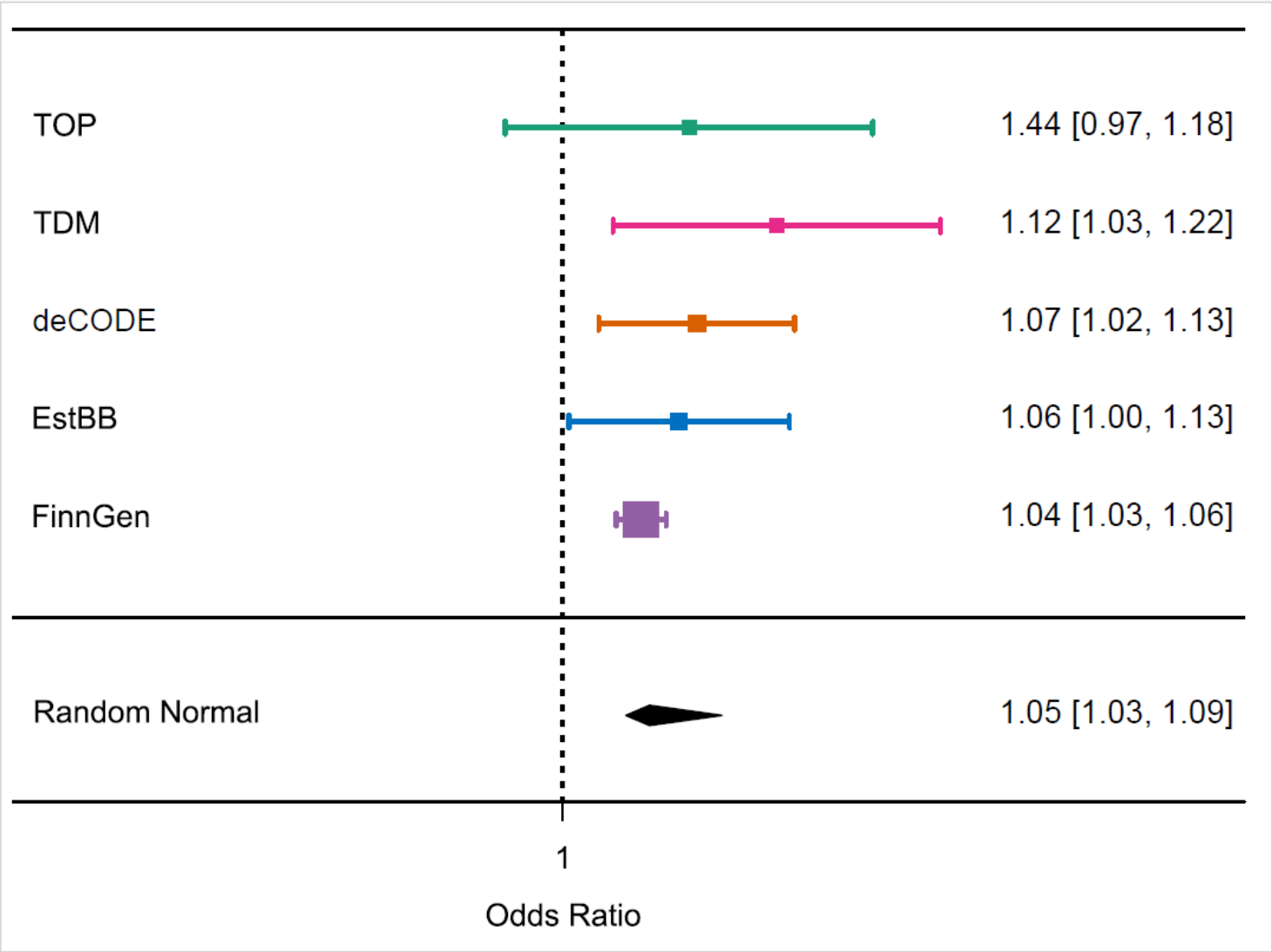

Figure 2

Forest plots showing the association between schizophrenia PRS and antipsychotic dosage in five independent cohorts, as well as across these cohorts.

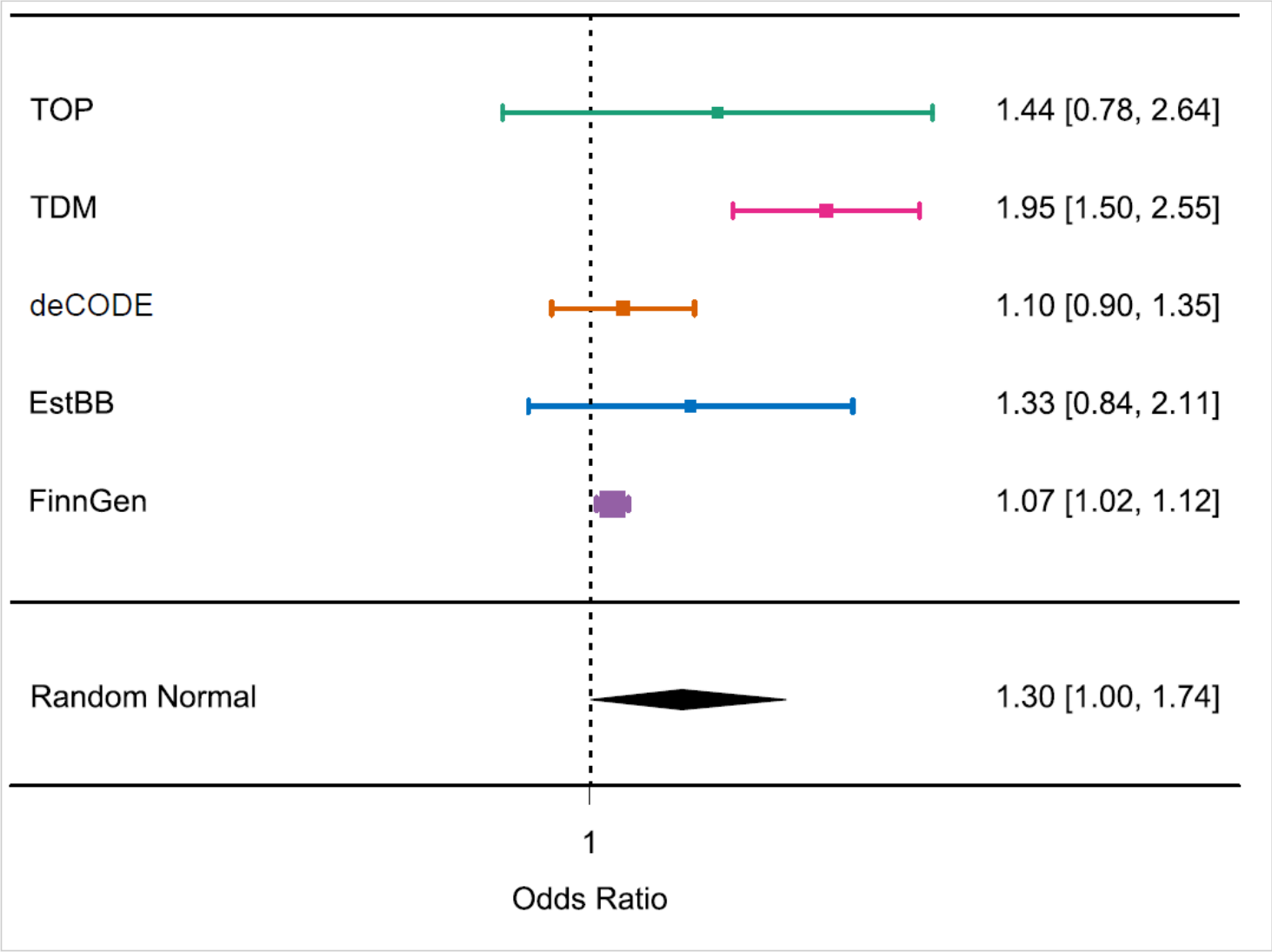

Figure 3

Forest plots showing the association between schizophrenia PRS and antipsychotic polypharmacy (defined as taking ≥3 antipsychotics) in five independent cohorts, as well as across these cohorts.

Supplementary Files

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- SupplementaryMaterial.pdf