The Pharmacogenomics Journal www.nature.com/tpj

CONSENSUS STATEMENT

Polygenic score analyses on antidepressant response in late-life depression, results from the IRL-GRey study

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Late-life depression (LLD) is often accompanied by medical comorbidities such as psychiatric disorders and cardiovascular diseases, posing challenges to antidepressant treatment. Recent studies highlighted significant associations between treatment-resistant depression (TRD) and polygenic risk score (PRS) for attention deficit hyperactivity disorder (ADHD) in adults as well as a negative association between antidepressant symptom improvement with both schizophrenia and bipolar. Here, we sought to validate these findings with symptom remission in LLD. We analyzed the *Incomplete Response in Late Life Depression: Getting to Remission (IRL-GRey)* sample consisting of adults aged 60+ with major depression ($N = 342$) treated with venlafaxine for 12 weeks. We constructed PRSs for ADHD, depression, schizophrenia, bipolar disorder, neuroticism, general intelligence, antidepressant symptom remission and antidepressant percentage symptom improvement using summary statistics from the Psychiatric Genomics Consortium and the GWAS Catalog. Logistic regression was used to test the association of PRSs with venlafaxine symptom remission and percentage symptom improvement, co-varying for the genomic principal components, age, sex and depressive symptoms severity at baseline. We found a nominal (i.e., p value ≤ 0.05) association between symptom remission and both PRS for ADHD and (OR = 1.36 [1.07, 1.73], $p = 0.011$) and PRS for bipolar disorder (OR = 0.75 [0.58, 0.97], $p = 0.031$), as well as between percentage symptom improvement and PRS for general intelligence (beta = 6.81 (SE = 3.122), $p = 0.03$). However, the ADHD association was in the opposite direction as expected, and both associations did not survive multiple testing corrections. Altogether, these findings suggest that previous findings regarding ADHD PRS and antidepressant response (measured with various outcomes) do not replicate in older adults.

The Pharmacogenomics Journal (2024) 24:38; 1–7; https://doi.org/10.1038/s41397-024-00351-0

INTRODUCTION

Major depressive disorder (MDD) is a common mental illness that negatively affects thoughts, behavior and emotions. MDD affects more than 280 million people worldwide and 5.7% of people older than 60 years [1, 2]. Late-life depression (LLD), defined as MDD occurring after the age of 60, is often accompanied by other comorbidities (e.g., cerebrovascular and other psychiatric disorders) resulting in a unique pharmacokinetic and pharmacodynamic profile in older adults, which is associated with poor treatment response and increased risk of side-effects [3–5]. Current trial-and-error practices in prescribing antidepressants can result in prolonged periods of ineffective treatment, which is associated with overall poor prognosis. Therefore, studying the genetic basis underlying antidepressant response in elderly can potentially improve treatment outcomes in LLD [6–8].

Polygenic risk score (PRS), defined as the estimated combined genome-wide effect on an individual's phenotype, is a promising approach to identify patients at risk of treatment failure and side effects [9]. Recent studies [10–14] investigated the genetic basis of antidepressant response through genome-wide and PRS analyses of various phenotypes assessing response to antidepressants in MDD (e.g., remission and treatment-resistant depression). Improved antidepressant treatment response (assessed with various clinical symptom scales) has shown to be negatively associated with PRSs for MDD [13], schizophrenia [13], openness personality trait [10], attention deficit hyperactivity disorder

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Received: 16 May 2023 Revised: 2 August 2024 Accepted: 17 September 2024
Published online: 22 November 2024

(ADHD) [14], coronary artery disease and obesity [11], and stroke [12].

Pain et al. [13] performed a large genome-wide association study (GWAS) and post-GWAS analyses of symptom remission and percentage symptom improvement (i.e., percentage change in depressive symptoms - assessed with various measures - from baseline) in Europeans and East Asian ancestries, separately. Although the study did not reveal any significant variants from GWAS, and the heritability estimates was not significantly different from zero in percentage symptom improvement; it showed that genetic (i.e., SNP-based) heritability was higher in remission (~13.2%) than in percentage symptom improvement (~-1.80%), in accordance with previous studies [15]. Furthermore, their PRS analysis highlighted a negative association between both PRSs for schizophrenia and symptom remission and between PRS for MDD and percentage symptom improvement.

A recent study by Fabbri et al. [14] examined the association between a PRS for a number of psychiatric (including MDD, schizophrenia, bipolar disorder, ADHD, among others) and non-psychiatric (i.e., personality, cognitive, cardio-metabolic and related symptoms) traits with treatment-resistant depression (TRD) in patients with MDD. They used the UK Biobank [16] and the Extended Cohort for E-health, Environment and DNA (EXCEED) [17] cohorts to define TRD (using prescribing notes in electronic health records) as at least two switches between antidepressant drugs each prescribed for at least six weeks. The study reported a significant positive association between PRS for ADHD and TRD ($P_t = 0.2$, OR = 1.05 [1.04–1.14], $P = 4.38e{-}04$), with a stronger shared genetic predisposition of ADHD in patients with TRD (compared to non-TRD). PRSs for MDD, neuroticism, subjective well-being and intelligence showed nominal associations with TRD [14].

Although investigations of the genetic basis of antidepressant response combined various cohorts, this combination was challenged by the heterogeneity of outcomes. Additionally, no study has so far focused on assessing association between PRSs for psychiatric traits with antidepressant remission and percentage symptom improvement in older adults. In this exploratory study, we aimed to assess the association between antidepressant remission and percentage symptom improvement with PRS for ADHD and other psychiatric and non-psychiatric traits (in addition to antidepressant symptom remission and percentage symptom improvement) in a well-characterized sample of older adults with depression. We first assessed previously reported association between PRS for ADHD and TRD [14], with the main hypothesis that symptom remission is associated with PRS for ADHD. Using the Incomplete Response in Late Life Depression: Getting to Remission (IRL-GRey) sample of older adults and a well-powered, publicly available GWAS summary statistics, we constructed PRSs for eight traits (i.e., ADHD, depression, schizophrenia, bipolar disorder, neuroticism, general intelligence, symptom remission and percentage symptom improvement), and examined their association with symptom remission and percentage symptom improvement.

MATERIALS AND METHODS

Target and discovery samples

In this secondary analysis, we used datasets collected in the NIH funded clinical trial (NCT00892047) [18]; Incomplete Response in Late Life Depression: Getting to Remission (IRL-GRey) [19] study, as a target sample for calculation of PRS. Recruitment of participants in the IRL-GRey study took place from July 2009 to December 2013 at three Centers (University of Pittsburgh, USA; Centre for Addiction and Mental Health, Canada; and Washington University, USA). ADHD [20] and five other GWAS summary statistics for psychiatric and non-psychiatric traits, including MDD [21] (excluding the 23andme cohort), schizophrenia [22], bipolar disorder [23], neuroticism [24], general intelligence [25], as well as antidepressant symptom remission and percentage symptom improvement [13] from well-powered GWASs were utilized as discovery samples in our PRS analyses (see Table 1 for more details).

The first phase of this study targeted older adults (age ≥60; $N = 453$) with MDD (single or recurrent) and who have a Montgomery-Åsberg Depression Rating Scale (MADRS) [26] ≥15, treated openly with antidepressant (i.e., venlafaxine XR 37.5 mg/day, up to 300 mg/day) for 12 weeks. The exclusion criteria included patients with dementia, life-time diagnosis of bipolar I or II, schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional, current psychotic symptoms, dependence on alcohol or any substances (within the past 3 months from baseline visit), and high risk of suicide. For more detailed information about the IRL-GRey study, please refer to the methods paper [19]. All participants provided informed consent to participate and allow use of their unidentified data for research purposes. Research ethics approval for the work presented here was obtained from the Center for Addiction and Mental Health (CAMH) Research Ethics Board (REB) office, as well as from institutional review boards at the aforementioned recruiting sites.

Table 1. Discovery sample used to construct polygenic risk scores and obtained from previous and publicly available GWAS summary statistics.

Phenotype	Sample size	SNPs	Ethnicity	Authors	Source	Year
ADHD[a]	55,374	8,094,095	Mixed[b]	Demontis et al.	PGC[c]	2019
MDD exc 23andme[d]	173,005	9,600,000	Europeans	PGC-MDD2, Wray et al.	PGC	2018
Schizophrenia	243,649	9,500,000	Mixed[e]	PGC-SCZ, Trubetskoy et al.	PGC	2022
Bipolar disorder	413,466	7,605,225	Europeans	PGC-BP, Mullins et al.	PGC	2021
Neuroticism	63,661	6,949,614	Europeans	GPC, De Moor et al.	GPC[f] and GC	2015
General Intelligence	269,867	9,295,118	Europeans	Savage et al.	CTGlab and GC[g]	2018
AD[h] Symptom non-remission	5151	9,612,897	Europeans	PGC-MDD, Pain et al.	PGC	2022
AD Symptom Percentage improvement	5218	9,623,990	Europeans	PGC-MDD, Pain et al.	PGC	2022

[a]Attention-deficit/hyperactivity disorder.
[b]Denmark, European, North American and Chinese cohorts.
[c]Psychiatric Genomics Consortium.
[d]Summary statistics excluding the 23andme cohort.
[e]Europeans and East Asian.
[f]Genetics of Personality Consortium.
[g]GWAS Catalog.
[h]Antidepressant.

Table 2. Summary of demographic characteristics and MADRS change by remission status in the complete IRL-GRey sample ($N = 342$).

	Non remitters ($N = 167$)		Remitters ($N = 175$)		Total ($N = 342$)	
	Mean (SD; min; max)	***N* (Row%)**	**Mean (SD; min; max)**	***N* (Row%)**	**Mean (SD; min; max)**	***N***
Age	67.44 (6.08; 60; 91)	–	69.88 (7.65; 60; 93)	–	68.69 (7.03; 60; 93)	–
Sex Female	–	91 (41.9%)	–	126 (58.1%)	–	217
BL MADRS[a]	28 (5; 15; 43)	–	25 (5; 15; 39)	–	27 (6; 15; 43)	–
End MADRS[b]	23 (7; 11; 39)	–	4 (3; 0; 10)	–	14 (11; 0; 39)	–
Improvement[c]	−16.62 (22.42; −61.11; 53.33)	–	−82.28 (12.67; −100; −43.75)	–	−50.32 (37.50; −100; 53.33)	–

[a]BL MADRS, Montgomery-Åsberg Depression Rating Scale (MADRS) score at baseline.
[b]End MADRS, score at week 12.
[c]Improvement, percentage symptom improvement (defined as a quantitative variable of the MADRS change from baseline until week 12 divided by the MADRS at baseline score); a better symptom improvement corresponds to a negative and higher value of the Percentage Symptom Improvement variable.

Genotyping of the samples was done using the Illumina PsychArray BeadChip genotyping array. A standard quality control of the genotype data was performed using PLINK 2.00 [27] (https://www.cog-genomics.org/plink2). Specifically, SNPs with genotyping rate < 95%, minor allele frequency (MAF) < 1%, and Hardy-Weinberg equilibrium test with $P < 5 \times 10^{-7}$ were excluded prior to imputation. From an initial pool of 453 patients, 107 individuals were excluded due to reasons such as withdrawal, excessive heterozygosity, discordance between self-reported and genetic sex, Y-chromosome abnormalities, excessive relatedness, and missing genotypes. One individual with a baseline MADRS score of 13 met one of the IRL-GRey's exclusion criteria (i.e., MADRS < 15) and was removed from this analysis. The final sample for genetic imputation comprised 345 individuals who passed quality control criteria. Imputation of genotype data was then carried out using IMPUTE v2.2 [28] implemented under the *genipe* pipeline where an estimation of haplotypes (pre-phasing) was carried out using *SHAPEIT2*. Genotype imputation and haplotype phasing was done in 5-Mb chunks for each chromosome (information threshold = 0.7; probability threshold = 90%; average completion rate = 90%) using Phase 3 of the 1000 Genomes reference panel [29–32]. After imputation, basic MAF quality control was then conducted to include variants with MAF ≥ 5% and genotyping rate >99.1% as well as individuals with <10% missing genotypes. A total of 342 individuals and 5,728,647 SNPs (306 individuals and 4,471,676 for self-reported Europeans subsample) were retained after post-imputation quality control. Detailed quality control and imputation pipeline was described previously [12]. In Tables 2 and S1, we show demographic and descriptive summary of the data for the whole samples, and the European subsample, respectively.

Data analysis

Our primary outcome of interest was *symptom remission*, defined as a binary variable that takes a value of 1 if MADRS score ≤10 (remitter) or 0 otherwise (non-remitter). As a secondary outcome, we analyzed the *percentage symptom improvement*, defined as a quantitative variable of the MADRS change from baseline until week 12 divided by the MADRS at baseline score. A better improvement corresponds to a negative and higher value of the latter outcome variable. We conducted PRS in the whole IRL-GRey sample ($N = 342$; 63.5% females) and the European subsample ($N = 306$; 62.1% females) to reduce the possible bias caused by the genetic diversity included in the whole sample which contains mixed populations (e.g., European, African, Asian and Indian). PRS analyses in the remaining diverse group of various ancestries were challenging due to low sample sizes.

We constructed a standardized PRSs for eight traits, including ADHD, using the clumping and thresholding method (with PRSice version 2.3.5) [33], where a number of PRSs for each trait is generated at different p value thresholds p_t (the lower the threshold, the fewer SNPs included; nine thresholds were used in our analysis including, 5e−8, 1e−7, 1e−6, 1e−5, 1e−4, 1e−3, 0.01, 0.05, 0.1, 0.5, and 1) [34] and the best threshold corresponding to the most predictive (of our outcome) PRS is chosen. Logistic and linear regression was used to test the association of PRSs with symptom remission and percentage symptom improvement, respectively, co-varying for the first two genomic principal components to adjust for population stratification, age and sex as well as baseline MADRS score (in case the outcome is remission). In addition, we ran 10,000 permutations in PRSice to avoid inflation and overfitting in our p values. All permutation p values were reported alongside the actual p values in our result tables.

We have further performed PRS principal component analysis (PRS-PCA) using the method proposed by Coombes et al. [34]. This approach mitigates issues related to parameter sensitivity and optimization by computing PRS across a range of settings (i.e., the nine p_t thresholds mentioned above) using PCA. We fitted linear and logistic regression to predict our outcomes (i.e., symptom percentage improvement and remission status, respectively) using the first principal component computed by PRS-PCA, co-varying for sex, age, MADRS at baseline, and the first two genomic principal components. Our PRS-PCA results along with the thresholding method were reported in Tables 3, 4 and S2, S3.

We adjusted for the multiple-comparison testing in both PRS analyses using the Nyholt method [35]. We corrected for multiple testing to account for the 16 tests being performed in each analysis, separately. Since psychiatric traits are highly related and genetically correlated, we estimated the number of effective tests using the Nyholt method [35], implemented through the *meff* function of the *poolr* [36] package in R. The Nyholt adjusted threshold was 0.0045 (i.e., Nyholt method yielded 11 independent tests).

RESULTS

A brief descriptive statistics that summarize demographic and outcome variables in our whole sample as well as European subsample is shown in Tables 2 and S1, respectively. In brief, the sample consisted of 342 older adults diagnosed with LLD and aged between 60 and 93 years, with an average of 68.7 years (SD = 7.03). Overall, 51.17% ($N = 175$) remitted by week 12, and the percentage symptom improvement ranged between -100 and 53.3 (average = −50.3 [SD = 37.5]; see Table 2).

Polygenic risk score analyses

Remission status. In accordance with our main hypothesis, we found a nominal (i.e., with $p \leq 0.05$) association between the PRS for ADHD and symptom remission (OR = 1.36 [1.073, 1.73], $p = 0.011$). This finding was consistent in our European subsample (OR = 1.41 [1.095, 1.820], $p = 0.0079$). As for the association

Table 3. Association analysis for PRS with symptom remission in the IRL-GRey whole sample ($N = 342$).

Method	PRSice thresholding method						PRS-PCA
Statistics[a]	P_t	Full.R^2	*P*	*N* SNPs	Empirical *P*	OR [CI]	OR ([CI], full model R^2, *P*)
ADHD	1e−06	0.251	0.011*	32	0.074	1.36 [1.073, 1.730]	1.18 ([0.915, 1.518], 0.199, 0.203)
MDD exc 23andme	0.2	0.241	0.086	48,737	0.368	0.12 [0.01, 1.343]	1.67 ([0.586, 4.741], 0.196, 0.338)
Schizophrenia	0.01	0.231	0.360	11,277	0.688	0.84 [0.579, 1.219]	0.91 ([0.631, 1.32], 0.194, 0.627)
Bipolar disorder	0.01	0.246	0.031*	8125	0.130	0.75 [0.58, 0.975]	0.83 ([0.613, 1.123], 0.198, 0.227)
Neuroticism	1e−04	0.234	0.210	129	0.695	1.16 [0.919, 1.461]	0.98 ([0.764, 1.253], 0.193, 0.863)
General Intelligence	1	0.240	0.078	114,251	0.197	0.59 [0.339, 1.059]	0.71 ([0.484, 1.049], 0.203, 0.085)
AD[b] symptom non-remission*	0.05	0.228	0.705	10,728	0.998	0.95 [0.739, 1.226]	0.99 ([0.775, 1.268], 0.193, 0.944)
AD percentage symptom improvement*	0.3	0.232	0.324	42,265	0.809	1.12 [0.889, 1.426]	1.07 ([0.848, 1.351], 0.194, 0.568)

All null model *p* values were 0.0998 for the whole sample, and 0.1140 for the European sample. *indicates nominally significant *p* value (i.e., $p < 0.05$). **P*-value threshold search range was limited to (1e−4, 1e−3, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5) due to the very low number of SNPs in some of the lower thresholds in the defined search range as per our "Data analysis" section.
[a]Definition of all columns: P_t best *P* value threshold, *PRS.*R^2 PRS R^2, *Full.R2* full model R^2, *P p* value estimated from *t* distribution, *N SNPs* number of SNPs in PRS, *Empirical P p* values estimated from an empirical 10,000 permutations.
[b]Antidepressant.

Table 4. Association analysis for PRS with percentage symptom improvement* in the IRL-GRey whole sample ($N = 342$).

Method	PRSice thresholding method						PRS-PCA
Statistics[a]	P_t	Full.R^2	Beta (SE)	*P*	*N* SNPs	Empirical *P*	Beta (SE, full model R^2, *P*)
ADHD	1e−06	0.088	−5.07 (1.97)	0.011*	32	0.072	−1.44 (2.142, 0.072, 0.503)
MDD exc 23andme	0.2	0.074	21.86 (18.974)	0.250	48,737	0.838	0.84 (9.001, 0.07, 0.926)
Schizophrenia	0.2	0.071	−2.92 (5.144)	0.570	52,038	0.947	−0.34 (3.155, 0.07, 0.913)
Bipolar disorder	0.01	0.081	4.27 (2.171)	0.049*	8125	0.190	1.98 (2.556, 0.072, 0.438)
Neuroticism	1e−04	0.072	−1.7 (1.978)	0.390	129	0.921	0.62 (2.114, 0.071, 0.769)
General intelligence	0.01	0.083	6.81 (3.122)	0.030*	12,172	0.120	7.75 (3.238, 0.086, 0.017*)
AD[b] symptom non-remission*	0.05	0.077	3.29 (2.162)	0.129	10,728	0.433	2.41 (2.088, 0.074, 0.25)
AD percentage symptom improvement*	0.3	0.074	−2.17 (1.973)	0.271	42265	0.731	−1.35 (1.98, 0.072, 0.495)

All null model *p* values were 0.0721 for the whole sample, and 0.0746 for the European sample. *indicates nominally significant p value (i.e., $p < 0.05$). **P*-value threshold search range was limited to (1e−4, 1e−3, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5) due to the very low number of SNPs in some of the lower thresholds in the defined search range as per our "Data analysis" section.
[a]Definition of all columns: P_t best *P* value Threshold, *PRS.R2.adj* adjusted PRS R^2, *Full.R2* full model R^2, *P p* value estimated from *t* distribution, *N SNPs* number of SNPs in PRS, *Empirical P p* values estimated from an empirical 10,000 permutations.
[b]Antidepressant.

between symptom remission and PRSs for the other traits (i.e., MDD (excluding the 23andme cohort), schizophrenia, bipolar disorder, neuroticism, general intelligence, antidepressant non-remission and percentage symptom improvement), nominal associations were detected with the PRS for bipolar disorder (OR = 0.75 [0.58, 0.97], $p = 0.031$) in the whole IRL-GRey sample. Results from the PRSs association tests with remission status in the whole sample and the European subsample are reported in Tables 3 and S2, respectively.

Percentage symptom improvement. Our secondary outcome, percentage symptom improvement, also showed a nominal association with PRS for ADHD in the whole sample (beta = −5.07 [SE = 1.97], $p = 0.011$) as well as in the European subsample (beta = −5.43 [SE = 2.069], $p = 0.048$). Percentage symptom improvement was nominally associated with PRS for general intelligence (beta = 6.81 [SE = 3.12], $p = 0.03$) in the whole sample. Moreover, and consistent with the findings from the remission outcome, we found a nominal association between PRS for bipolar disorder with percentage symptom improvement (beta = 4.27 [SE = 2.171], $p = 0.049$) in the whole sample. Figure 1 shows bar plots and scatter plots of the distribution of the top PRSs from our analysis (i.e., ADHD: $P_t = 1e{-}06$; bipolar disorder: $P_t = 0.01$ and general intelligence: $P_t = 1$ and 0.01) with remission status, biological sex and percentage symptom improvement in the whole IRL-GRey sample. Results from the PRSs association tests with percentage symptom improvement in the whole sample and the European subsample are reported in Tables 4 and S3, respectively.

In both outcomes, i.e., remission status and percentage symptom improvement, no test (or permutation test) survived the multiple testing correction, see Tables 3, 4 and S2, S3.

PRS-PCA. In the last column of Tables 3, 4 and S2, S3 we report the association of both symptom remission and percentage symptom improvement with the PRSs for the eight traits of interest. Although no association survived the multiple testing correction, there was nominal association observed between PRS for general intelligence and symptom improvement in the whole IRL-GRey sample (beta = 7.75 [SE = 3.24], $p = 0.017$).

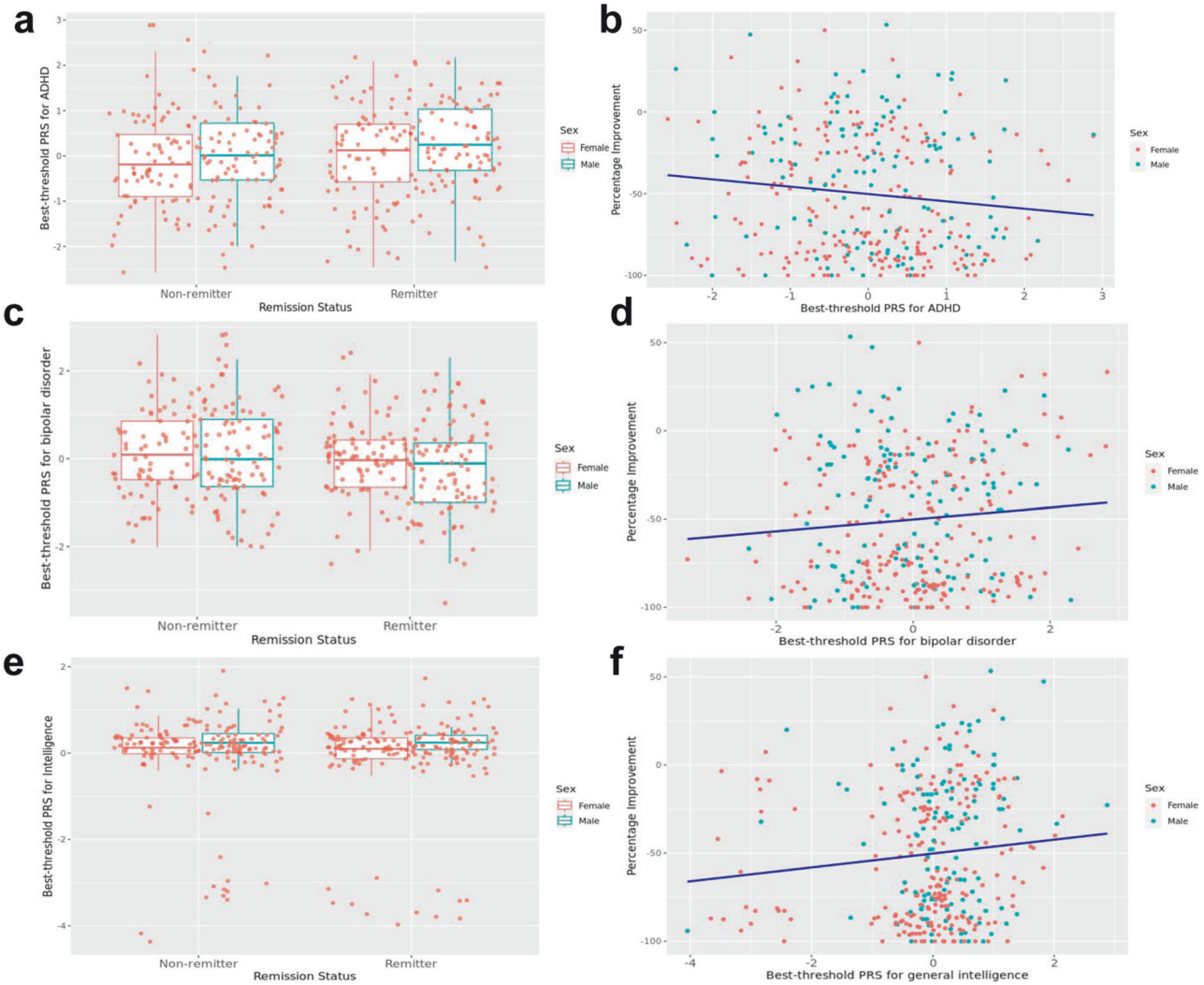

Fig. 1 Distribution of top PRS findings accross remission status and symptom percentage improvement. Bar plots and scatter plots visualizing the distribution of; biological sex and PRS for ADHD ($P_t = 1e{-}06$) with **a** remission status and **b** percentage symptom improvement; biological sex and PRS for bipolar disorder ($P_t = 0.01$) with **c** remission status and **d** percentage symptom improvement; biological sex and PRS for intelligence with **e** remission status ($P_t = 1$) and **f** percentage symptom improvement ($P_t = 0.01$) in the whole IRL-GRey sample. A better symptom improvement corresponds to a negative and higher value of the Percentage Symptom Improvement variable.

DISCUSSION

To the best of our knowledge, this is the first study investigating the association between PRSs for psychiatric disorders and related non-psychiatric traits with antidepressant remission and percentage symptom improvement in LLD. Particularly, we were interested in validating previous studies reporting associations between PRS for various psychiatric phenotypes (e.g., ADHD, MDD and schizophrenia) and failure to respond to antidepressants [13, 14] in a sample of older adults with LLD. Our results indicate that PRS for ADHD is nominally (i.e., $p \leq 0.05$) and positively associated with symptom remission and percentage improvement after venlafaxine treatment. This finding is in contrast to the finding by Fabbri et al. [14] who reported a significant association with PRS for ADHD and treatment-resistant depression. However, and in accordance with the investigations conducted by Li et al. [37], our study has revealed a nominal yet positively correlated association between PRS for ADHD and symptoms percentage improvement.

Possible reasons for discrepancies in the direction of effect of the PRS for ADHD associations between our findings and that reported by Fabbri et al. [14] include; 1) Differences in defining the outcomes between the two studies. Although both studies focused on pharmacological treatment of depression, our study defined remission/non-remission in individuals treated with venlafaxine as the outcome, while the study by Fabbri et al. used TRD as an outcome and was defined as two or more switches between any antidepressants in routine depression care; 2) the dataset used by our study were obtained from an interventional clinical trial (i.e., IRL-GRey) [38] and are well-characterized with inclusion/exclusion criteria, while Fabbri et al. used datasets from the UK Biobank and used their prescribing records to define TRD; 3) our study targeted older adults with depression which is often accompanied by drug metabolism changes, medical comorbidity, and polypharmacy as compared to adults in the UK Biobank cohort (average age at first antidepressant prescription is 48.4 and 44.17, respectively); 4) adherence to treatment is associated with age, patient-professional relationship, previous experiences and other socioeconomic factors, all these factors could be different between the two samples (i.e., our LLD sample versus the UK Biobank cohort). Specifically, it was shown that adherence to antidepressants is predictive of treatment response in middle-aged and older adults [39], with older patients tending to have a better adherence to treatment [40].

We then conducted PRS analyses for other psychiatric traits including MDD, schizophrenia and bipolar disorder, antidepressant treatment outcomes as well as non-psychiatric traits including neuroticism and general intelligence with symptom remission and percentage symptom improvement.

Our study provided further insight into the genetic basis of antidepressant response in the older adult population. We show that PRS for general intelligence is positively associated with percentage improvement (i.e., with worse treatment response), however, this finding was not significant in the European-only analyses. Of note, these findings are in the opposite direction of the previously reported association in MDD sample between PRS for intelligence and TRD, which used the same discovery sample [14]. Additionally, our findings for remission (although not significant) suggest higher PRS for intelligence as a risk factor for non-remission. Both findings appear counterintuitive, and are in the opposite direction as in the study by Fabbri et al. reporting that PRS for intelligence was nominally associated with a reduced risk of treatment-resistant depression [14].

A major strength in the presented study is the well-defined target sample of older adults from the IRL-GRey clinical trial [38]. This work also has some limitations. Although (computationally) we managed to estimated genetic correlation between outcomes in our sample (i.e., symptom remission and percentage symptom improvement) and other traits, these estimates are not well-powered due to our limited sample size [41] (we did not report these underpowered estimates). Given the low sample size, we were unable to estimate genetic heritability for remission or percentage symptom improvement. Therefore, heritability estimation and genetic correlation in a larger sample of older adults remains one of our future goals [41]. Our target sample size was relatively small and mostly European, which did not allow us to run PRS analyses in the remaining diverse group of various ancestries (i.e., Asians and Africans). These ancestries were also limited by the availability of corresponding summary statistics. Furthermore, we noticed instability in our results when using different approaches to calculate PRS.

In summary, we were prompted to validate a reported association (in adults) between PRS for ADHD and failure to respond to antidepressants in our LLD sample. Our results indicate that PRS for ADHD is nominally associated with remission after venlafaxine treatment. However, we found the association in the opposite direction as expected, which might be due to the higher age range and higher comorbidities in our sample. We also highlighted a positive nominal association between PRS for bipolar disorder and intelligence with our measure of antidepressant response. Our findings however, did not survive the multiple testing correction. Altogether, our findings warrant further replication in larger samples of older adults with depression.

DATA AVAILABILITY

The GWAS summary statistics for the psychiatric disorders used in this analysis are publicly available from: the Psychiatric Genomics Consortium; https://www.med.unc.edu/pgc/download-results/, and the GWAS Catalogue; https://www.ebi.ac.uk/gwas.

CODE AVAILABILITY

To obtain the results presented here, we mostly followed the tutorials and general usage available from PLINK 2.0 alpha; https://www.cog-genomics.org/plink/2.0/, PRSice-2; https://choishingwan.github.io/PRS-Tutorial/.

REFERENCES

1. Institute of Health Metrics and Evaluation. Global Health Data Exchange (GHDx). Institute for Health Metrics and Evaluation, Seattle, Washington: University of Washington; 2019. http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/d780dffbe8a381b25e1416884959e88b.
2. The World Health Organization (WHO). Depression. 2022. https://www.who.int/news-room/fact-sheets/detail/depression.
3. Paolucci S. Epidemiology and treatment of post-stroke depression. Neuropsychiatr Dis Treat. 2008;4:145–54.
4. Alexopoulos GS. "Vascular Depression" hypothesis. Arch Gen Psychiatry. 1997;54:915. https://doi.org/10.1001/archpsyc.1997.01830220033006.
5. Davydow DS, Levine DA, Zivin K, Katon WJ, Langa KM. The association of depression, cognitive impairment without dementia, and dementia with risk of ischemic stroke: a cohort study. Psychosom Med. 2015;77:200–8.
6. Tiwari AK, Zai CC, Altar CA, Tanner JA, Davies PE, Traxler P, et al. Clinical utility of combinatorial pharmacogenomic testing in depression: a Canadian patient- and rater-blinded, randomized, controlled trial. Transl Psychiatry. 2022;12:101.
7. Murphy LE, Fonseka TM, Bousman CA, Müller DJ. Gene-drug pairings for antidepressants and antipsychotics: level of evidence and clinical application. Mol Psychiatry. 2021. https://doi.org/10.1038/s41380-021-01340-6.
8. Marshe VS, Islam F, Maciukiewicz M, Bousman C, Eyre HA, Lavretsky H, et al. Pharmacogenetic implications for antidepressant pharmacotherapy in late-life depression: a systematic review of the literature for response, pharmacokinetics and adverse drug reactions. Am J Geriatr Psychiatry. 2020;28:609–29.
9. Meerman JJ, Ter Hark SE, Janzing JGE, Coenen MJH. The potential of polygenic risk scores to predict antidepressant treatment response in major depression: a systematic review. J Affect Disord. 2022;304:1–11.
10. Amare AT, Schubert KO, Tekola-Ayele F, Hsu YH, Sangkuhl K, Jenkins G, et al. Association of the polygenic scores for personality traits and response to selective serotonin reuptake inhibitors in patients with major depressive disorder. Front Psychiatry. 2018;9:65.
11. Amare AT, Schubert KO, Tekola-Ayele F, Hsu YH, Sangkuhl K, Jenkins G, et al. The association of obesity and coronary artery disease genes with response to SSRIs treatment in major depression. J Neural Transm. 2019;126:35–45.
12. Marshe VS, Maciukiewicz M, Hauschild AC, Islam F, Qin L, Tiwari AK, et al. Genome-wide analysis suggests the importance of vascular processes and neuroinflammation in late-life antidepressant response. Transl Psychiatry. 2021;11:127.
13. Pain O, Hodgson K, Trubetskoy V, Ripke S, Marshe VS, Adams MJ, et al. Identifying the common genetic basis of antidepressant response. Biol Psychiatry Glob Open Sci. 2022;2:115–26.
14. Fabbri C, Hagenaars SP, John C, Williams AT, Shrine N, Moles L, et al. Genetic and clinical characteristics of treatment-resistant depression using primary care records in two UK cohorts. Mol Psychiatry. 2021;26:3363–73.
15. Tansey KE, Guipponi M, Hu X, Domenici E, Lewis G, Malafosse A, et al. Contribution of common genetic variants to antidepressant response. Biol Psychiatry. 2013;73:679–82.
16. Biobank UK. UK Biobank Primary Care Linked Data. Version 1.0. 2019.
17. John C, Reeve NF, Free RC, Williams AT, Ntalla I, Farmaki AE, et al. Cohort profile: extended cohort for E-health, Environment and DNA (EXCEED). Int J Epidemiol. 2019;48:1734.
18. Incomplete Response in Late Life Depression: Getting to Remission (IRL GREY)—Full Text View—ClinicalTrials.Gov [Internet]. 2022. https://clinicaltrials.gov/ct2/show/NCT00892047.
19. Lenze EJ, Mulsant BH, Blumberger DM, Karp JF, Newcomer JW, Anderson SJ, et al. Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomised, double-blind, placebo-controlled trial. Lancet. 2015;386:2404–12.
20. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet. 2019;51:63–75.
21. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet. 2018;50:668–81.
22. Trubetskoy V, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature 2022;604:502–8.
23. Jones L, Gordon-Smith K, Perry A. Genome-wide association study of over 40,000 bipolar disorder cases provides novel biological insights. Nat Genet. 2021. http://eprints.worc.ac.uk/10304/.
24. van den Berg SM, de Moor MHM, McGue M, Pettersson E, Terracciano A, Verweij KJH, et al. Harmonization of neuroticism and extraversion phenotypes across inventories and cohorts in the Genetics of Personality Consortium: an application of Item Response Theory. Behav Genet. 2014;44:295–313.
25. Savage JE, Jansen PR, Stringer S, Watanabe K, Bryois J, de Leeuw CA, et al. Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. Nat Genet. 2018;50:912–9.
26. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382–9.
27. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. Gigascience. 2015;4:7.

28. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS Genet. 2009;5:e1000529.
29. Lemieux Perreault LP, Legault MA, Asselin G, Dubé MP. genipe: an automated genome-wide imputation pipeline with automatic reporting and statistical tools. Bioinformatics. 2016;32:3661–3.
30. van Leeuwen EM, Kanterakis A, Deelen P, Kattenberg MV, Genome of the Netherlands Consortium, Slagboom PE, et al. Population-specific genotype imputations using minimac or IMPUTE2. Nat Protoc. 2015;10:1285–96.
31. Consortium GP, Auton A, Brooks LD, Durbin RM. A global reference for human genetic variation. Nature. 2015;526:68–74.
32. Loh PR, Danecek P, Palamara PF, Fuchsberger C. Reference-based phasing using the Haplotype Reference Consortium panel. Nature. 2016. https://idp.nature.com/authorize/casa?redirect_uri=https://www.nature.com/articles/ng.3679.pdf%3Forigin%3Dppub&casa_token=K0H1LVsq2l4AAAAA:5T4wwiAwm5ddV2nDaJVlMertO95YFB-xYJv6-0WE-kmhZOAZWgDXQWo9d6J1NT1HqCmXqeP7Pbt78pCFPEXg.
33. Choi SW, O'Reilly PF. PRSice-2: Polygenic Risk Score software for biobank-scale data. Gigascience. 2019;8. https://doi.org/10.1093/gigascience/giz082.
34. Coombes BJ, Ploner A, Bergen SE, Biernacka JM. A principal component approach to improve association testing with polygenic risk scores. Genet Epidemiol. 2020;44:676–86.
35. Nyholt DR. A simple correction for multiple testing for single-nucleotide polymorphisms in linkage disequilibrium with each other. Am J Hum Genet. 2004;74:765–9.
36. Cinar O, Viechtbauer W. The poolr package for combining independent and dependent p values. J Stat Softw. 2022. http://statistik-jstat.uibk.ac.at/article/view/v101i01.
37. Li QS, Wajs E, Ochs-Ross R, Singh J, Drevets WC. Genome-wide association study and polygenic risk score analysis of esketamine treatment response. Sci Rep. 2020;10:12649.
38. Incomplete Response in Late Life Depression: Getting to Remission (IRL GREY)—Study Results—ClinicalTrials.gov. 2022. https://clinicaltrials.gov/ct2/show/results/NCT00892047?view=results.
39. Sirey JA, Woods A, Solomonov N, Evans L, Banerjee S, Zanotti P, et al. Treatment adequacy and adherence as predictors of depression response in primary care. Am J Geriatr Psychiatry. 2020;28:1164–71.
40. Hung CI. Factors predicting adherence to antidepressant treatment. Curr Opin Psychiatry. 2014;27:344–9.
41. Zheng J, Erzurumluoglu AM, Elsworth BL, Kemp JP, Howe L, Haycock PC, et al. LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. Bioinformatics. 2017;33:272–9.

ACKNOWLEDGEMENTS

This work was supported by funding from (1) CIHR #; (2) funding from CANSSI Ontario: Trainee SSME is a fellow of STAGE (Strategic Training for Advanced Genetic Epidemiology); (3) the CAMH Discovery Fund Postdoctoral Fellowship supporting SSME; (4) Temerty-Tanz-TDRA Research Fellowships supporting SSME. Computations were performed on the CAMH Specialized Computing Cluster (SCC). The SCC is funded by: The Canada Foundation for Innovation, Research Hospital Fund.

AUTHOR CONTRIBUTIONS

The study was conceptualized by Samar S. M. Elsheikh (SSME) and Daniel J. Müller (DM). The methodology was designed by SSME, DM and Victoria S. Marshe (VM). Formal analysis of the data was performed by SSME. The manuscript was drafted by SSME. Comprehensive reviewing and editing of the manuscript were carried out by all authors.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41397-024-00351-0.

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