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.

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

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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 nonpsychiatric (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 $(P_t = 0.2, \text{ OR} = 1.05 [1.04-1.14], P = 4.38e-04)$, 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.

Phenoty	/pe	Sample size	SNPs	Ethnicity	Authors	Source	Year
Table 1.	Discovery sample used to	construct polygenic risk	scores an	d obtained from	previous and pu	blicly available GWAS summary st	atistics.

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

^aAttention-deficit/hyperactivity disorder.

^bDenmark, European, North American and Chinese cohorts.

^dSummary statistics excluding the 23andme cohort.

^eEuropeans and East Asian.

^fGenetics of Personality Consortium.

^gGWAS Catalog.

^hAntidepressant.

^cPsychiatric Genomics Consortium.

Table 2.	Summary of demogra	phic characteristics and MADRS	change by remission status in	the complete IRL-GRey sample ($N = 342$).
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	Non remitters (N = 167)		Remitters (N = 175)	Total (<i>N</i> = 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)	-

^aBL MADRS, Montgomery-Åsberg Depression Rating Scale (MADRS) score at baseline.

^bEnd MADRS, score at week 12.

^cImprovement, 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 $\ge 5\%$ 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 guality 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

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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 $p \le 0.05$) 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 the	resholding	PRS-PCA				
Statistics ^a	Pt	Full.R ²	Р	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.

^aDefinition of all columns: *P*_t best *P* value threshold, *PRS.R*² PRS R², *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.

^bAntidepressant.

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

Method	PRSice the	resholding	method		PRS-PCA		
Statistics ^a	Pt	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.

^aDefinition 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. ^bAntidepressant.

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., $p \le 0.05$) 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].

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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 wellpowered 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/.

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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

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