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Predicting treatment resistance in positive and negative symptom domains from first episode psychosis: Development of a clinical prediction model

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ABSTRACT

Background: Treatment resistance (TR) in schizophrenia may be defined by the persistence of positive and/or negative symptoms despite adequate treatment. Whilst previous investigations have focused on positive symptoms, negative symptoms are highly prevalent, impactful, and difficult to treat. In the current study we aimed to develop easily employable prediction models to predict TR in positive and negative symptom domains from first episode psychosis (FEP).

Methods: Longitudinal cohort data from 1027 individuals with FEP was utilised. Using a robust definition of TR, $n = 51$ (4.97 %) participants were treatment resistant in the positive domain and $n = 56$ (5.46 %) treatment resistant in the negative domain 12 months after first presentation. 20 predictor variables, selected by existing evidence and availability in clinical practice, were entered into two LASSO regression models. We estimated the models using repeated nested cross-validation (NCV) and assessed performance using discrimination and calibration measures.

Results: The prediction model for TR in the positive domain showed good discrimination (AUC = 0.72). Twelve predictor variables (male gender, cannabis use, age, positive symptom severity, depression and academic and social functioning) were retained by each outer fold of the NCV procedure, indicating importance in prediction of the outcome. However, our negative domain model failed to discriminate those with and without TR, with results only just over chance (AUC = 0.56).

Conclusions: Treatment resistance of positive symptoms can be accurately predicted from FEP using routinely collected baseline data, however prediction of negative domain-TR remains a challenge. Detailed negative symptom domains, clinical data, and biomarkers should be considered in future longitudinal studies.

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1. Introduction

Treatment resistance (TR) in schizophrenia poses challenges for patients, family, and clinicians (Nucifora Jr et al., 2019). Whilst some individuals may show a good initial response to treatment before failing to respond after relapse (Ajnakina et al., 2020), literature suggests that as many as 25 % of individuals demonstrate a lack of treatment response from first episode (Bozzatello et al., 2019; Lally et al., 2016).

TR is defined as an inadequate response to two antipsychotic trials (non-clozapine), each of adequate dose, duration, and adherence (Howes et al., 2017). Individuals with TR tend to have greater cognitive impairment, increased number of hospitalisations, more prominent negative symptoms, higher levels of smoking, alcohol and drug abuse, more suicide ideation, and reduced life expectancy compared to those without TR (Andrew et al., 2012; Iasevoli et al., 2016; Kennedy et al., 2014). In addition to this personal 'cost' is the economic burden of long-term illness. Schizophrenia is estimated to cost £11.8 billion annually in England with TR responsible for over $34 billion in direct medical costs per year in the US (Andrew et al., 2012; Kennedy et al., 2014).

Individuals experiencing TR may present with different symptom profiles (i.e. positive, negative or cognitive) and this profile should be clarified in research given the different impact, treatment options, and underlying aetiology associated with each profile (Correll and Schooler, 2020; Howes et al., 2017; Huhn et al., 2019; Sabe et al., 2021). Negative symptoms in particular present a major challenge for patients and clinicians; they are associated with low remission rates, poor quality of life and functioning, and unlike positive symptoms, have limited response to treatment (Cerveri et al., 2019; Galderisi et al., 2018).

Currently, the only medication indicated to have any effect on negative symptoms is clozapine (NICE, 2014). There is ample evidence that early identification of TR in positive symptoms and intervention with clozapine is beneficial (Jones et al., 2022). This includes avoiding polypharmacy and ensuring patients aren't receiving medication doses that exceed recommendations (Howes et al., 2012); treatment continuation (Stroup et al., 2015; Vanasse et al., 2016); reduced number of inpatient days (Gee et al., 2016), and a decrease in hospital admissions (Stroup et al., 2015). Early identification of TR in the negative domain could lead to improved outcomes including higher levels of social and personal functioning, increased remission of negative symptoms, and better long-term clozapine response (Muñoz-Manchado et al., 2023; Shah et al., 2020).

Given the personal and economic impact of TR it would be beneficial to predict which individuals are likely to present with TR early in the course of illness. Whilst there are relatively few clinical prediction models targeting FEP populations (Lee et al., 2022) prediction research has started to investigate TR in these individuals (Ajnakina et al., 2020; Osimo et al., 2023; Smart et al., 2022). Several predictive factors are repeatedly implicated in TR including longer DUP, cannabis use, male gender, and younger age of onset (Legge et al., 2019; Smart et al., 2022; Smart et al., 2021). However, research in this area is still in its infancy and there is insufficient empirical evidence to suggest the inclusion of any specific feature or combination of features in TR prediction studies. LASSO (least-absolute shrinkage and selection operator) models can perform feature selection of given variables through the shrinkage of coefficients (Hastie et al., 2015; Steyerberg, 2019). In the current study we aimed to utilise LASSO modelling to predict TR in FEP individuals using routinely collected clinical data. In line with best practice guidelines that acknowledge distinct clinical profiles (Howes et al., 2017), we aimed to develop one model to predict TR in the positive domain and one to predict TR in the negative domain.

2. Materials and methods

We followed the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement for reporting the models (Collins et al., 2015) (Supplementary Table 1).

2.1. Data

The current study utilised data from the National Evaluation of the Development and Impact of Early Intervention Services (NEDEN) study, full details of which have been provided previously (Birchwood et al., 2014). In brief, this was a prospective cohort study that recruited FEP participants between 2005 and 2009 from 14 early intervention services across the UK (beyond experiencing FEP, there wasn't any further inclusion criteria). Several measures, including assessments of psychosis, functioning, substance misuse and relapse, were collected at multiple timepoints. The current study used 12-month follow up data of all recruited participants.

2.2. Outcome definition

The Treatment Response and Resistance in Psychosis (TRRIP) criteria (Howes et al., 2017) guided our definition of TR. In line with their symptom criteria, an individual's condition was defined as treatment resistant if they experienced at least two symptoms at a moderate severity or one symptom at a severe severity; <20 % symptom reduction overall as well as for the domain of interest; at least moderate functional impairment, with the above remaining persistent from baseline to 12-month follow-up. We relaxed the medication criteria in line with evidence that antipsychotic response within the first four weeks is indicative of future response (Agid et al., 2003; Long et al., 2023; Samara et al., 2015). Therefore, an individual needed to have received a therapeutic dose of at least one antipsychotic medication for a minimum of four weeks (Supplementary Table 2).

The Positive and Negative Syndrome Scale (Kay et al., 1987) instrument was used to measure symptom severity and symptom reduction. PANSS items are scored from 1 to 7; ratings for moderate and severe symptoms are identified with scores of 4 and 6, respectively. To meet TR criteria, participants had to have recorded at least two symptoms rated 4 or above, or one symptom rated 6 or above.

The PANSS instrument is measured on an interval scale (1–7). As ratio calculations require a true zero (Obermeier et al., 2010) we needed to translate this into a ratio scale. In line with research (Obermeier et al., 2010) we reduced the PANSS total score by 30 and the domain-specific subtotals by 7. Upon translating the PANSS into a ratio scale we could calculate the percentage change in symptom reduction from baseline to 12-months follow-up, and identify which participants met the TR criteria of experiencing <20 % symptom reduction.

The Global Assessment of Functioning (GAF) scale which previously constituted Axis V of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Aas, 2011) was used to measure functional impairment. A dual-scale GAF approach was used which documented symptoms and disability separately. To comply with TRRIP criteria that functioning should be measured independently of symptoms, we utilised the disability measure with a threshold of 60 or lower used to classify moderate impairement.

2.3. Baseline predictors

A total of 20 routinely available sociodemographic and clinical predictor variables were included based on existing literature. Variables (for both domains) included age at onset; gender; education (number of years); cannabis use; and adjusted DUP, defined as the time (in days) from the onset of psychotic symptoms to initiating treatment. The positive domain model contained items P1, P2, P3, P4, P5, P6, P7 and the PANSS Negative Subtotal score; the negative domain model contained items N1, N2, N3, N4, N5, N6, N7, and the PANSS Positive Subtotal score. Clinical variables from standardized clinical assessments were also included in each model, as described below.

Depression: Calgary Depression Scale for Schizophrenia (Addington et al., 1990). The CDSS scale is extensively used and distinguishes between depression, and positive and negative symptoms (Addington

et al., 2014; Collins et al., 1996).

Premorbid adjustment: Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982). PAS scores have been utilised in a multitude of ways (Larsen et al., 2004). In line with schizophrenia-related research that has compared premorbid adjustment by combining the social components and the academic components of the scale (Kilian et al., 2017; Larsen et al., 2004; Norman et al., 2005), we utilised a similar approach. We combined the social components (Childhood period: Sociability and withdrawal + Peer relationships; Early/Late Adolescence periods: Sociability and withdrawal + Peer relationships + Social sexual aspects of life) and the academic components (Scholastic performance + Adaptation to school) to obtain an overall Social PAS score and Academic PAS score for the Childhood period, Early Adolescence period, and Late Adolescence period.

2.4. Statistical analysis

Model development and validation was conducted in R (version 2023.06.1 + 524).

2.4.1. Missing data

The current study utilised a two-stage imputation method to handle missing data: first for outcome classification (where participants had missing symptom data), and second, for missing variable data. Following outcome classification, the total missing values for the positive and negative domain models were 9.59 % and 9.62 %, respectively; (Supplementary Table 3 for the percentage of missingness per variable).

As the analysis of only individuals with complete data can lead to bias (Sterne et al., 2009), we imputed the missing values. As we included variables based on existing literature, we assumed the missing values were not a result of unobserved data (Sterne et al., 2009) and imputed these values using multiple imputation by chained equations (Azur et al., 2011).

2.4.2. Model fitting, training and performance estimation

For the prediction of TR, we fit a LASSO model for each symptom domain. LASSO is a regression modelling approach that can address problems of overfitting and overestimation of performance by applying regularisation terms to the cost function (Ranstam and Cook, 2018; Tibshirani, 1996). A benefit of LASSO is that it performs feature selection through the shrinkage of coefficients (Hastie et al., 2015; Steyerberg, 2019). This results in a final list of variables and their respective coefficients that minimises the prediction error of the model (Ranstam and Cook, 2018). This is of particular importance to the replication of studies with clinical impact, whereby a limited number of variables known to be of importance can be collected but other features can be eliminated.

Model estimation was achieved through nested cross-validation (NCV). In brief, NCV contains an inner cross-validation loop, used to perform hyperparameter selection, and an outer cross-validation loop, used to provide an unbiased estimate of performance (Wainer and Cawley, 2021). First, we specified a grid of 100 λ values. We then performed hyperparameter tuning through 50 repeats of 10-fold cross validation. Model performance was then estimated through 5 outer-loop iterations. We assessed performance using measures of discrimination and calibration. Discrimination refers to a model's ability to distinguish between someone with and without the outcome of interest whilst calibration compares the predicted and observed values (Steyerberg and Vergouwe, 2014). We present ROC (receiver operating characteristic) curves and concordance (c) statistics for measures of discrimination, and calibration slope and calibration-in-the-large statistics for measures of calibration.

3. Results

3.1. Sample characteristics

The initial NEDEN sample consisted of 1027 participants. During outcome classification one participant was excluded from each domain (due to having 100 % missing treatment data after imputation of symptom data) resulting in a sample of 1026 participants per model. There were 51 participants (4.97 %) who were treatment resistant in the positive domain and 56 participants (5.46 %) treatment resistant in the negative domain (28 exclusively in the positive domain, 33 exclusively in the negative domain, and 23 in both domains).

Positive Domain: There were no significant differences in age at onset, education, or DUP between the positive-domain treatment resistant group (PTR) and the non-treatment resistant group (non-TR) (Table 1). There was an association between *gender* and treatment resistant outcome ($\chi^2(1) = 5.88$, $p = .015$) with a higher proportion of males in the PTR group (84.3 %) than the non-TR group (68.2 %). There was also an association between *cannabis use* and treatment resistant outcome ($\chi^2(1) = 4.412$, $p = .036$) with a higher proportion of cannabis use in the PTR group (41.2 %) than the non-TR group (27.6 %).

Negative Domain: There were no significant differences in gender, education, DUP, or cannabis use between the negative-domain treatment resistant group (NTR) and the non-TR group (Table 1). There was a significant difference in *age at onset* between the NTR group (mean = 19.73 years, SD = 3.44) and the non-TR group (mean = 21.38 years, SD = 5.08), $t(69.44) = 3.39$, $p = .001$.

3.2. Positive-domain treatment resistance model

The positive domain model demonstrated good discrimination and calibration (AUC = 0.72, calibration slope = 0.88, calibration-in-the-large = −0.36, accuracy = 0.68) (Table 2 shows performance measures; Fig. 1 and Fig. 2 show the ROC curves for each outer fold iteration of the NCV procedure and associated calibration plots, respectively).

Twelve out of the 20 predictor variables were retained by all five models (each outer fold iteration of the NCV): male gender, cannabis use, age, PANSS P7, PANSS P4, PANSS P3, PANSS P1, CDSS, late adolescence social functioning, late adolescence academic functioning, early adolescence academic functioning, childhood academic functioning, (Fig. 3 for predictor variables retained following NCV; Supplementary Table 4 details beta coefficients per model).

3.3. Negative-domain treatment resistance model

The negative domain model demonstrated poor discrimination and calibration (AUC = 0.56, calibration slope = 0.57, calibration-in-the-large = −1.213, accuracy = 0.57) (Table 2 shows performance measures; Fig. 4 and Fig. 5 show the ROC curves for each outer fold iteration of the NCV procedure and associated calibration plots, respectively).

However, two out of the 20 predictors were retained by all tested models: **childhood academic functioning and PANSS N6 (lack of spontaneity)** (Fig. 6 for predictor variables retained following NCV; Supplementary Table 5 details beta coefficients per model).

4. Discussion

This is the first study to develop clinical prediction models targeting specific clinical profiles, (positive and negative), for predicting TR in FEP individuals. Our study builds on research that investigated predictive factors of TR (Bozzatello et al., 2019; Legge et al., 2019; Smart et al., 2021), and offers support for the use of clinical prediction models in FEP populations alongside promising research with a similar focus (Ajnakina et al., 2020; Demjaha et al., 2017; Farooq et al., 2022; Kit and Wong, 2023; Osimo et al., 2023; Smart et al., 2022). It also highlights the need for increased focus on early negative symptom TR.

Table 1
Comparison of baseline characteristics between the non-TR and positive domain TR groups, and the non-TR and negative domain TR groups.

Baseline characteristics	Non TR = 975 Mean (SD)/*n* (%)	PTR = 51 Mean (SD)	*P* value	Non TR = 970 Mean (SD)/*n* (%)	NTR = 56 Mean (SD)	*P* value
Age at onset	21.37 (4.96)	20.08 (4.43)	0.069	21.38 (5.08)	19.73 (3.44)	**0.001**
Sex (Male)	665 (68.2 %)	43 (84.3 %)	**0.015**	664 (68.45)	44 (78.6)	0.111
Education (in years)	11.74 (1.86)	11.59 (1.43)	0.574	11.75 (1.87)	11.63 (1.70)	0.623
DUP (in days)	308.06 (640.99)	298.98 (447.77)	0.920	305.88 (613.71)	346.80 (863.76)	0.636
Cannabis use (yes)	269 (27.6 %)	21 (41.2 %)	**0.036**	268 (27.6)	21 (37.5)	0.110
P1/N1	2.82 (1.68)	3.22 (1.75)	0.106	2.13 (1.40)	2.71 (1.57)	**0.003**
P2/N2	1.94 (1.25)	1.96 (1.22)	0.924	2.33 (1.34)	2.52 (1.32)	0.303
P3/N3	2.92 (1.68)	3.45 (1.80)	**0.028**	1.71 (1.07)	2.11 (1.42)	**0.043**
P4/N4	1.56 (0.98)	1.18 (0.65)	**<0.001**	2.64 (1.55)	3.18 (1.69)	**0.012**
P5/N5	1.59 (1.07)	1.55 (1.14)	0.795	2.29 (1.36)	2.63 (1.29)	0.073
P6/N6	2.93 (1.61)	2.78 (1.59)	0.522	2.04 (1.37)	2.73 (1.76)	**0.005**
P7/N7	1.58 (1.09)	1.37 (0.799)	0.084	1.61 (0.98)	1.59 (0.99)	0.888
PANSS Negative/PANSS Positive Total	14.88 (6.59)	15.63 (7.14)	0.434	15.36 (6.11)	15.02 (5.22)	0.684
CDSS	6.32 (5.37)	5.35 (5.11)	0.211	6.33 (5.34)	5.36 (4.97)	0.184
Childhood Social (PAS)	2.40 (2.48)	2.94 (2.53)	0.127	2.34 (2.48)	2.88 (2.42)	0.113
Childhood Academic (PAS)	3.12 (2.49)	4.08 (2.51)	**0.008**	3.10 (2.48)	3.98 (2.74)	**0.011**
Early Adolescence Social (PAS)	4.05 (3.50)	4.45 (3.50)	0.428	4.06 (3.52)	3.91 (2.83)	0.750
Early Adolescence Academic (PAS)	4.45 (2.93)	4.84 (2.53)	0.348	4.41 (2.93)	4.98 (3.02)	0.154
Late Adolescence Social (PAS)	4.68 (3.82)	5.76 (4.27)	**0.05**	4.65 (3.82)	5.39 (4.04)	0.158
Late Adolescence Academic (PAS)	4.58 (3.09)	6.00 (3.37)	**0.002**	4.69 (3.16)	5.09 (3.15)	0.357

Abbreviations: Non-TR = Non Treatment Resistant; PTR = Positive domain treatment resistant group; NTR = Negative domain treatment resistant group; DUP = Duration of Untreated Psychosis; PANSS = Positive and Negative Syndrome Scale; CDSS = Calgary Depression Scale for Schizophrenia; PAS = Premorbid Adjustment Scale.

Table 2
Performance measures for the positive-domain and negative-domain LASSO models.

Performance measure	Positive-domain	Negative-domain
AUC	0.72	0.56
Calibration slope	0.88	0.57
Calibration-in-the-large	−0.36	−1.213
Sensitivity	0.65	0.50
Specificity	0.69	0.57
PPV	0.10	0.06
NPV	0.97	0.95
Accuracy	0.68	0.57

Abbreviations: AUC = Area under the curve; PPV = Positive Predictive Value; NPV = Negative Predictive Value.

The performance of our positive domain model identifies an ability to predict positive domain-TR from initial clinical contact using routine data. Theoretically, TR could be identifiable after 12 weeks (Howes et al., 2017) however, delays in clozapine initiation often exceed this timescale (John et al., 2018; Stokes et al., 2020). Whilst the relative effectiveness of clozapine may not be conclusively greater if initiated earlier (Jones et al., 2020), delays in administration can worsen quality of daily life and negatively impact treatment response (Gee et al., 2016; Howes et al., 2012; Stroup et al., 2015; Vanasse et al., 2016; Yoshimura et al., 2017). As clozapine has shown to be superior to other antipsychotics in the treatment of positive symptoms, in the short and long term (Siskind et al., 2016), the accurate early identification of FEP individuals with a positive domain profile could be invaluable from a personal and economic standpoint.

We intentionally selected feature variables based on their evidence and likelihood of being routinely collected upon presentation to services. This was to ensure the models were as clinically appropriate as possible. Male gender and cannabis use were retained in each positive domain model. These findings align with research which has reported men to be 1.57 times more likely to be treatment resistant (Siskind et al., 2022), with cannabis use associated with worse clinical outcomes (Ajnakina et al., 2020; Legge et al., 2019; Patel et al., 2016). Additionally, items P1 (Delusions), P3 (Hallucinatory behaviour), P4 (Excitement), and P7 (Hostility) from the PANSS scale were also retained in each model. These results suggest some PANSS items may be more predictive of TR than others and individual items of the PANSS should be included in predictive studies in addition to the positive subtotal score which is more commonly reported.

Our decision to combine the social and academic components of the PAS scale for each life period, to investigate premorbid adjustment, is similar to other approaches (Kilian et al., 2017; Larsen et al., 2004; Norman et al., 2005). The academic component of each life period was retained by each positive domain model. The idea of academic performance being a premorbid marker of future disease outcome has been suggested previously (Dickson et al., 2020); of relevance to the current study, they report those who later developed schizophrenia, those with a family history of schizophrenia, and those reporting psychotic-like experiences, had poorer academic achievement. The current study offers support for academic achievement being implicated in FEP outcomes. Our study suggests that academic performance could be a predictive factor of future illness trajectories, particularly in those identified as being at risk of FEP, and an opportunity for early preventative approaches.

Whilst the model for predicting positive domain-TR discriminated between those with and without the outcome, the model for negative domain-TR did not perform well. Negative symptoms are a multifaceted problem presenting a complex challenge for clinicians. They are one of the first reported symptoms in those with schizophrenia (Correll and Schooler, 2020) yet one of the most persistent (Chang et al., 2011). There may be primary negative symptoms as well as secondary negative symptoms resulting from comorbidities, treatments, medications, environmental factors, psychosocial factors, and brain abnormalities (Correll and Schooler, 2020; Galderisi et al., 2018; Kelley et al., 1999; Sarkar et al., 2015). With a prevalence of up to 90 % for the presence of at least one negative symptom during FEP (Heiden et al., 2016) these symptoms remain an immense burden on the people living with them (Cerveri et al., 2019; Galderisi et al., 2018). The complexities of negative domain-TR are further exacerbated by their appearance at any point during illness (Correll and Schooler, 2020). Cumulatively, these factors may contribute to the difficulty of predicting negative domain-TR in the current study. Our findings reflect research which reported baseline assessments may not predict the development of negative symptoms (Chang et al., 2011). It is important to acknowledge two considerations 1) if negative symptoms are secondary to FEP related causes, these may not be identifiable from illness onset and 2) the variables included in the

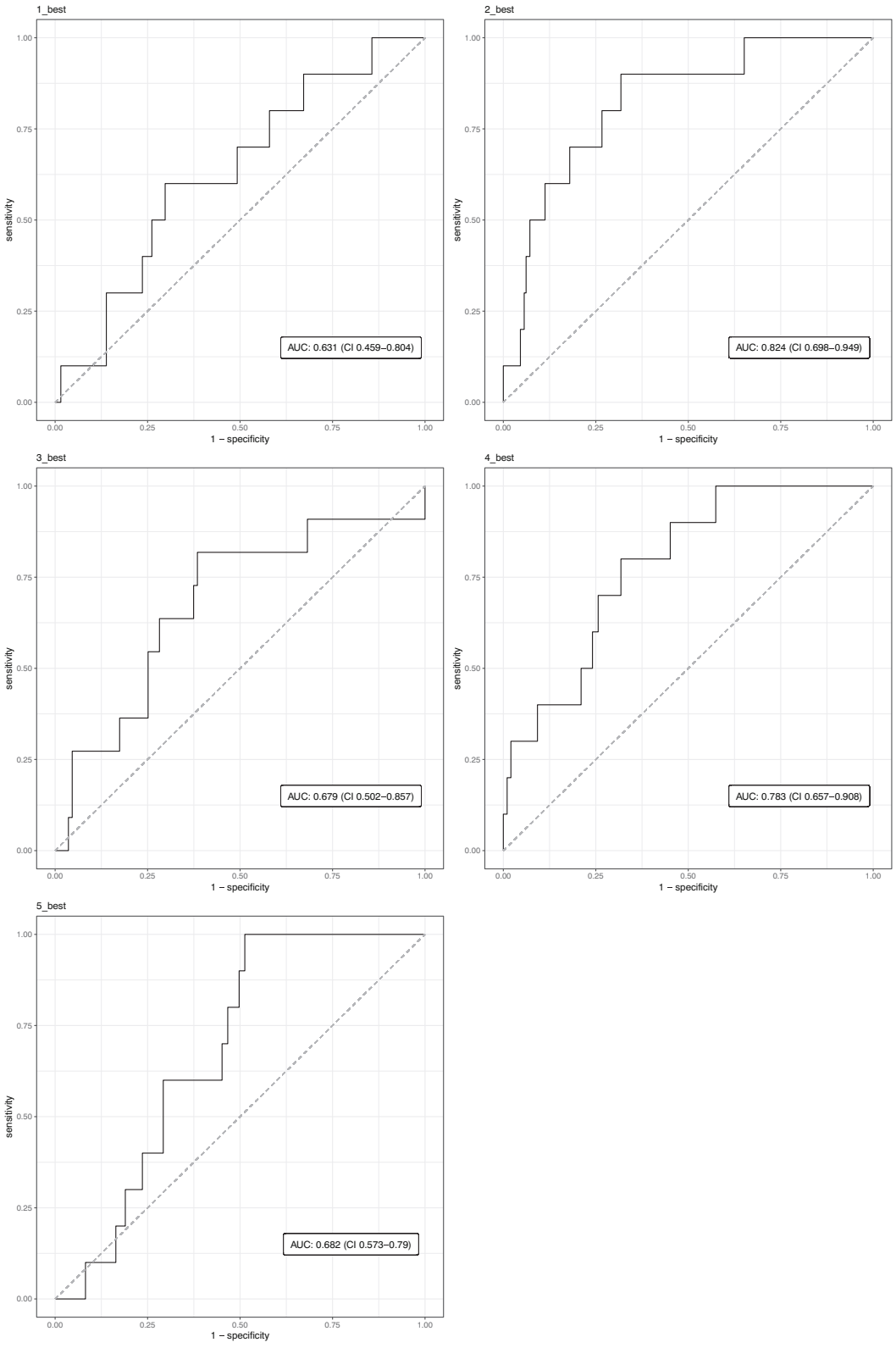

Fig. 1. shows the receiver operating characteristic curves for each positive domain model. The AUC (area under the curve) is presented (with confidence intervals).

current study are indicative of positive domain-TR and not negative domain-TR. As this is the first study to investigate different symptom profiles, the essential predictive features of TR for negative symptoms are less well known.

Whilst our study highlights the difficulty in predicting negative domain-TR, it highlights the need for future research to unpack the complexities surrounding these symptoms. Research has identified that certain medications are more effective in reducing negative symptoms than others (Cerveri et al., 2019; Huhn et al., 2019; Sabe et al., 2021). Several recommendations for the treatment of negative symptoms have also been made including the provision of social skills training, an antidepressant add-on to antipsychotic medication, cognitive remediation,

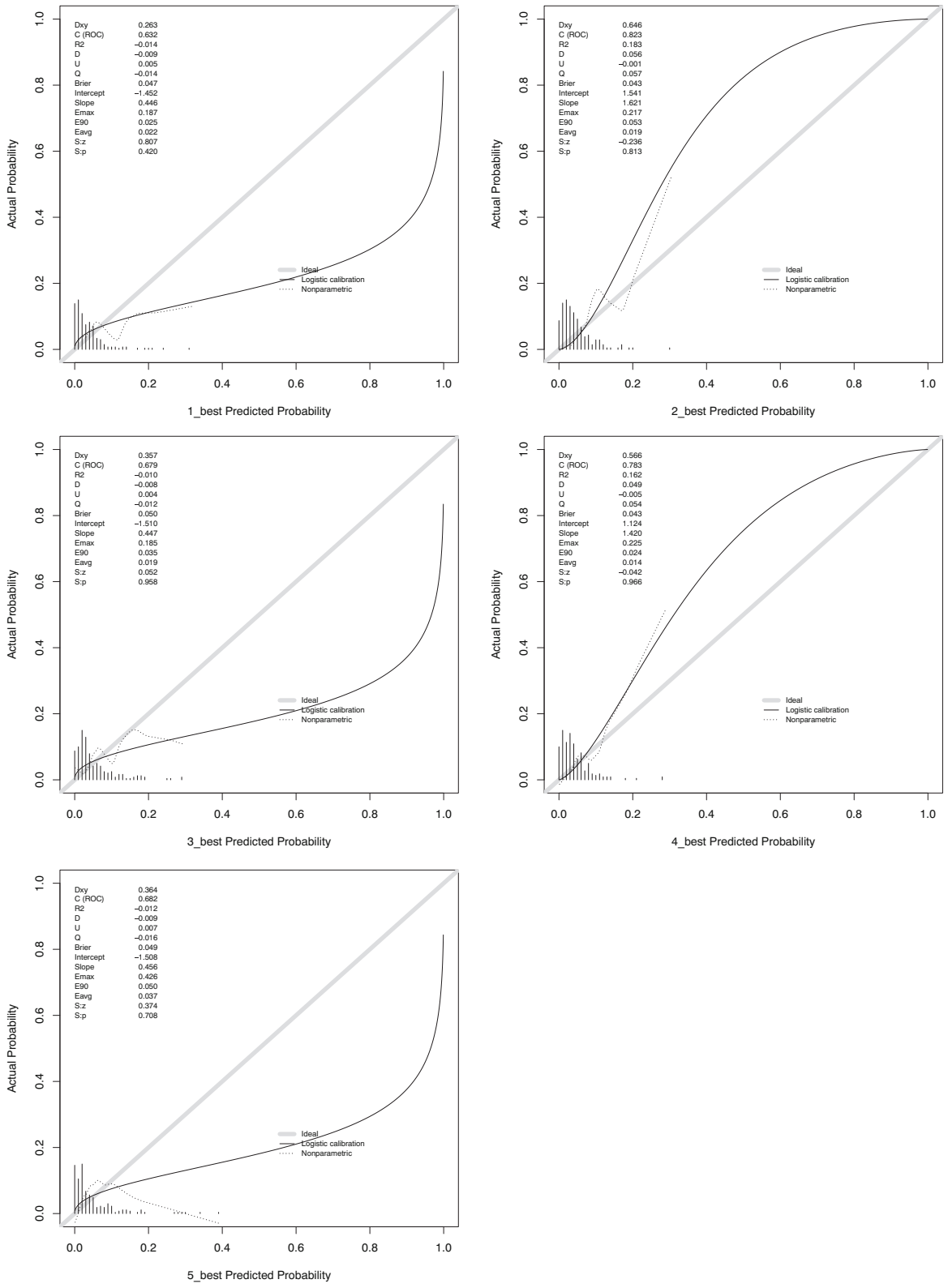

Fig. 2. shows the calibration plots associated with each positive domain model (plots created using the val.prob. function in the Regression Modelling Strategies (rms) package in r).

exercise interventions, and rehabilitation interventions (Galderisi et al., 2021). Thus, the early identification of individuals who are treatment resistant in the negative domain could result in a targeted pharmacological and psychosocial approach.

Despite an inability to predict which individuals will be treatment resistant in the negative domain our study highlights several concepts regarding positive and negative symptom profiles. 33 participants were treatment resistant exclusively in the negative domain. Research acknowledges that the typical treatment resistant patient is one with positive symptoms and that antipsychotic medication primarily seeks to

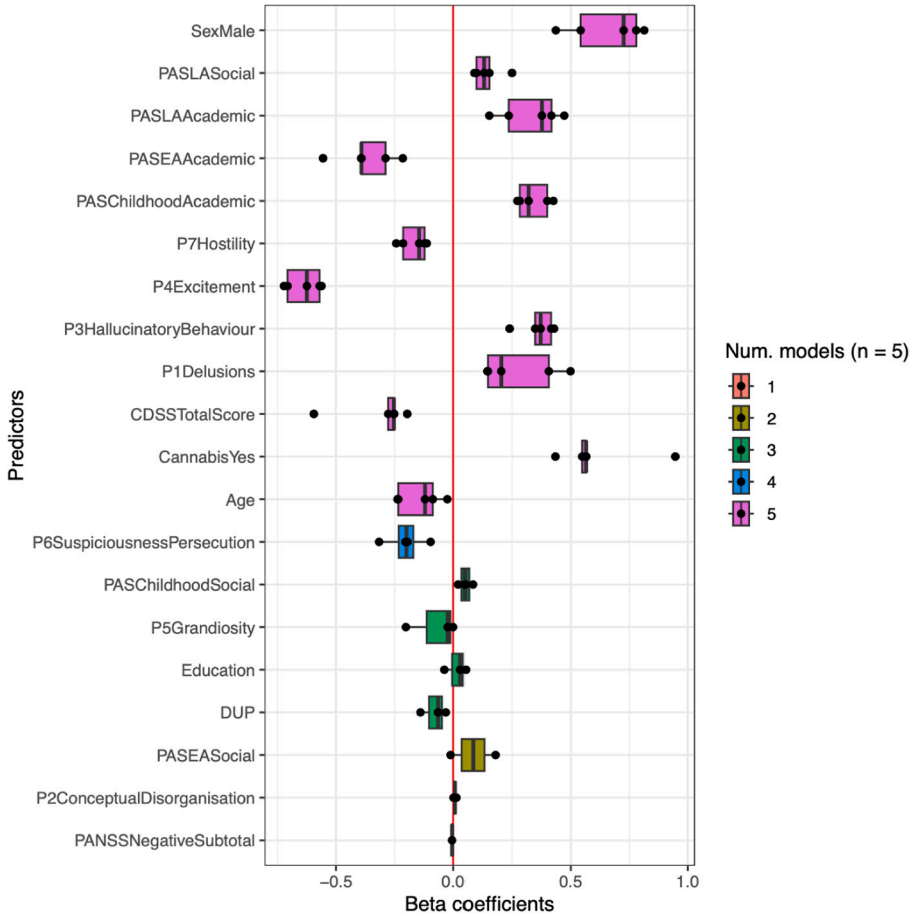

Fig. 3. shows how many models (each outer fold iteration of the nested cross validation procedure) retained each baseline predictor variable. The boxplots demonstrate the beta coe > icient values, and range of values, assigned to each variable (positive domain model).

address these (Correll and Schooler, 2020; Howes et al., 2017). However, with 33 negative domain treatment resistant patients and 23 individuals treatment resistant in both domains, this highlights the importance of addressing both symptom profiles; these symptoms co-exist and need to be co-treated (Sarkar et al., 2015). Our model pipeline did identify variables that may contribute to negative domain TR (Fig. 6), including PANSS N6 (Lack of Spontaneity). This finding supports literature investigating the overlap between schizophrenia and autistic spectrum disorder and specifically, the convergent symptoms between them (Duffy and Healy, 2011; Jutla et al., 2022), and research which has identified autistic traits in treatment resistant schizophrenia patients (Nakata et al., 2020), offering a potential new avenue to explore in negative domain TR. Cumulatively, these findings add to existing literature that explores the contribution of individual assessment items, and combination of these items, in FEP patient outcomes (Izquierdo et al., 2021; Ortiz et al., 2020).

Strengths of our study include developing, for the first time, prediction models distinguishing between positive and negative treatment resistant clinical profiles in FEP. We utilised a relatively large dataset from a longitudinal cohort study that allowed for the identification of TR at 12 months (Birchwood et al., 2014). With LASSO regression and repeated NCV we generated unbiased estimates of model performance with the identification of predictive features. It has been identified that psychiatric research suffers from missing data not being handled correctly and that multiple imputation methods can be a statistical advantage (they offer a robust approach, accounting for statistical uncertainty with the benefit of handling different variable types (Azur et al., 2011; Moons et al., 2006)). Further, we included variables readily available upon patient presentation to services, ensuring an easily employable, clinically appropriate model.

Limitations include a small number of outcome cases for the positive and negative domain models. Whilst research has acknowledged that the 10 events per variable (EPV) rule is not a strict criterion (Riley et al., 2020; van Smeden et al., 2019), low EPVs tend to result in poorer performance (Steyerberg et al., 2003). The low number of outcome cases may be explained by our strict TR criterion; we may have underestimated the prevalence of TR in the current dataset. Future studies may investigate alternative definitions of TR, including different antipsychotic treatment criteria and symptom improvement thresholds (Haddad and Correll, 2018; Leucht et al., 2009; Schennach-Wolff et al., 2010; Suzuki et al., 2012). The low number of outcome cases may explain why there were no significant differences in DUP between the PTR and non-TR groups. It should be noted, our positive domain model still performed relatively well. This could be explained by our use of LASSO which has shown to handle cases with low EPVs and is recommended where prespecified predictors are used in small datasets (Pavlou et al., 2016; Steyerberg et al., 2000). Another limitation is the lack of an external validation. Whilst NCV allows for an unbiased estimate of model performance, it is limited to one dataset. An external validation allows for an examination of reproducibility and it determines how the model generalises to new individuals (Ramspek et al., 2021). A next step for the current study is to externally validate our positive domain model. Another consideration is our prespecified predictor variables. Whilst our selection was based on clinical expertise and literature as is recommended (Steyerberg, 2019), we may inadvertently have omitted variables that were predictive factors of TR. The results of our negative domain model highlight a gap in the literature regarding predictive factors of negative domain-TR and future research should seek to

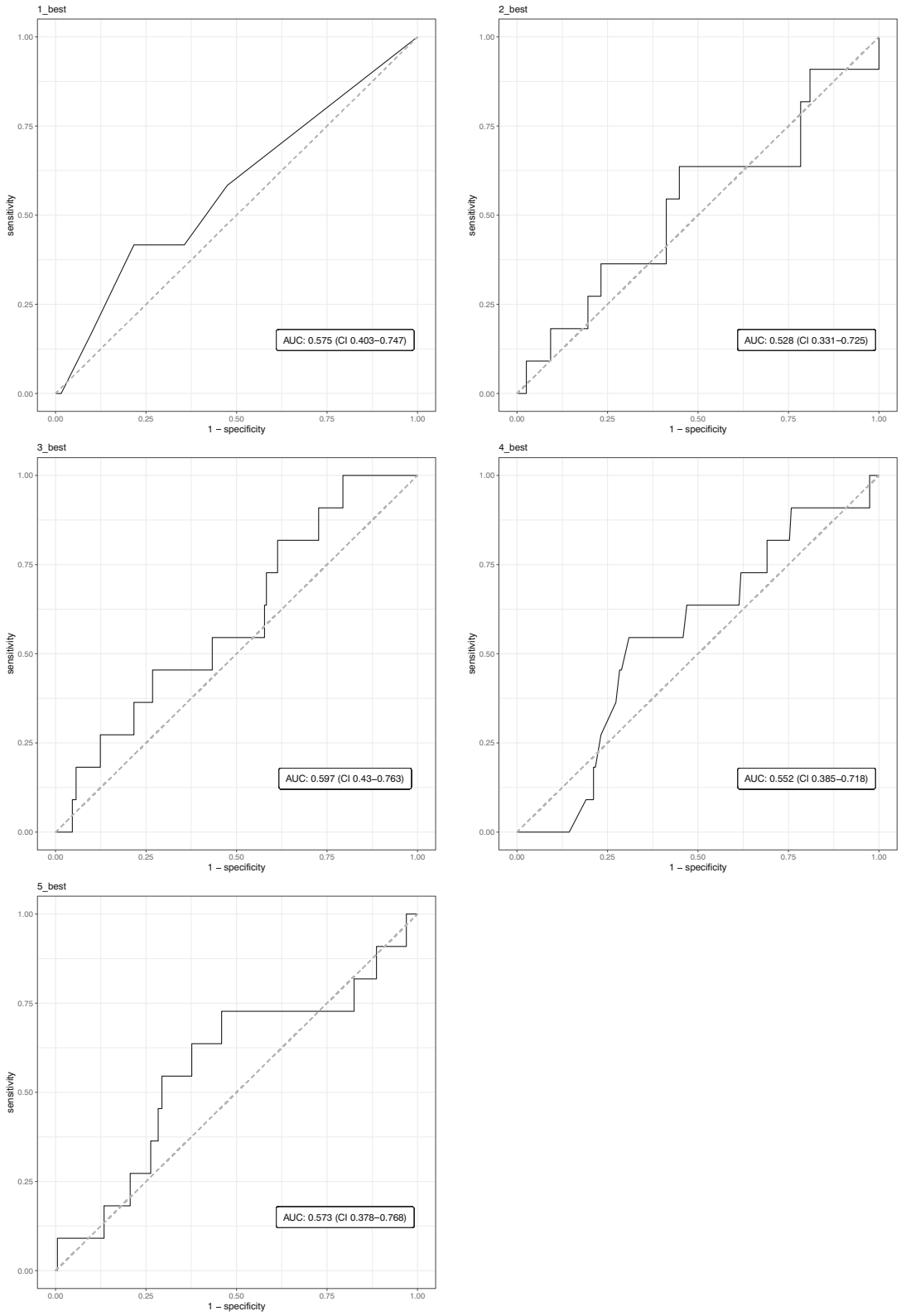

Fig. 4. shows the receiver operating characteristic curves for each negative domain model. The AUC (area under the curve) is presented (with confidence intervals).

investigate this. With growing support for the existence of two subdomains of negative symptoms (avolition/apathy and diminished expression) (Correll and Schooler, 2020), and research investigating the trajectory and predictors of apathy in FEP individuals (Lyngstad et al., 2020) as well as psychological factors underpinning and associated with diminished expression in schizophrenia (García-Mieres et al., 2020), there may be potential for predicting individual negative symptoms. As these subdomains have a unique association with functioning and quality of life (García-Fernández et al., 2022) they may have a unique association with TR. Future research may investigate cognition in

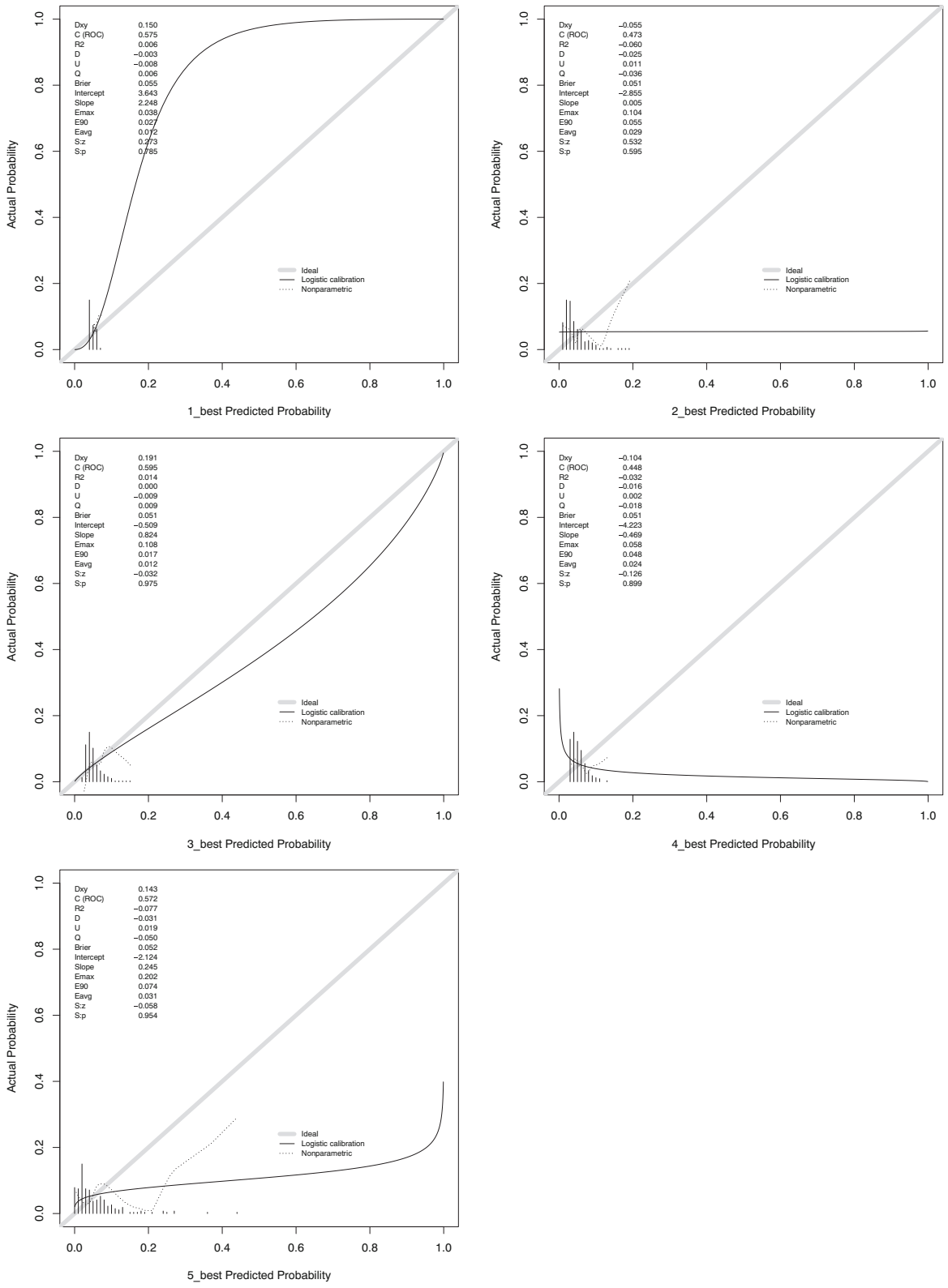

Fig. 5. shows the calibration plots associated with each negative domain model (plots created using the val.prob. function in the Regression Modelling Strategies (rms) package in r).

negative domain-TR, which is linked to negative symptoms (Foussias et al., 2014), but has so far proven problematic to explore as cognition data is often not routinely collected. Relatedly, as the PANSS scale doesn't exclusively measure negative symptoms and has questions regarding the validity of cognitive measures (Kumari et al., 2017) future studies may seek to utilise scales with more detailed psychopathology investigation.

In conclusion, we have shown that it is possible, using routinely

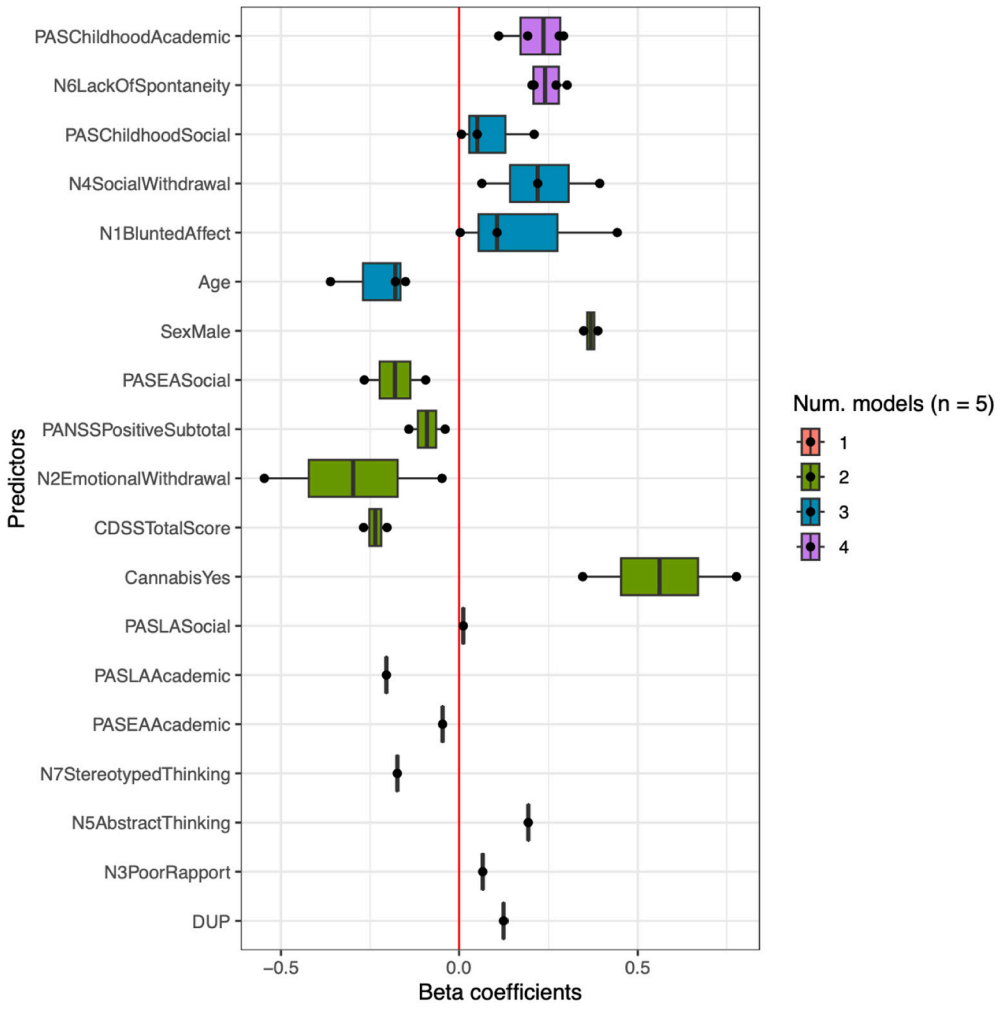

Fig. 6. shows how many models (each outer fold iteration of the nested cross validation procedure) retained each baseline predictor variable. The boxplots demonstrate the beta coefficient values, and range of values, assigned to each variable (negative domain model).

collected information, to predict positive domain-TR in FEP individuals from initial clinical contact. This demonstrates an opportunity for early intervention and provides an exciting outlook for the research and implementation of clinical predictions models in psychiatric populations.

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CRediT authorship contribution statement

Rebecca Lee: Writing – original draft, Software, Methodology, Formal analysis, Conceptualization. **Sian Lowri Griffiths:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Georgios V. Gkoutos:** Writing – review & editing, Supervision. **Stephen J. Wood:** Writing – review & editing, Supervision, Conceptualization. **Laura Bravo-Merodio:** Writing – review & editing, Visualization, Software, Formal analysis. **Paris A. Lalousis:** Writing – review & editing, Methodology, Conceptualization. **Linda Everard:** Writing – review & editing. **Peter B. Jones:** Writing – review & editing. **David Fowler:** Writing – review & editing. **Joanne Hodegkins:** Writing – review & editing. **Tim Amos:** Writing – review & editing. **Nick Freemantle:** Writing – review & editing. **Swaran P. Singh:** Writing – review & editing. **Max Birchwood:** Writing – review & editing. **Rachel Upthegrove:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

None.

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