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Polygenic risk scores and the prediction of onset of mood and psychotic disorders in adolescents and young adults

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Abstract

Aim: To examine whether polygenic risk scores (PRS) for neuroticism, depression, bipolar disorder and schizophrenia are higher in individuals manifesting trans-diagnostic risk factors for the development of major mental disorders and whether PRS enhance prediction of early onset full-threshold disorders.

Methods: Using data from the Brisbane Longitudinal Twin Study, we examined individual PRS for neuroticism, depression, bipolar disorder and schizophrenia, recorded evidence of subthreshold syndromes and family history of mood and/or psychotic disorders and noted progression to trans-diagnostic clinical caseness (onset of major mental disorders) at follow-up. We undertook multivariate, receiver operating curve and logistic regression analyses that were adjusted for known variables of influence (age, twin status, and so on).

Results: Of 1473 eligible participants (female = 866, 59%; mean age 26.3 years), 28% ($n = 409$) met caseness criteria for a mood and/or psychotic disorder. All PRS were higher in cases versus non-cases but associations with different levels of risk were inconsistent. The prediction of caseness (reported as area under the curve with 95% confidence intervals [CI]) improved from 0.68 (95% CI: 0.65, 0.71) when estimated using clinical risk factors alone up to 0.71 (95% CI: 0.69, 0.73) when PRS were added to the model. Logistic regression identified five variables that optimally classified individuals according to caseness: age, sex, individual risk characteristics, PRS for depression and mental health case status of cotwins or siblings.

Conclusions: The findings need replication. However, this exploratory study suggests that combining PRS with other risk factors has the potential to improve outcome prediction in youth.

KEYWORDS
family history, mental disorders, onset, polygenic risk scores, youth

1 | INTRODUCTION

It is well established that the first onset of full-threshold mood and psychotic disorder occurs before the age of 30 in 75% cases (Gore et al., 2011; McGorry et al., 2018). However, illness evolution is complex, and comorbidity is the rule rather than the exception for disorders presenting during emerging adulthood (Shah et al., 2020). As such, trans-diagnostic staging models are increasingly applied in

research and clinical practice in youth mental health and early intervention services (Iorfino et al., 2019; McGorry et al., 2018; Shah et al., 2020). Clinically, it has been demonstrated that some early expressions of psychopathology and risk (e.g. personal experience of a subthreshold syndrome (SubT), such as brief hypomania or attenuated psychotic symptoms), may precede the onset of the first full-threshold illness episode (Iorfino et al., 2019; Scott, Crouse, et al., 2021; Scott, Martin, et al., 2021). Using these observations, researchers have developed a range of screening tools to detect 'at-risk' individuals and to estimate the probability of transition to more enduring states of clinical and functional impairment (Iorfino et al., 2019; McGorry et al., 2018; Shah et al., 2020). These instruments attempt to quantify the additive effects of multiple risk factors but typically rely on the clinical assessment of family history (FH) as a proxy measure of genetic burden. However, research demonstrates that many major mental disorders traditionally thought to be distinct share certain genetic traits and has identified that genetic risk variants, as represented by polygenic risk scores (PRS), may depict this predisposition in a more subtle manner (Zwicker et al., 2018). PRS are typically expressed as a single-value estimate of the degree to which an individual is at risk of common illnesses owing to their genetic makeup (Wray et al., 2021). Individual PRS are not viewed as stand-alone predictors of phenotypes or complex conditions, but it is notable that persons who are at higher risk, for example, those with a strong FH of a disorder, often (but not always) have a higher-than-average PRS (Musliner et al., 2020; Wray et al., 2021; Zwicker et al., 2018).

Researchers are beginning to examine the utility of PRS in predicting illness trajectories in youth mental health settings (Wray et al., 2021). However, most publications focus on disorder-specific outcomes (i.e. the association between PRS for schizophrenia and the development of full-threshold psychotic episodes) or differentiation of one diagnosis from another (Musliner et al., 2020; Rodriguez et al., 2022) and have not considered the trans-diagnostic comorbid nature of clinical presentations in emerging adulthood. As such, we decided to examine whether the prediction of first onset of full-threshold major mental disorder (i.e. an episode of a major depression, bipolar and/or psychotic disorder) can be improved by including data about PRS scores for neuroticism [NSM], depression [MDD], bipolar disorder [BIPOLAR] and schizophrenia alongside information about other putative risk factors derived from a community-residing cohort of twins and non-twin siblings (Brisbane Longitudinal Twin Study [BLTS]; Couvy-Duchesne et al., 2018; Mitchell et al., 2019). We included NSM as it is closely associated to anxiety and depression and is known to exacerbate self-reported distress (associated other symptoms) and may increase help-seeking.

We studied the same BLTS cohort that was included in previous publications on early expressions of psychopathology and risk (i.e. FH and/or SubT) and subsequent onset of mood and psychotic disorders (herewith referred to as 'caseness'). This sample was chosen because cohort members repeatedly participated in cross-sectional mental health assessments (including the Composite International Diagnostic Interview [CIDI]) throughout adolescence and early adulthood (Kessler et al., 2004). Furthermore, we have already established that (after adjusting analyses for age, sex, twin status, environment, etc.), the risk of meeting criteria for CIDI caseness was 64% in individuals with a history of one or more SubT, increasing to 68% in those with a FH and SubT (Scott, Crouse, et al., 2021; Scott, Martin, et al., 2021). The current study extends the investigation by using a planned sequence of analyses (all of which were adjusted for variables of influence) to examine the following questions about the BLTS cohort:

- Do PRS for NSM, MDD, BIPOLAR and SCZ vary across subgroups defined according to the putative level of clinical risk (SubT and/or FH) for early onset of CIDI caseness?
- Is the prediction of CIDI caseness improved if PRS for NSM, MDD, BIPOLAR and SCZ are combined with individual clinical risk characteristics (SubT and/or FH)?
- What is the optimal combination of clinical risk factors and/or PRS for predicting the early onset of trans-diagnostic CIDI caseness in emerging adulthood?

2 | METHODS

Ethical approval was obtained from the Human Research Ethics Committee at the University of Sydney and Queensland Berghofer Institute of Medical Research (references: EC00278 and P1212).

The current study follows Strengthening the Reporting of Observational Studies in Epidemiology guidelines (online Appendix 1 provides the STROBE checklist). Additional descriptions of the protocol, procedures and data collection processes are provided in online materials (Appendix 2). Further details and research findings (including health service use and treatment profiles) are also available in other recent cohort publications.

2.1 | Brief overview of the BLTS

The BLTS is a community-based cohort study of twins and non-twin siblings, recruited via Brisbane-area schools, media appeals and word of mouth from 1992 onwards. Ethnically, the cohort reflects the population structure of the greater Brisbane area at the time of recruitment, with nearly all participants of European ancestry (Couvy-Duchesne et al., 2018; Mitchell et al., 2019). Individuals were eligible to join the cohort from age 12 onwards with written parental consent. However, the current article focuses only on data collected between the ages of about 15–25 years when the cohort members completed a set of mental health and FH assessments. Repeated self-ratings and interview assessments were performed during this peak age range for the onset of mood and psychotic disorders, and individuals who missed a follow-up could be invited to participate at the next wave (Couvy-Duchesne et al., 2018). Due to the nesting of the data collection within a longitudinal framework, findings from recent cross-sectional assessments can be linked to those from earlier waves (Mitchell et al., 2019).

2.2 | Cohort eligible for this study

As this study uses data about individuals included in previous publications (Scott, Crouse, et al., 2021; Scott, Martin, et al., 2021), we provide only a brief summary of eligibility criteria and clinical assessments (online Appendix 2 provides additional details, including recruitment and assessments of 19Up and 25Up cohorts).

De-identified individual data were extracted from the BLTS data set according to the following inclusion criteria:

i. The cohort member had completed all self-ratings of psychopathology at a follow-up undertaken between age 15–19.
ii. The CIDI (Kessler et al., 2004) and FH of major mental disorders (Milne et al., 2009) assessments were available from the 19Up or 25Up follow-ups.
iii. Age at onset of self-rated psychopathology, for example, subthreshold syndromes, and/or of the first full-threshold CIDI episode was recorded (or could be estimated from information available).

Individuals were excluded if no PRS estimates were available. Likewise, we excluded individuals: if the age at completion of the CIDI assessment and/or estimated age at onset of any full-threshold syndrome *preceded* the age at completion of the symptom self-ratings and/or if insufficient data were recorded and/or ages at onset could not be estimated or specific age data were missing.

Using the above criteria, we identified that 1473 individuals (out of 1815 potential participants) met all the eligibility criteria (Table 1S in online Appendix 3 compares the baseline characteristics of the 1473 cohort members who were included versus the 342 who were excluded).

2.3 | Clinical assessments

Demography: key characteristics were recorded (see Section 3).

Self-rated psychopathology: In this study, individuals completed self-ratings of Hypomanic-Like Experiences, Psychotic-Like Experiences and Depressive-Like Experiences and these data were used to record the prevalence of SubT of mood and psychotic disorders (Iorfino et al., 2019; Scott, Crouse, et al., 2021; Scott, Martin, et al., 2021). Online Appendix 2 gives information regarding the rationale for the selection of these self-rating instruments, details of symptoms assessed and rating scale properties (including psychometrics and clinimetrics), and so on. In part, the instruments were chosen as they have been widely used to evaluate psychopathology experienced by young people in community and clinical settings (including trans-diagnostic early intervention centres) and the ratings can be examined from several perspectives, including prediction of transition to caseness in studies of bipolar disorders, psychotic disorders and staging models (Iorfino et al., 2019; Scott, Crouse, et al., 2021; Scott, Martin, et al., 2021).

CIDI caseness: We applied established algorithms to CIDI assessment data to determine the presence or absence of a range of fourth edition of the diagnostic and statistical manual mental disorders and their age at onset (13). For this study, we extracted data regarding the presence or absence of major depressive, hypo/manic and/or psychotic syndromes that met CIDI criteria for caseness (see online Appendix 2).

FH of mood and psychotic disorders: The presence or absence of any FH of mood and/or psychotic disorders in first degree family members were identified using an online assessment based on the Family History Screen (14; see also Appendix 2).

2.4 | Estimating PRS

Genotyping and quality control procedures have been described elsewhere for the BLTS (Couvy-Duchesne et al., 2018; Mitchell et al., 2019). The PRS used in this study were constructed from well-powered multi-national genome-wide association studies (GWAS) conducted in adult populations.

PRS can be defined as 'a single-value estimate of an individual's common genetic liability to a phenotype, calculated as a sum of their genome-wide genotypes, weighted by corresponding genotype effect size estimates (or *Z*-scores) derived from summary statistic GWAS data' (Wray et al., 2021; Zhou & Zhao, 2021). In this article, we report PRS based on SBayesR estimates for NSM, MDD, BIPOLAR and SCZ. In brief, SBayesR is a non-parametric Bayesian method that estimates the effect sizes of all genetic markers in an accurate and efficient way (see online Appendix 2). We chose this method because it gives the highest prediction accuracy for psychiatric disorders in independent samples (Zhou & Zhao, 2021). In the results, individual PRS for NSM, MDD, BIPOLAR and SCZ are expressed as a single-value estimate (which represents a standardized score that can be positive or negative; and where higher positive scores indicate an individual has a higher genetic predisposition for the trait in question) (Wray et al., 2021).

2.5 | Statistical analyses

Analyses were undertaken using SPSS (version 28.0) and R (using https://CRAN.R-project.org/package=gbm, version 2.1.8.1; /package = logistf; /package = stepwiseLogit version 1.4.4; /package = ROCR, version 1-11.0) and are described briefly below. Additional details regarding all analyses are provided in the online supplementary materials (Appendix 2).

We used bootstrapped MANOVA to assess variations in each PRS according to clinical risk group (FH; SubT; FH and SubT) and CIDI caseness. As described in online Appendix 2 these analyses were adjusted for variables of influence (including twin status, etc.). Statistical significance was assessed using Pillai's trace test statistic and Roy's largest root test statistic (Roy's gives more robust results in balanced samples and Pillai's in unbalanced samples) (Ates et al., 2019).

We used receiver operating curve (ROC) analyses to estimate the prediction of CIDI caseness using a combination of clinical risk factors

with or without the inclusion of all four PRS. Findings are reported as area under the curve (AUC) with 95% confidence intervals (CI).

Finally, we undertook a backward stepwise logistic regression (BSLR) analysis to determine the optimal combination of clinical risk factors and PRS that best predicted clinical outcome (i.e. CIDI caseness at follow-up). Variables of influence (age, sex, mental health status of co-twins and siblings, etc) were included at step one; clinical risk factors (FH and/or SubT) were included at step two; and the four PRS were included at step three of the model. These analyses were replicated in split-half samples (one twin/sibling per sample) to cross-validate findings (see online Appendix 2).

3 | RESULTS

The sample comprised 1473 participants (female = 866; 59%) with a mean age of 26.3 (SD = 4.4); about 93% ($n = 1370$) were of European ancestry, 55% were single and 59% were in full-time employment (see Table 1).

About 26% ($n = 383/1473$) of the cohort had symptoms that met criteria for ≥1 SubT and 346 (23%) individuals had a FH of a mood and/or psychotic disorder (online supplementary Figure 1S). Of these individuals, 198 (13%) reported both a SubT and FH. About 29% of the study cohort ($n = 409$) met criteria for a subsequent full-threshold CIDI diagnosis, 116 (i.e. 28%) of these cases met criteria for ≥2 disorders (online supplementary Figure 2S). The median age at onset for the first SubT, was about 16 years (inter-quartile range (IQR): 14–18) and the median age at first onset of a full-threshold syndrome meeting CIDI diagnostic criteria was about 20 years (IQR: 18–23).

TABLE 1 Key characteristics of the study cohort ($n = 1473$).

Characteristic	Current study cohort ($n = 1473$)
Mean Age in years (SD)	26.3 (4.4)
	Number (%)
Females	866 (59%)
Educational level: junior or senior school only	267 (18%)
Full-time employment	869 (59%)
Civil status: single	998 (55%)
Zygosity	
Monozygotic twins	427 (29%)
Dizygotic twins	530 (36%)
Non-twin siblings	516 (35%)
Clinical risk factors	
Family history mood and/or psychotic disorder	346 (19%)
≥1 Subthreshold syndrome	383 (21%)
Family history and subthreshold syndrome	198 (11%)

Figure 1 shows the distribution plots for each PRS score. As shown, the mean score for each PRS was slightly below zero, whilst the ranges were −3.17 to +3.94 for NSM-PRS, −3.80 to +3.39 for MDD-PRS, −4.16 to +3.80 for BIPOLAR-PRS and −3.10 to +2.97 for SCZ-PRS (also see online supplementary Table 2S).

Figure 2 shows the estimates for NSM-PRS, MDD-PRS, BIPOLAR-PRS and SCZ-PRS across subgroups defined by the presence or absence of different clinical risk factors stratified according to CIDI caseness (also see online supplementary Table 3S and Figures 3S and 4S). Analyses demonstrated that the PRS differed significantly between CIDI cases and non-cases (Pillai's and Roy's tests: $p = .000$). However, as shown by the Tests of Between-Subjects Effects in supplementary Table S3, the statistical significance of differences in PRS across clinical risk groups were less robust (Roy's test $p = .019$; Pillai's $p = .17$), with clearer evidence of a 'dose–response'-type gradient for NSM_PRS ($p = .005$) and MDD_PRS ($p = .000$), a trend towards significance for BIPOLAR-PRS ($p = .059$), but non-significant findings for SCZ-PRS ($p = .224$).

The ROC analyses showed that (after adjusting analyses for variables of influence) the AUC was 0.56 (95% CI: 0.53, 0.59) for the correct classification of CIDI status according to FH alone; the AUC was 0.64 (95% CI: 0.60, 0.67) according to ≥1 SubT alone; and the AUC was .68 (95% CI: .65, .71) according to overall level of risk (i.e. combining FH and SubT status). When we performed a new set of ROC analyses, we found that the AUC ranged from .50 to .54 for each PRS alone (see online supplementary Figure 5S). However, if the four PRS are combined with the SubT (and FH is excluded from the ROC model), the correct classification of CIDI status was marginally improved (AUC 0.70; 95% CI 0.66, 0.74). When the four PRS, and all clinical risk groups (FH, SubT, FH and SubT) are considered, the correct classification of CIDI status increased to 0.71 (95% CI: 0.69, 0.73).

The cross-validated regression model identified five variables that optimally classified study participants according to CIDI caseness (AUC: 0.71; 95% CI: 0.68, 0.74): age, sex, clinical risk group, MDD-PRS and mental health status of cotwins or siblings (i.e. whether one of these family members had a CIDI diagnosis). No other PRS met criteria for inclusion in the final model. The estimate plots for the probability of caseness (P) for each of the variables are shown in Figure 3 (with coefficients and additional details in online Appendix 3, Table 4S).

4 | DISCUSSION

PRS provide an estimate of the degree to which an individual is at risk for a wide range of health problems because of their genetic makeup and may aid decision-making in clinical practice (Murray et al., 2021). As mental disorders are polygenic, construction of PRS is frequently employed in research to estimate associations between genetic vulnerability and psychiatric phenotypes (Wang et al., 2017). Our results show that a combination of clinical risk factors and PRS improved our

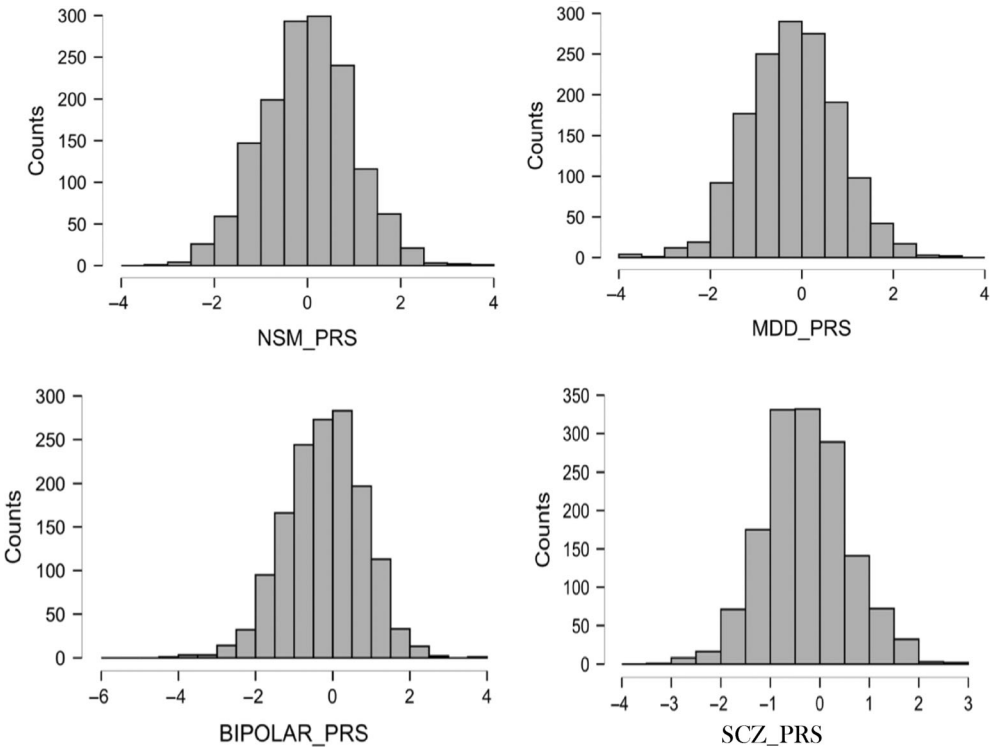

FIGURE 1 Distribution plots for polygenic risk scores (PRS) for neuroticism (NSM), depression (MDD), bipolar disorder (BIPOLAR) and schizophrenia (SCZ).

ability to detect individuals at highest risk of transition to clinical caseness in emerging adulthood.

Previously, Wray et al. (2021) argued that PRS cannot establish or definitively predict the diagnosis of complex conditions such as mental disorders, as PRS only capture part of the genetic contribution, and genetic factors only contribute part of the absolute risk (Murray et al., 2021). Similarly, Lee et al. (2013) suggested that PRS are unlikely to contribute to differential diagnosis in psychiatry because the genetic risks of different mental disorders are moderately to highly correlated and heterogeneity in clinical presentations mean that few PRS are disorder-specific (Lee et al., 2013). Despite the arguments against the predictive validity of PRS and the potential shortcomings we have noted above, there is a growing desire to understand the potential utility of PRS in mental health settings and it is suggested that PRS could be viewed in a similar way to putative biomarkers of course and outcome (Maj et al., 2020; Wray et al., 2021). For example, recent studies indicate that higher PRS for depression, anxiety and neuroticism predict an earlier age at onset of major depression and an accelerated rate of change in depressive symptoms throughout adolescence and early adulthood (Kwong et al., 2021; Mitchell et al., 2021). Also, PRS for schizophrenia may improve the prediction of onset of a full-threshold psychotic disorder in individuals with other clinical indicators of high risk (AUC for caseness ~0.65) (Perkins et al., 2020). From a trans-diagnostic perspective, it is notable that, whilst PRS for major depression are associated with first onset of depression in the general population, the PRS for bipolar disorders can predict the age at onset of depression and the PRS for bipolar disorder and schizophrenia are associated with different clinical manifestations of depression (Musliner et al., 2019). The findings of this study contribute to the notion that PRS can subtly enhance our understanding of early illness processes and highlight some avenues for further research in youth mental health.

This study examined the potential utility of PRS in predicting transition to clinical caseness in a community-residing cohort that was repeatedly assessed during the peak age range for onset of major mental disorders. We confirm previous suggestions (Murray et al., 2021; Wray et al., 2021), that the accuracy of prediction of outcome of caseness can be marginally improved by combining PRS with other measures of risk (age, sex, twin/sib status, FH, SubT). The added value of this study is that it demonstrated that, in a general population sample in this critical age group, there are different patterns of PRS across different risk groups and that the MDD-PRS was the only PRS that significantly contributed to the optimal model for classifying trans-diagnostic caseness. However, it would be premature to assume the other PRS should be excluded from further similar studies and further replications are needed to confirm the validity and generalisability of our findings. This is especially important as there are several limitations to the current study that need to be considered alongside the reported results. First, this is a young adult population and many of those who do not meet CIDI criteria for a major mental disorder currently may yet develop a mood or psychotic disorder in the future. Second, the nature and resourcing of large scale, multidimensional community cohort studies meant that brief self-rated instruments were employed to assess SubT, rather than, for example, more detailed assessments or semi-structured interviews. Third, the PRS employed were constructed from previous GWAS that mostly comprised adults with established, stable diagnoses recruited from clinical settings. Those samples may differ in important ways from our

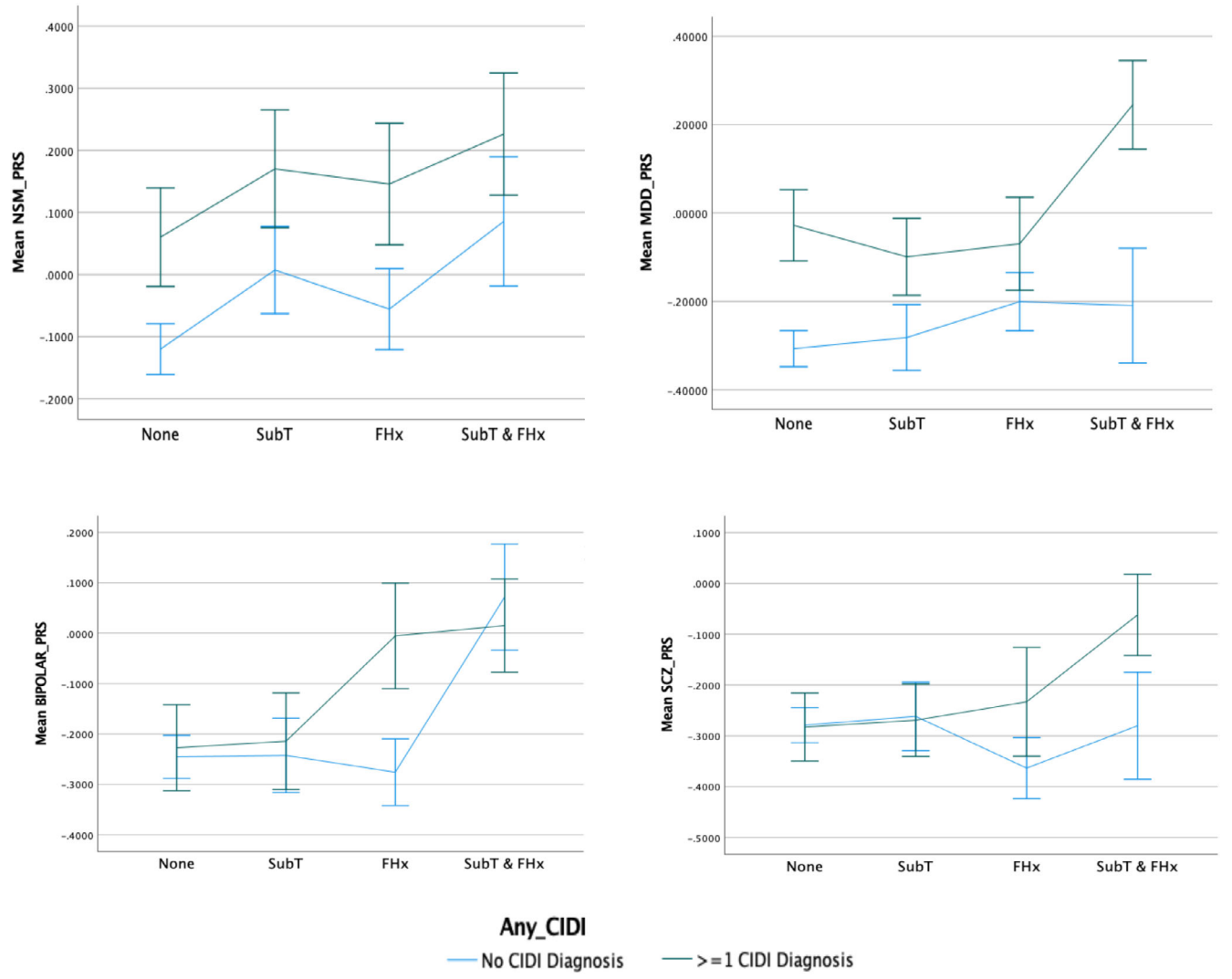

FIGURE 2 Mean polygenic risk scores (PRS, +/− standard error) for neuroticism (NSM), depression (MDD), bipolar disorder (BIPOLAR) and schizophrenia (SCZ) for subgroups defined by the presence or absence of different clinical risk factors and stratified according to Composite International Diagnostic Interview (CIDI) caseness (dotted line represents presence of one or more CIDI syndromes).

younger cohort of twins and siblings recruited from the community, including the pattern of mental disorders, rates of comorbidities, and so on. Fourth, although analyses were cross-validated and adjusted to consider key variables of influence, we did not use some of the specific analyses that are employed for twin studies but chose to extend the approaches used in our previous publications of risk and outcome prediction in this cohort (Couvy-Duchesne et al., 2018; Mitchell et al., 2019; Scott, Crouse, et al., 2021; Scott, Martin, et al., 2021). In addition, it should be noted that the CIDI syndrome of psychosis does not incorporate negative symptoms, and we did not limit the analyses to help-seeking individuals. This may undermine the utility of the SCZ-PRS in our study, especially as Lee et al. (Lee et al., 2013) previously highlighted that, when applying a PRS built from schizophrenia GWAS data obtained from specialist settings to cohorts in other settings (such as community or primary care), it might be more informative to view it as an indicator of more severe or rapidly developing trajectory of ill health. This is a potentially important avenue for research in the BLTS cohort, especially as the patterns of mental disorders will evolve further over time. Regarding the BIPOLAR-PRS, the most striking finding was the robust association with FH. In some ways this is unsurprising as BD shows strong familial patterns. This is notable given that FH is known to tip the balance in favour of early intervention in many circumstances (Musliner et al., 2019; Wang et al., 2017; Zwicker et al., 2018); however, a major limitation of the latter is that a detailed reliable and valid assessment FH is resource intensive (Scott, Crouse, et al., 2021). However, the current study indicates that PRS and FH are not entirely overlapping measures of genetic risk, so the use of both measures may be more informative than selecting one over the other (Verduijn et al., 2017).

In summary, this exploratory study of the prediction of trans-diagnostic CIDI caseness in adolescence and early adulthood demonstrated that PRS incrementally increased the accuracy of the classification of outcomes, and identifies several further important avenues of research including the association of PRS with social and

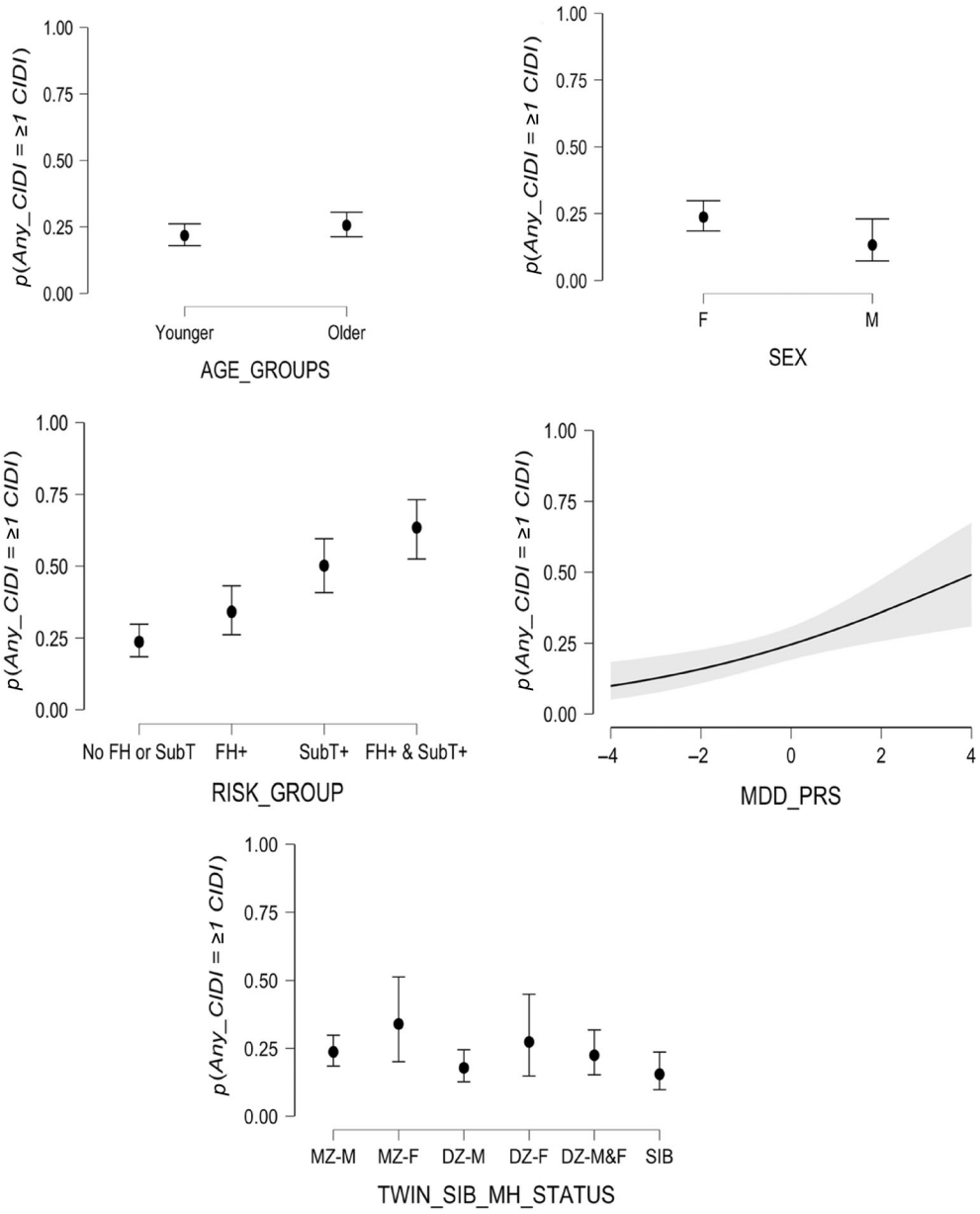

FIGURE 3 Probability estimates for the five variables included in the final model for predicting Composite International Diagnostic Interview (CIDI) caseness (see the text for details). AGE_GROUPS were categorized as below/above (younger/older) the sample median. TWIN_SIB_MH_STATUS identified whether a twin or sibling is classified as a clinical case. ≥1 CIDI, individual presents with a mood and/or psychotic syndrome that meets criteria for the onset of a full-threshold disorder; DZ, dizygotic twins; F, female; FH, family history of mood or psychotic disorders; M, male; MZ, monozygotic twins; SIB, other sibling(s); SubT, any subthreshold syndrome (for a mood and/or psychotic disorder); *p*, probability.

occupational functioning, help-seeking and/or the likelihood of treatment (especially as the PRS are expected to become more powerful as GWAS discovery samples become larger).

Additional references that are relevant to this study are included in the Appendices or are available from the authors.

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CONFLICT OF INTEREST STATEMENT

Sarah Medland is supported by an NHMRC SRF APP1103623. Jacob J. Crouse is supported by an NMHRC Emerging Leadership Fellowship (GNT2008197). Nicholas Martin and Jacob J. Crouse declare no conflict of interest. Jan Scott is a visiting professor at the Brain and Mind Centre and at Universite de Paris, the Norwegian University of Science and Technology (Trondheim) and is a 'Science without Borders' fellow (Brazil). She has received grant funding from the UK Medical Research Council and from the UK NIHR Research for Patient Benefit programme; she declares no financial or other conflict of interests in relation to the topics addressed in this article. Ian B. Hickie is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney. The BMC operates an early intervention youth service at Camperdown under contract to headspace. He is the Chief Scientific Advisor to, and a 3.2% equity shareholder in, InnoWell Pty

Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the $30 M Australian Government-funded Project Synergy (2017–2020; a 3-year programme for the transformation of mental health services) and to lead transformation of mental health services internationally through the use of innovative technologies.

DATA AVAILABILITY STATEMENT

The data sets generated during and/or analysed during the current study are not publicly available due to privacy regulations but are available from the senior authors on reasonable request (and subject to requests receiving ethical approval from the Human Research Ethics Committee at the Queensland Institute of Medical Research [QIMR] in Brisbane).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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