Original Article

*Joint senior author; these authors made similar contributions.

Cite this article: Rodriguez V et al (2023). Use of multiple polygenic risk scores for distinguishing schizophrenia-spectrum disorder and affective psychosis categories in a first-episode sample; the EU-GEI study. Psychological Medicine 53, 3396–3405. https://doi.org/10.1017/S0033291721005456

Received: 12 July 2021
Revised: 5 December 2021
Accepted: 15 December 2021
First published online: 25 January 2022

Keywords:
Affective psychosis; bipolar disorder; diagnosis; genetics; polygenic score; psychosis; psychotic depression; schizophrenia-spectrum disorder

Author for correspondence:
Victoria Rodriguez,
E-mail: victoria.1.rodriguez@kcl.ac.uk

Abstract

Background. Schizophrenia (SZ), bipolar disorder (BD) and depression (D) run in families. This susceptibility is partly due to hundreds or thousands of common genetic variants, each conferring a fractional risk. The cumulative effects of the associated variants can be summarised as a polygenic risk score (PRS). Using data from the European Network of national schizophrenia networks studying Gene-Environment Interactions (EU-GEI) first episode case–control study, we aimed to test whether PRSs for three major psychiatric disorders (SZ, BD, D) and for intelligent quotient (IQ) as a neurodevelopmental proxy, can discriminate affective psychosis (AP) from schizophrenia-spectrum disorder (SSD).

Methods. Participants (842 cases, 1284 controls) from 16 European EU-GEI sites were successfully genotyped following standard quality control procedures. The sample was stratified based on genomic ancestry and analyses were done only on the subsample representing the European population (573 cases, 1005 controls). Using PRS for SZ, BD, D, and IQ built from the latest available summary statistics, we performed simple or multinomial logistic regression models adjusted for 10 principal components for the different clinical comparisons.

Results. In case–control comparisons PRS-SZ, PRS-BD and PRS-D distributed differentially across psychotic subcategories. In case–case comparisons, both PRS-SZ [odds ratio (OR) = 0.7, 95% confidence interval (CI) 0.54–0.92] and PRS-D (OR = 1.31, 95% CI 1.06–1.61) differentiated AP from SSD; and within AP categories, only PRS-SZ differentiated BD from psychotic depression (OR = 2.14, 95% CI 1.23–3.74).

Conclusions. Combining PRS for severe psychiatric disorders in prediction models for psychosis phenotypes can increase discriminative ability and improve our understanding of these phenotypes. Our results point towards the potential usefulness of PRSs in specific populations such as high-risk or early psychosis phases.

Introduction

More than 100 years have passed since Kraepelin established the dichotomy of manic-depression and dementia praecox as the two fundamental pillars of psychotic illness, which still constitutes the basis of current diagnostic criteria (Kraepelin, 1899). However, it is a matter of debate whether schizophrenia (SZ) and bipolar disorder (BD) are discrete illnesses or conditions which are part of an overall conceptual continuum (Craddock & Owen, 2010; Demjaha, MacCabe, & Murray, 2012; Murray et al., 2004). Given the high heritability of these disorders (Smoller et al., 2019), genetic tools can be used to dissect possible biological differences between these diagnostic categories.

Genome-Wide Association Studies (GWAS) have shown that, as with other psychiatric conditions, many hundreds or thousands of common alleles influence susceptibility to SZ and BD (Ripke et al., 2013; Stahl et al., 2019). We can calculate individual polygenic risk scores...
GWAS according to their nucleotide polymorphisms (SNPs) selected in a discovery (PRS) based on the summation of the carried risk of single genetic variants.

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Corvin, & Walters, 2014), 18.2% (Stahl et al., 2019), and 8.5% (Wray et al., 2018) respectively.

In line with the previous family and twin studies (Cardno & Owen, 2014; Cardno, Rijssijk, Sham, Murray, & McGuffin, 2002; Craddock & Owen, 2005), GWAS findings have also supported the notion of genetic overlap among severe mental disorders. A study from the Cross-Disorder Group of PGC (Lee et al., 2019) showed genetic correlation using common SNPs, of around 0.70 between SZ and BD, 0.34 between SZ and MDD, and 0.36 between BD and MDD.

On the other hand, some studies provide support for a link between genetic predisposition and current diagnostic categories. A study investigating diagnostic subcategories across the psychosis spectrum employing PRS-SZ and PRS-BD (Tesli et al., 2014) provided some validation for the existence of subcategories across the SZ and BD continuum. In line with this, in a more recent study, PRS for SZ discriminated SZ from BD; and within BD cases, between those with and without psychosis (Allardyc et al., 2017). Moreover, Markota et al. (Markota et al. 2018), found that PRS-SZ seemed to be more closely related with bipolar disorder type I (BD-I) with psychotic symptoms during manic phases as compared with BD-I with psychotic symptoms during depressive episodes or those without psychosis. Taken together, these findings shed light on the genetic architecture of these severe mental disorders and support the discriminability potential of the polygenic score on diagnostic categories.

To the best of our knowledge, only one study has previously examined the relationship between different diagnostic categories by employing three polygenic scores, specifically PRS-SZ, PRS-BD and PRS-MDD (Charney et al., 2017), but only examined cases within the BD spectrum. They found a PRS-SZ gradient among affective psychotic categories, with the highest association being schizoaffective followed by BD-I and BD type II (BD-II).

Consistent evidence suggests that cognitive deficits can be considered a core feature for SZ (Green, 2006). It has been long accepted that subjects affected by SZ perform worse than those with BD on a variety of cognitive domains (Goldberg, 1999; Zanelli et al., 2010), and this has been validated by a meta-analysis showing that subjects with BD show better cognitive performance than those with SZ (Krabbendam, Arts, van Os, & Aleman, 2005). Although there remains debate over the extent to which these differences in cognition predate or follow the onset of psychosis (Trotta, Murray, & Maccabe, 2015), it is important to include genetic differences in cognitive ability and intelligence in models aiming to differentiate subgroups of patients with psychosis.

Given the above, this study aims to explore the potential of joint modelling PRS from three major mental disorders (SZ, BD, D) and intelligence quotient (IQ) for discriminating affective psychosis (AP) from schizophrenia-spectrum disorder (SSD). We built on a previous study from South London, where we have shown that PRS-SZ differentiated SZ from other psychoses (Vassos et al., 2017).

Methods
Sample
The present study is based on the case–control sample from the (EUropean Network of national schizophrenia networks studying Gene-Environment Interactions) EU-GEI study; a multisite incidence and case–control study of genetic and environmental determinants involved in the development of psychotic disorders (Gayer-Anderson et al., 2020).

The baseline sample comprises a total of 2627 participants, including 1130 patients aged 18 to 64 years who were resident within the study areas and presented to the adult psychiatric services between 1 May 2010 and 1 April 2015 in 17 sites across 6 countries: England, the Netherlands, Italy, France, Spain and Brazil. All participants provided informed, written consent. Ethical approval was provided by relevant research ethics committees in each of the study sites. All data were stored anonymously.

Cases were selected if they were experiencing their first episode of psychosis (FEP) including SZ and related psychosis, BD and Major Depression Disorder with Psychotic features (MDD-P). In addition, 1497 unaffected screened controls with no lifetime psychotic disorder were also recruited in the areas served by the services with a quota sampling approach, a non-probability sampling method in which a specific subgroup is chosen in order to represent the local population. Details on recruitment of the sample are provided in online Supplementary Material; and further information about the methodology of the study is available on the EU-GEI website (http://www.eu-gei.eu/) and can be found in previous publications (Di Forti et al., 2019; Gayer-Anderson et al., 2020; Jongsm, Gayer-Anderson, Lasalvia, Quattrone, & Mulè, 2018; Quattrone et al., 2018).

One of the problems when using current PRS is the limited predictive power in multi-ethnic samples as they have derived from mostly European samples (Curtis, 2018). This has been shown in a previous study on FEP patients (Vassos et al., 2017), where PRS-SZ had much lower predictive power in the African ancestry population. Given the wide variance across ancestral groups, for the scope of the present study, we constrained the sample to those categorised as of European ancestry based on PCA (details provided in online Supplementary Material). Characteristics of the final sample are summarised in Table 1.

Measures
Socio-demographics
Socio-demographic data were collected using the Medical Research Council (MRC) Socio-demographic Schedule modified version (Mallett, Leff, Bhugra, Pang, & Zhao, 2002), and supplemented by clinical records, with additional information on educational attainment and social functioning measured through employment, marital and living status.

Diagnosis
We used DSM-IV diagnosis(American Psychiatric Association, 1994) from interviews and mental health records utilising the Operational Criteria Checklist (OPCRIT) at baseline (McGuffin, Farmer, & Harvey, 1991) by centrally trained investigators, whose reliability was assessed throughout the study (κ = 0.7). These diagnoses were grouped into SSD group (codes 295.1–295.9 and 297.1–298.9) or AP group (patients diagnosed with codes 296–296.9), which was later stratified into BD (codes 296.0–296.06 and 298.9) or AP group (patients diagnosed with codes 296–296.9), which was later stratified into BD (codes 296.0–296.06 and 298.9).
and the selected GWAS (Savage et al., 2018). All PRS were built using PRSice software (Howard et al., 2019; Ripke et al., 2014; Stahl et al., 2019), built from a GWAS combining PGC, 23andMe and UK Biobank groups (i.e. undefined diagnosis) were not grouped into either of the groups (n = 52) and were excluded from further analyses.

Genotyping and PRS building

All participants were invited to provide a genetic sample. DNA from blood tests or saliva samples was obtained from the majority of participants at baseline (73.6% of cases and 78.5% of controls), with no sociodemographic differences observed between those without genetic data except for minor age differences (please refer to the online Supplementary section 1.7). All DNA data collected were genotyped at the Cardiff University Institute of Psychological Medicine and Clinical Neurology, using a custom Illumina HumanCoreExome-24 BeadChip genotyping array covering 570 038 genetic variants; and quality control was performed locally (details provided in online Supplementary Material).

In order to control for population stratification, a Principal Component Analysis generating 10 principal components (PC) was run on pruned variants. After quality control of genetic and clinical data, and selection of individuals of European ancestry (details provided in online Supplementary Material), the genetic analyses included 573 cases (409 SSD, 74 BD and 90 MDD-P patients) and 1005 controls.

The measure of the aggregate genetic load is based on a PRS, which is an individual quantitative risk factor calculated from the weighted summation of the odds ratios of carried risk alleles taken which is an individual quantitative risk factor calculated from the weighted summation of the odds ratios of carried risk alleles taken from a discovery sample. It is represented by the following equation (Evans, Visscher, & Wray, 2009):

$$\text{PRS} = \sum x_i \times \log(OR_i)$$

where $x_i$ is the number of risk alleles of each included variant (i) and OR the respective odds ratio. To build the PRSs, results from the latest available GWAS which did not include the current EU-GEI sample, were used as discovery samples. In the case of SZ and BD, these were derived from the last mega-analyses of the PGC (Ripke et al., 2014; Stahl et al., 2019). Depression PRS was built from a GWAS combining PGC, 23andMe and UK Biobank samples (Howard et al., 2019; Ripke et al., 2014; Stahl et al., 2019). Finally, we further included PRS for IQ based on a large GWAS (Savage et al., 2018). All PRS were built using PRSice software (Choi & O’Reilly, 2019) at 10 different $p$ value thresholds, and the selected $p$ value threshold of 0.05 for SNP inclusion was chosen across the phenotypes on the basis of the published literature explaining the most variance in case-control analysis (Howard et al., 2019; Savage et al., 2018; Stahl et al., 2019; Wray et al., 2018). Each PRS was standardised to a mean of zero and a standard deviation of 1 (Lewis & Vassos, 2017). Variance explained in our sample at the different $p$-value thresholds are provided in online Supplementary Material (eFig. 1).

Results

Socio-demographics

Socio-demographics of the case–control sample are shown in Table 1, comparing SSD (n = 409) and AP (n = 164) with controls (n = 1005) separately. Compared with controls, patients were younger (mean age of 31.6, s.d. = 10.91 and 32.84, s.d. = 11.56 in SSD and AP respectively; 36.9, s.d. = 13 in controls); and a greater proportion of patients with SSD were men (68% v. 47%). Both SSD and AP were less likely to have received tertiary education and consequently reported fewer total years of education than controls (around over 12.5 years in cases and around 14.7 years for controls). Generally, cases were more likely not to be in a relationship and not to live independently. More SSD patients were unemployed, but no differences between AP and controls were found. Sociodemographic differences between clinical groups are provided in online Supplementary Material (eTable 3).

PRS distribution in different clinical subgroups

In the direct comparison between AP and SSD, both PRS-SZ and PRS-D were significantly associated with these diagnoses but in...
Table 1. Sociodemographic of European subsample (n = 1659), case-control comparisons

<table>
<thead>
<tr>
<th>Descriptive at baseline</th>
<th>Number (%)/Mean (s.d.)</th>
<th>Statistics</th>
<th>Number (%)/Mean (s.d.)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong> n = 1005</td>
<td><strong>Schizophrenia-spectrum disorder</strong> n = 409</td>
<td><strong>Tests (df)</strong></td>
<td><strong>p value</strong></td>
<td><strong>Affective psychosis</strong> n = 164</td>
</tr>
<tr>
<td>Gender</td>
<td>X² (1) = 50.54 &lt;0.001</td>
<td></td>
<td>X² (1) = 0.67 0.413</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>474 (47.2) 278 (68)</td>
<td></td>
<td>83 (50.6)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>531 (52.8) 131 (32)</td>
<td></td>
<td>81 (49.4)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.9 (13) 31.6 (10.92)</td>
<td>Z = 7.21 &lt;0.001</td>
<td>32.84 (11.56)</td>
<td>Z = -3.76 &lt;0.001</td>
</tr>
<tr>
<td>Ever used Cannabis</td>
<td>X² (1) = 40.26 &lt;0.001</td>
<td></td>
<td>X² (1) = 15.9 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>528 (53) 136 (34.2)</td>
<td></td>
<td>58 (36)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>469 (47) 262 (65.8)</td>
<td>&lt;0.001</td>
<td>103 (64)</td>
<td></td>
</tr>
<tr>
<td>Education level</td>
<td>X² (2) = 81.22</td>
<td></td>
<td>X² (2) = 51.64 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>No qualification</td>
<td>40 (4) 65 (16.1)</td>
<td></td>
<td>25 (15.3)</td>
<td></td>
</tr>
<tr>
<td>School education</td>
<td>416 (41.5) 197 (48.6)</td>
<td></td>
<td>87 (53.4)</td>
<td></td>
</tr>
<tr>
<td>Tertiary education</td>
<td>546 (54.5) 143 (35.3)</td>
<td>&lt;0.001</td>
<td>51 (31.3)</td>
<td></td>
</tr>
<tr>
<td>Years in education</td>
<td>14.69 (4.19) 12.94 (4.12)</td>
<td>Z = 7.07 &lt;0.001</td>
<td>12.58 (3.84)</td>
<td>Z = 5.92 &lt;0.001</td>
</tr>
<tr>
<td>Social functioning</td>
<td>X² (1) = 25.26 &lt;0.001</td>
<td></td>
<td>X² (1) = 0.48 0.487</td>
<td></td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td>X² (1) = 11.42 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>615 (61.6) 141 (45.5)</td>
<td></td>
<td>56 (41.5)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>383 (38.4) 169 (54.5)</td>
<td></td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td>X² (1) = 126.23 &lt;0.001</td>
<td></td>
<td>X² (1) = 11.42 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Steady relationship</td>
<td>626 (62.4) 105 (28.3)</td>
<td></td>
<td>74 (48.1)</td>
<td></td>
</tr>
<tr>
<td>No relationship</td>
<td>378 (37.7) 266 (71.7)</td>
<td></td>
<td>80 (52)</td>
<td></td>
</tr>
<tr>
<td>Living arrangements</td>
<td>X² (1) = 96.98 &lt;0.001</td>
<td></td>
<td>X² (1) = 11.85 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Independent living</td>
<td>683 (68.5) 119 (37.5)</td>
<td></td>
<td>73 (53.7)</td>
<td></td>
</tr>
<tr>
<td>No independent living</td>
<td>314 (31.5) 198 (62.5)</td>
<td></td>
<td>63 (46.3)</td>
<td></td>
</tr>
</tbody>
</table>

s.d., standard deviation; df, degrees of freedom.
opposite directions (Fig. 1a). Whereas PRS-D (OR = 1.31, 95% CI 1.06–1.61, p = 0.011) was associated with increased risk of AP compared with SSD, the opposite was observed for PRS-SZ (OR = 0.7, 95% CI 0.54–0.92, p = 0.010). Hence, individuals with high PRS-SZ and low PRS-D have more chances of receiving a diagnosis of SSD, while low PRS-SZ and high PRS-D increases the chances of AP.

Regarding case–control comparisons with clinical subgroups, the first multinomial logistic regression showed that higher scores on both PRS-SZ and PRS-BD were associated with SSD (OR = 1.87, 95% CI 1.57–2.2, p < 0.001 and OR = 1.34, 95% CI 1.15–1.57, p < 0.001 respectively), whereas positive associations with AP were found for PRS-BD and PRS-D (OR = 1.35, 95% CI 1.09–1.67, p = 0.006 and OR = 1.37, 95% CI 1.14–1.64, p = 0.001 respectively). These effects are shown in Fig. 1a with additional details given in online Supplementary Material (eTable 4 and eFig. 2).

**PRS distribution between diagnostic categories within psychosis**

In the second multinomial logistic regression, we tested whether PRSs could differentiate the two diagnostic categories included in AP (BD and MDD-P) from the broad group of SSD. As shown in Fig. 1b, no PRS was able to distinguish BD when compared with SSD. Nonetheless, the patterns for SSD and MDD-P diagnoses followed those observed above for SSD and broader AP comparisons. Thus, SSD and MDD-P diagnoses were differentiated by both PRS-SZ (OR = 0.52, 95% CI 0.37–0.74, p = 0.011) and PRS-D (OR = 1.49, 95% CI 1.14–1.94, p = 0.003) in the opposite direction. Further details are given in the online Supplementary Material (eTable 5).

When running simple logistic regression for discriminability between BD and MDD-P, only PRS-SZ could discriminate people diagnosed with BD from those diagnosed with MDD-P (OR = 2.14, 95% CI 1.23–3.74, p = 0.007) showing a positive association with the former.

**Fitting the model optimising PRS for SSD and AP discrimination**

In order to test which combination of PRSs better-differentiated SSD and AP as our main outcome, we built a series of regression models starting with a baseline model including PRS-SZ with covariates and sequentially adding the other three PRSs variables, models starting with a baseline model including PRS-SZ with covariates and sequentially adding the other three PRSs variables, models starting with a baseline model including PRS-SZ with covariates and sequentially adding the other three PRSs variables, models starting with a baseline model including PRS-SZ with covariates and sequentially adding the other three PRSs variables, and sequentially adding the other three PRSs variables.

**Interpretation of findings and comparison with other studies**

The observed PRS-SZ associations which followed a gradient from SSD to AP categories (SSD > BD > MDD-P), are in line with the notion of a psychosis continuum across psychosis diagnostic categories and the observed genetic overlap between disorders (Cardno & Owen, 2014). Other studies have previously shown a similar PRS-SZ gradient (SZ > BD type I > BD type II) (Allardyce et al., 2017; Charney et al., 2017). However, PRS-SZ could not differentiate MDD-P from controls in our study. In a recent study, PRS-SZ seemed to be specially associated with those presenting psychotic features in the mania phase when compared with the depressive pole (Markota et al., 2018), which could explain our lack of association with MDD-P.

Previous research showed evidence of PRS for major depression (MDD) discriminated cases with depression from controls (Wray et al., 2018). Moreover, PRS for MDD failed to identify diagnostic subtypes in some case-only comparisons in BD (Charney et al., 2017), but seemed to be significantly associated with schizoaffective disorder depressed subtype when compared with SZ cases (Dennison et al., 2020). In our study, PRS-D differentiated psychotic depression from both controls and SSD, showing similar effect sizes as PRS-SZ in opposite direction. The discriminability potential of PRS-D in our sample may be due to the increased variance explained when selecting more severe patients with MDD (Verduijn et al., 2017) – only with psychotic features in our case –; the use of more powerful PRS-D built from PGC, UK Biobank, and 23andMe data (Howard et al., 2019); or that psychotic depression may be phenomenologically different to MDD without psychosis.

In relation to our main aim (i.e. whether we could use PRSs in order to distinguish between affective v. schizophrenia spectrum disorder subgroups), both PRS-SZ and PRS-D differentiated global AP from SSD, and psychotic depression from SSD. Nonetheless, when trying to differentiate BD from SSD, all PRSs failed to differentiate between them. This could be partly an artefact of the observed diagnostic instability in FEP; or be due to the fact that PRS-BD and PRS-D were underpowered for such analyses (more details in online Supplementary Material), but it is also plausible that this reflects the large genetic correlation between the two disorders, that may only be present to a lesser extent in depressive patients with psychotic features. Indeed, with over 80% power, PRS-SZ was able to distinguish BD from MDD-P, supporting the notion of lower common genetic liability for SZ in those suffering with psychotic depression than in those with BD, in line with the literature (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013).

Our results are in line with a recently observed differentiation between psychotic disorders by using an aggregated genetic score based on family correlation (Kendler, Ohlsson, Sundquist, & Sundquist, 2021) and shed new light on the existence of yet unclear and blurred genetic boundaries between current diagnosis categories
in their psychotic manifestation. Beyond the evidence of a gradient for risk of psychosis associated with PRS-SZ from SSD to the AP group, we could also observe an inverse gradient in the case of PRS-D. This allows the conceptualisation of a model in which the genetic vulnerability of psychotic disorders is distributed across a multidimensional continuum with SSD at one end, BD in the middle and MDD-P at the other extreme (Fig. 3). Among these groups, only the categories in the extremes were able to be differentiated by current polygenic scores. Further studies with larger samples or when the predictive power by PRSs increase, will allow further discrimination between categories, for example between SZ and BD or between BD and psychotic depression.

We failed to observe differences in PRS-IQ distribution, with effect sizes almost identical across clinical groups. Among AP, BD has been more widely compared with SZ as the paradigm disorder within SSD. We know from previous studies that patients with BD tend to present less cognitive impairment than those with SZ (Demjaha et al., 2017; Murray et al., 2004), but this difference seems to be less clear between SZ and BD patients with a history of psychotic symptoms (Hill, Harris, Herbener, Pavuluri, & Sweeney, 2007). Indeed, and in line with this, PRS-IQ showed no statistically significant differences within the case-only comparisons. However, the lack of discriminability potential of PRS-IQ would also be expected under the consideration that some cognitive changes are due to factors associated with the prodromal phase, the onset of the disorder or its treatment, rather than purely being neurodevelopmental, which is yet to be established.

These results should be interpreted in the context of some limitations. First, the number of patients with psychotic depression and BD was relatively small which could have led to low power in analyses comparing these groups and possibly contributing to the lack of association between those categories and most PRS variables. Furthermore, comparisons between models are...
also limited by the different discriminative power of each PRS (PRS-SZ is currently more powerful than PRS-BD and PRS-D). Indeed, post-hoc power calculations of the employed PRS suggest over 80% power only for PRS-SZ (more detail information in online Supplementary Material). These prediction models are expected to improve as bigger discovery samples are available for the affective psychotic categories and as we increase the size of our training sample. With FEP samples there are two main limitations to consider. One relates with the previously noted lower liability explained by PRS in incident samples (Meier et al., 2016), suggesting that part of the captured effect of SNPs is on the deteriorative course of illness, which may have implied type II error in our sample based on the FEP. The second limitation to consider refers to the changeability of diagnoses. As shown in some studies, shifts in diagnoses occur with a predominant direction from AP to SSD in a frequency of around 14–29% after 2 years (Schwartz et al., 2000; Veen et al., 2004). Moreover, it should be noted that all of our patients presented with psychosis, which could have enhanced the observed genetic overlap and prevented finding more clear differences between groups, and which make these results not generalisable to those BD or MDD without psychosis. Finally, all analyses were performed in the people of European ancestry population, which limits the generalisability of the findings in other populations. However, the fact that this is a multicentre well-characterised sample of FEP, allows it to have generalisability within Caucasian European populations.

Overall, this study provides support for the presence of a genetic psychosis continuum (shown by the ability of PRS-SZ to differentiate most case groups from controls following a gradient across categories). Nonetheless, we also observed genetic differences between clinical categories, with schizophrenia spectrum disorders at one end and psychotic depression at the other when looking at genetic loading for SZ and D. This study also shows that combining PRSs for different disorders in a prediction model of psychosis related phenotypes improve our prediction models while contributing to our understanding of the biological underpinnings of these phenotypes. Despite not yet clinically applicable at an individual level, this study points towards the potential usefulness as a research tool in specific populations such as high-risk or early psychosis phases, where it may help to suggest different therapeutic approaches (i.e antidepressant v. antipsychotic) or to anticipate prognosis. However, further work is needed to explore if PRS have synergistic effects with environmental exposures before combining all the risk factors into a single prediction model.

Financial support. This work was supported by funding from the European Community’s Seventh Framework Programme under grant agreement No. HEALTH-F2-2010-241909 (Project EU-GEI). VR was funded by a PhD scholarship supported by Lord Leverhulme’s Charitable Trust and the Velvet Foundation. EV is funded by the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. CA was supported by the Spanish Ministry of Science and Innovation; Instituto de Salud Carlos III (SAM16PE07CP1, PI16/02012, PI19/024), co-financed by ERDF Funds from the European Commission, ‘A way of making Europe’, CIBERSAM. Madrid Regional Government (B2017/BMD-3740 AGES-CM-2), Fundación Familia Alonso and Fundación Alicia Koplowitz. MB was supported by the Ministry of Economy and Competitiveness (PI08/0208, PI11/00325, PI14/00612), Instituto de Salud Carlos III – ERDF Funds from the European Commission, ‘A way of making Europe’, CIBERSAM, by the CERCA Programme/Generalitat de Catalunya and Secretaria d’Universitats i Recerca del Departament d’Economia i Coneixement (2017SGR1355). Departament de Salut de la Generalitat de Catalunya, en la convocatoria corresponent a l’any 2017 de concessió de subvencions del PERIS.
2016-2020, modalitat Projectes de recerca orientats a l’atenció primària, amb el codi d’expedient SLT0617/00345; and grateful for the support of the Institut de Neurociències, Universitat de Barcelona.

**Conflicts of interest.** Dr Arango has been a consultant to or has received honoraria or grants from Acadia, Angelini, Gedeon Richter, Janssen Cilag, Lundbeck, Minerva, Otsuka, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda. Dr Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speaker’s/advisory board of ABBiotics, Adamed, Angelini, Casen Recordati, Janssen-Cilag, Lundbeck, Otsuka, Menarini and Takeda. Dr Peter B. Jones declare to have consulted for Ricordati and Janssen. The rest of the authors have no conflicts of interest to declare in relation to the work presented in this paper.

**Ethical standards.** The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721005456

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**Fig. 3.** Visual representation of PRSs distribution across diagnosis categories. Conceptual multidimensional distribution of SNPs for schizophrenia, bipolar disorder and depression across clinical groups. Based on mean case-control differences, using control as a reference of Standardised Residuals of PRS for SZ, BD and D adjusted by site and 10 principal components.

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