

1 **Associations between polygenic liability for schizophrenia and level of**
2 **psychosis and mood-incongruence in bipolar disorder**
3

4 Judith Allardyce¹ MRCPsych PhD, Ganna Leonenko¹ PhD, Marian Hamshere¹ PhD,
5 Antonio F. Pardiñas¹ PhD, Liz Forty¹ PhD, Sarah Knott² PhD, Katherine-Gordon Smith²
6 PhD, David J. Porteus³ PhD, Caroline Haywood³ PhD, Arianna Di Florio¹ MD PhD, Lisa
7 Jones² PhD, Andrew M. McIntosh³ FRCPsych MD, Michael J. Owen¹ FRCPsych PhD, Peter
8 Holmans¹ PhD, James T.R. Walters¹ MRCPsych PhD, Nicholas Craddock¹ FRCPsych PhD,
9 Ian Jones¹ FRCPsych PhD, Michael C. O'Donovan¹ FRCPsych PhD, Valentina Escott-Price¹
10 PhD

11 ¹MRC Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological
12 Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, UK

13 ²Department of Psychological Medicine, University of Worcester, Worcester, UK

14 ³ Medical Genetics Section, Centre for Genomic and Experimental Medicine, Institute of
15 Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

16 Division of Psychiatry, University of Edinburgh, Edinburgh, UK

17 **Correspondence to:** Judith Allardyce

18

19 MRC Centre for Neuropsychiatric Genetics & Genomics, Cardiff University, Hadyn Ellis
20 Building, Maindy Road, Cathays, Cardiff, CF24 4HQ

21 +44 (0)29 2068 8320

22 allardycej2@cardiff.ac.uk

23 Word count: 2973

24 Date of revision 19/09/2017

25

26 **Key Points**

27 **Question:** what is the relationship between schizophrenia related polygenic liability and
28 the occurrence and level of mood-incongruence of psychotic symptoms in bipolar
29 disorder (BD)?

30 **Findings:** in this case-control study including 4436 BD cases, 4976 schizophrenia cases
31 and 9012 controls, there was an exposure-response gradient of polygenic risk:
32 Schizophrenia > BD with prominent mood-incongruent psychotic features > BD with
33 mood-congruent psychotic features > BD with no psychosis, all differential associations
34 were statistically-significant.

35 **Meaning:** A gradient of genetic liability across schizophrenia and bipolar disorder,
36 indexed by the occurrence of psychosis and level of mood-incongruence has been
37 shown for the first time.

38 Abstract

39 Importance

40 Bipolar disorder (BD) overlaps schizophrenia in its clinical presentation and genetic
41 liability. Alternative approaches to patient stratification beyond current diagnostic
42 categories are needed to understand the underlying disease processes/mechanisms.

43 Objectives

44 To investigate the relationship between common-variant liability for schizophrenia,
45 indexed by polygenic risk scores (PRS) and psychotic presentations of BD, using clinical
46 descriptions which consider both occurrence and level of mood-incongruent psychotic
47 features.

48 Design

49 Case-control design: using multinomial logistic regression, to estimate differential
50 associations of PRS across categories of cases and controls.

51 Settings & Participants

52 4399 BDcases, mean [sd] age-at-interview 46[12] years, of which 2966 were woman
53 (67%) from the BD Research Network (BDRN) were included in the final analyses, with
54 data for 4976 schizophrenia cases and 9012 controls from the Type-1 diabetes genetics
55 consortium and Generation Scotland included for comparison.

56 Exposure

57 Standardised PRS, calculated using alleles with an association p-value threshold < 0.05
58 in the second Psychiatric Genomics Consortium genome-wide association study of
59 schizophrenia, adjusted for the first 10 population principal components and
60 genotyping-platform.

61 **Main outcome measure**

62 Multinomial logit models estimated PRS associations with BD stratified by (1) Research
63 Diagnostic Criteria (RDC) BD subtypes (2) Lifetime occurrence of psychosis.(3) Lifetime
64 mood-incongruent psychotic features and (4) ordinal logistic regression examined PRS
65 associations across levels of mood-incongruence. Ratings were derived from the
66 Schedule for Clinical Assessment in Neuropsychiatry interview (SCAN) and the Bipolar
67 Affective Disorder Dimension Scale (BADDSS).

68 **Results**

69 Across clinical phenotypes, there was an exposure-response gradient with the strongest
70 PRS association for schizophrenia (RR=1.94, (95% C.I. 1.86, 2.01)), then schizoaffective
71 BD (RR=1.37, (95% C.I. 1.22, 1.54)), BD I (RR= 1.30, (95% C.I. 1.24, 1.36)) and BD II
72 (RR=1.04, (95% C.I. 0.97, 1.11)). Within BD cases, there was an effect gradient, indexed
73 by the nature of psychosis, with prominent mood-incongruent psychotic features having
74 the strongest association (RR=1.46, (95% C.I. 1.36, 1.57)), followed by mood-congruent
75 psychosis (RR= 1.24, (95% C.I. 1.17, 1.33)) and lastly, BD cases with no history of
76 psychosis (RR=1.09, (95% C.I. 1.04, 1.15)).

77 **Conclusion**

78 We show for the first time a polygenic-risk gradient, across schizophrenia and bipolar
79 disorder, indexed by the occurrence and level of mood-incongruent psychotic
80 symptoms.

81

82 Introduction

83 Although classified as a discrete diagnostic category¹⁻³, bipolar disorder (BD) overlaps
84 considerably with schizophrenia (SCZ) in both its clinical presentation⁴⁻¹³ and genetic
85 liability¹⁴⁻²². BD is a phenomenologically heterogeneous construct and within the
86 diagnostic category, individuals may have quite different symptom profiles. It has been
87 proposed, that this clinical heterogeneity indicates underlying aetiological
88 heterogeneity and the degree of clinical similarity between BD and SCZ reflects,
89 overlapping alleles which selectively influence specific, shared clinical characteristics,
90 rather than the global risk for the disorders²³⁻²⁵.

91 Delusions and hallucinations are common in BD^{26,27} with around one third of all
92 psychotic features judged to be mood-incongruent^{28,29}. Mood-incongruent psychotic
93 features, are associated with poorer prognosis, poor lithium-response and are
94 qualitatively similar to the prototypic symptoms of SCZ³⁰⁻³², suggesting that BD with
95 psychosis and particularly mood-incongruent psychotic features, may specify a
96 subgroup/stratum with stronger aetiological links to SCZ. Stratified linkage and
97 candidate-gene studies of BD associations with chromosomal regions and genes
98 implicated in SCZ, show stronger effects in psychosis and mood-incongruent
99 subsamples³³⁻³⁶ providing some support for this causal heterogeneity hypothesis,
100 however lack of consistency in earlier linkage and candidate-gene studies renders the
101 overall support weak.

102 Recently, genome-wide association studies (GWAS) have found a substantial polygenic
103 component to both BD and SCZ risk, with a large proportion of their genetic variance
104 explained by common alleles, partially shared across the two disorders²⁰. Polygenic-
105 risk can be calculated for individuals, with a single summary measure: the polygenic

106 risk score (PRS), which allows us to examine the genetic basis of symptom domains,
107 within and across the two disorders ³⁷⁻³⁹ with greater power than the historical linkage
108 and candidate-gene approaches. PRS-SCZ differentiate BD from controls ^{20,40} and there
109 are differential associations across subtypes with schizoaffective bipolar disorder
110 (SABD) (intermediate subtype, characterised by admixture of SCZ and BD symptoms)
111 having a relatively larger burden of SCZ risk, compared to other BD subtypes ^{15,41}. To
112 date, lack of power in well phenotyped samples has hindered fine-scale examination of
113 the relationship between SCZ polygenic-risk and psychotic symptoms in BD.

114 We aimed to examine the relationship between polygenic liability for SCZ and psychotic
115 presentations of BD using PRS generated from the most powerful SCZ-GWAS discovery
116 set available, currently ²¹. Measures relevant to the occurrence and nature of psychotic
117 symptoms were considered. We hypothesised BD with psychosis would be associated
118 with higher polygenic-risk for SCZ and this association would be stronger when mood-
119 incongruent psychotic features were present, given their phenotypic similarity to the
120 psychotic symptoms of prototypic SCZ.

121 **Methods**

122 **Sample Ascertainment**

123 **Bipolar Disorder sample**

124 4436 cases of BD with deep phenotypic information, European ancestry, domicile in the
125 UK, collected between 2000 - 2013 were available via the UK BD Research Network
126 (BDRN) using recruitment methods reported previously ^{15,42,43}. The sample has 1399
127 cases not included in prior BDRN publications ^{15,41}. All participants were assessed using
128 a consistent protocol which included the Schedule for Clinical Assessment in
129 Neuropsychiatry interview (SCAN) ⁴⁴ administered by trained research psychologists

130 and psychiatrists, with very good to excellent inter-rater reliability for all domains of
131 psychopathology ⁴⁵. Using information from the SCAN and casenote review, the
132 Operational Criteria Checklist (OPCRIT) ⁴⁶ was completed. Research Diagnostic Criteria
133 (RDC) ³diagnoses, which differentiate individuals on the basis of the their pattern of
134 mood and psychotic symptoms better ⁴¹ than either DSM ² or ICD-10¹, were made using
135 the consensus lifetime best-estimate method, informed by all available information⁴⁷.

136 Schizophrenia sample

137 To allow comparison of BD with SCZ, we included a subset (N=4976) of the CLOZUK
138 sample, collected via the Zapronex[®] Treatment Access System as detailed in a previous
139 report⁴⁸, All were prescribed clozapine for treatment resistant SCZ (TRS) and are
140 independent of, and unrelated ($\pi\text{-hat} < 0.2$) to individuals in the discovery GWAS²¹. In
141 principle, TRS may carry higher polygenic-risk burden, however PRS in CLOZUK are
142 similar to the other SCZ samples used by the Psychiatric Genomics Consortium²¹.

143 Control Samples

144 The controls came from two UK sources: the Type-1 diabetes genetics consortium
145 (TIDGC) (n = 2,532) are unscreened controls, recruited through the 1958 birth-cohort
146 ⁴⁹ and the other is a subsample of the Generation Scotland (n = 6,480) study, screened
147 for psychiatric disorders ⁵⁰. Controls are unrelated ($\pi\text{-hat} < 0.2$) to individuals in the
148 PGC-SCZ discovery set, and were matched ancestrally to our case datasets ⁴⁸.

149 All samples have appropriate ethics approvals.

150 Genotyping, quality control (QC), phasing and imputation

151 Bipolar cases

152 Genotypic data for the BD cases were processed in 3 batches, each on a different
153 platform. To mitigate against potential bias from batch effects⁵¹, stringent QC was

154 performed on each platform separately prior to merging. Single nucleotide
155 polymorphisms (SNPs) were excluded if the call rate was $< 98\%$, MAF was < 0.01 or
156 they deviated from HWE at $p < 1 \times 10^{-6}$. Individuals were excluded if they had minimal or
157 excessive autosomal homozygosity ($|F| > 0.1$), high pairwise relatedness ($\pi\text{-hat} > 0.2$)
158 or mismatch between recorded and genotypic sex. Following QC, the data for each
159 platform were phased using SHAPEIT⁵² and imputed with IMPUTE2⁵³, using the 1000
160 Genomes reference panel (Phase3, 2014). Imputed data were converted into the most
161 probable genotypes (probability > 0.9) and merged on shared SNPs. 4399 BD cases
162 remained after QC.

163 CLOZUK cases and Controls

164 The CLOZUK and control samples had been through strict QC separately, before being
165 phased and imputed simultaneously as part of a larger SCZ study⁴⁸.

166 Merging BD, CLOZUK and control imputed genotypic datasets

167 After excluding SNPs with strand ambiguity; BD, CLOZUK and control samples were
168 merged and the imputed markers underwent a second QC filter⁵¹, excluding SNPs with;
169 missingness in $> 5\%$ of individuals, (INFO) < 0.8 , MAF < 0.01 or deviation from HWE at p
170 $< 1 \times 10^{-6}$.

171 Principal Component Analysis

172 To adjust for potential confounding from population structure, we performed PCA using
173 PLINK v1.9, after LD pruning and frequency filtering the SNPs from the merged sample,
174 keeping the eigenvectors for the first 10 principal components (PCs) to use as
175 covariates in the association analysis.

176 Polygenic Risk Scores (PRS)

177 We generated PRS²⁰, using the 2014 PGC-SCZ meta-analysis as our discovery set²¹
178 calculated for each individual, based on a set of alleles with association p-values < 0.05.
179 This decision was informed by the PGC leave one-cohort-out PRS analyses, for all SNP
180 selection p-value thresholds, which found the median and mode of the cut-off = 0.05.
181 This represents the association that best optimises the balance of false and true risk
182 alleles, at the current discovery sample size ²¹. The most informative and independent
183 markers were selected to minimise statistical noise where possible, using p-value
184 informed clumping, at $r^2 < 0.2$ with 1MB windows and by excluding the extended MHC
185 (Chr6: position 25-35MB) because of its complex LD structure .

186 Outcome measure of lifetime psychosis & mood incongruence

187 Subtypes of BD

188 RDC subtypes were used as categorical outcomes in case-control analyses. The RDC ³
189 and Diagnostic and Statistical Manual of Mental Disorders (DSM) ², though not the ICD-
190 10 Classification of Mental and Behavioural Disorder (ICD-10) ¹, subdivides BD into
191 bipolar I disorder (BD I) and bipolar II disorder (BD II) depending on the nature of the
192 mood states; mania in (BP I) and hypomania in (BP II). All classification systems
193 recognise SABD. Psychotic symptoms are most prominent in SABD, then BD I, and least
194 prominent in BD II ^{54,55}.

195 The Bipolar Affective Disorder Dimension Scale

196 Outcome measures were generated from The Bipolar Affective Disorder Scale (BADDs)
197 Psychosis (P) and mood-incongruence (I) subscales, which provide an ordered (not
198 necessarily linear) measure of lifetime symptom domain severity⁵⁶. An inter-rater

199 reliability exercise for this sample demonstrates excellent interclass correlation: (P)
200 0.91 and (I) 0.89.

201 1) A binary categorical outcome measure for lifetime occurrence of psychosis defined as
202 an unambiguous episode of positive and/or disorganised psychotic symptoms,
203 generated by dichotomising the (P) domain scale at a score > 9 ⁵⁶.

204 2) A binary categorical outcome measure for lifetime occurrence of predominant mood-
205 incongruent psychotic features (high v low prominence of mood-incongruence),
206 generated by dichotomising the (I) domain scale at a score >19 .

207 3) An ordinal measure of mood-incongruent psychotic features which assesses the
208 overall balance between mood-congruent and mood-incongruent psychosis across the
209 lifetime, rated using all available information according to BDRN protocol (E
210 supplement : Note 1)

211 **Statistical Analysis**

212 A multinomial logit model (MNL) was used to estimate differential associations of
213 standardised PRS, adjusted for the first 10 PCs and genotyping-platform, across
214 categories of cases and controls. We report the estimated coefficients transformed to
215 relative risk-ratios (RR), defined as the exponentiated regression coefficient. PRS
216 association across levels of mood-incongruent psychotic features using ordinal logistic
217 regression was also estimated. To examine whether SABD subtypes were driving
218 observed PRS associations with mood-incongruent psychotic features, we did a
219 sensitivity analysis excluding SABD cases. Post-estimation predicted probabilities were
220 plotted to aid interpretation of the PRS associations across RDC subtypes of BD⁵⁷. To
221 correct for multiple comparisons of PRS associations across different phenotypic strata
222 within each model, bootstrapped standard errors and 95% confidence intervals were

223 generated, as an approximation to exact permutation methods⁵⁸(supplementary E -
224 Note 2). Possible family-wise type-1 error proliferation was controlled for using the
225 Bonferroni Method, calculated by multiplying the bootstrapped p-values by four⁵⁹.

226 Post-hoc analyses used a MNLM case-control design to examine differential associations
227 across composite phenotypic categories defined by subtype BDI and BD II stratified by
228 psychosis status and a complementary logistic regression analyses comparing the effect
229 of PRS on lifetime occurrence of psychosis, across BD I and BD II subtypes. To examine
230 the distribution of RDC defined cases across levels of PRS, we converted PRS to deciles
231 and generated a stacked bar-chart (SCZ (CLOZUK), SABD, BD I, BD II), by decile.

232 Analyses were performed using PLINK v1.9⁶⁰ or STATA (*Stata Statistical Software:*
233 *Release 14*. College Station, TX: Stata Corp, LP).

234 Results

235 Sample description, Genotyping and quality control

236 After merging BD, CLOZUK and control imputed-genotyped samples and further QC,
237 18,387 cases and controls (E-supplementary Table 1) with 3,451,354 SNPs with INFO
238 score > 0.8 and MAF >1% were available for analysis. Within the BD sample 52% (N =
239 2296) of cases endorsed lifetime occurrence of definite psychosis, with <1%
240 missingness in this variable (N=25). Of the BD cases with definite psychosis, 43% (N=
241 981) were classed as having high lifetime mood-incongruent psychotic features. There
242 was a 9% (N=214) missingness rate for the mood-incongruence variable, within the BD
243 cases with psychosis.

244 Case Control PRS associations

245 As expected (Table 1 Section A), PRS discriminated CLOZUK from controls. PRS in those
246 with a diagnosis of SABD or BD I, but not BD II, were significantly higher than controls.

247 PRS associations within cases

248 PRS discriminated SCZ from all BD subtypes (Table 2). Within BD, PRS discriminates BD
249 II from both BD I and SABD (Figure 1). The percentage of CLOZUK cases increased
250 monotonically with increasing decile PRS, while the percentage of bipolar subtypes
251 decreased (Figure 2).

252 PRS associations with psychotic BD

253 Compared to controls, the PRS were higher in BD, regardless of whether there was a
254 history of psychosis (Table 1, Section B, Figure 2). However, PRS were significantly
255 higher in BD with psychosis, compared to BD without psychosis (Table 1, Section B,
256 figure 3). Within BD cases, PRS discriminated those with and without psychosis
257 (RR=1.25, 95% bootstrapped adjusted p-value < 001, C.I. (1.16, 1.33)).

258 Post hoc analyses showed the association between PRS and psychosis was present in BD
259 I (OR = 1.21, 95% C.I. 1.10, 1.32) but were not statistically significant in BD II (OR =
260 0.98, 95% C.I. 0.80, 1.18). Composite subgroup defined as BD I with psychosis - had
261 higher PRS compared to controls (RR = 1.38, 95% C.I. 1.31, 1.46) this association was
262 significantly stronger than that of the composite BD I/no psychosis (RR= 1.16, 95% C.I.
263 1.08, 1.25). Within BD II, there was no differential association across subgroups defined
264 by presence/absence of psychosis as compared to controls (supplementary-E: Table-1).

265 PRS associations with mood-incongruent psychotic features

266 Psychotic BD characterised by high mood-incongruence has a higher SCZ polygenic risk
267 burden than controls, with a one standard-deviation increase in PRS increasing the RR
268 of being in the high mood-incongruence category by 46% (RR= 1.46, bootstrapped,
269 95% C.I. 1.36, 1.57) (Figure 3, Table 1 Section C). Although the association was
270 significantly weaker than for the high mood-incongruent group, schizophrenia risk-
271 alleles were enriched in those with low mood-incongruence compared with controls
272 (RR= 1.24, bootstrapped 95% C.I. (1.17, 1.33). Sensitivity analysis excluding the SABD
273 group from analyses found comparable results (Table 1: Section D). Finally, a within-
274 BD-case analysis, measuring mood-incongruence on an ordinal scale found the odds of
275 having higher levels of mood-incongruence, increased with increasing PRS (OR=1.17,
276 (bootstrapped p-value < .001, 95% C.I. 1.08 - 1.27)). Analyses excluding the SABD
277 sample found comparable results (OR=1.20, bootstrapped p-value < .001, 95% C.I.
278 1.09, 1.32).

279 Discussion

280 Main Findings

281 Higher PRS-SCZ in BD ^{20,61} is well established. Here, we replicate and extend this
282 observation, demonstrating a gradient of PRS associations across SCZ and BD subtypes
283 (CLOZUK > SABD > BD I with psychosis > BD I without psychosis > BD II). We also
284 show BD cases with psychosis carry a higher burden of SCZ risk-alleles, compared to BD
285 without a history of psychosis. Furthermore, individuals with psychotic BD
286 characterised by prominent mood-incongruent psychotic features, carry the highest
287 burden of schizophrenia risk-alleles. There is a clear exposure-response gradient, with
288 increasing PRS associated with psychotic BD and increasing mood-incongruence

289 (mood-incongruent > mood-congruent > no psychosis), supporting our hypothesis that
290 mood-incongruence indexes phenotypic features linked to SCZ liability.

291 Previously published work examining PRS for SCZ across BD, stratified by psychosis, did
292 not find significant discrimination^{41,62} although a trend was observed, consistent with
293 the findings presented here. The most likely explanations for the enhanced signal in the
294 current analysis are: PRS were constructed using alleles derived from a larger SCZ-
295 GWAS discovery set which reduces measurement error plus improved power from both
296 this and the larger BD sample⁶³. This group has shown⁴¹, PRS-SCZ significantly
297 differentiate SABD from non-SABD subtypes, while finding no statistically significant
298 differential between BD stratified by psychosis, suggesting it is the nature of the
299 psychotic symptoms rather than their presence which better indexes liability shared
300 with SCZ. The current analysis supports this proposition that it is the level of mood-
301 incongruence rather than the presence of psychosis *per se* which better specifies a
302 shared biologically-validated dimensional trait, captured, but with less precision by the
303 SABD diagnostic category.

304 Psychosis and mood-incongruent psychotic features are known to be correlated to
305 poorer prognosis and treatment response³⁰⁻³² It is possible the trans-diagnostic
306 exposure-response gradient for PRS with the occurrence and nature of psychotic
307 symptoms presented here, could be the result of a general psychopathological factor
308 cutting across psychiatric disorders which influences the severity of psychopathology
309 generally, as well as, or rather than a psychosis-specific domain and that PRS derived
310 from SCZ GWAS may be indexing a general liability for psychopathology severity (at
311 least in part)⁶⁴ rather than a (SCZ) disease specific liability.

312 Implications

313 Our study supports the hypothesis that within BD, positive and disorganized psychotic
314 symptoms, and in particular mood-incongruent psychotic features, represent a
315 dimensionally defined stratum with underpinning biological validity. These features are
316 not only phenotypically similar to those observed in prototypal schizophrenia but also
317 index a greater shared genetic aetiology suggesting they share more pathophysiology ⁶⁵.
318 It is notable that in those diagnosed with BD I with no history of psychosis, the
319 association with schizophrenia liability was weaker but still on average higher than in
320 the control group, while in the BD II subsample there was no overlap with SCZ liability.
321 We are not suggesting psychotic features are the best or only index of shared
322 pathophysiology, but having established stronger genetic links between the risk for SCZ
323 and BD characterised by the occurrence of psychosis and level of mood-incongruence,
324 we now have a basis to refine this signal. These findings represent a step towards the
325 goal of reconceptualising phenotypic definitions using richer clinical signatures,
326 measured across quantitative/qualitative domains including, symptom loadings and
327 biomarker expression, outlined in the rationale for the Research Domain Criteria
328 (RDoC) ^{66,67} and the road map for mental health research (ROAMER) ⁶⁸ projects. It is
329 probable however a multidimensional stratification process will harness the observed
330 clinical heterogeneity better and define more precise patient-strata/subgroups in closer
331 alignment with the underlying pathophysiology ⁶⁸⁻⁷⁰

332 Methodological considerations

333 The phenotypic ratings used in the current analyses are based on both SCAN interviews
334 and case-note review by raters with excellent inter-rater reliability, which is expected to
335 minimise rates of missing data and reduce the likelihood of phenotypic

336 misclassification⁷¹. Our psychosis phenotypes are broadly defined and likely to
337 represent imperfect measurements of a continuously distributed phenotype⁷², imposing
338 categorical constraints as we have done may reduce power. We generated PRS using a
339 single discovery set p-value threshold < 0.05 and dealt with multiple comparisons,
340 across different phenotypic categories/strata using bootstrap re-sampling approaches
341 within each of our 4 independent analyses, adjusting for family-wise type-1 error
342 proliferation using Bonferroni's correction. We have mitigated against potential
343 confounding due to population stratification and potential batch effects across cases
344 and controls, by partialling out the first 10 PCs and genotyping platforms from the PRS.
345 The PRS were generated using most probable genotypes which can potentially reduce
346 power due to a small (non-differential) loss of information at some markers making our
347 results conservative, but the conclusions are unlikely to change. Finally, we have only
348 examined the effect of common variants, as rare variants are not captured by current
349 GWAS.

350 **Conclusions**

351 We show for the first time a gradient of polygenic liability across schizophrenia and
352 bipolar disorder, indexed by the occurrence and level of mood-incongruence of positive
353 and disorganised psychotic symptoms. This highlights the usefulness of genetic data to
354 dissect clinical heterogeneity within and across disorders, and suggests further research
355 could potentially aid in defining patient stratifiers with improved biological
356 precision/validity, moving us tentatively towards precision medicine in psychiatry.

357

358 Acknowledgements

359 The work at Cardiff University was funded by Medical Research Council (MRC) Centre
360 (MR/L010305/1) and Program Grants (G0800509). The CLOZUK sample was
361 genotyped with funding from the European Union's Seventh Framework Programme for
362 research, technological development and demonstration under grant agreement n°
363 279227 (CRESTAR Consortium; <http://www.crestar-project.eu/>). For the CLOZUK
364 sample we thank Leyden Delta (Nijmegen, Netherlands) for supporting the sample
365 collection, anonymisation and data preparation (particularly Marinka Helthuis, John
366 Jansen, Karel Jollie and Anouschka Colson) and Andy Walker from Magna Laboratories
367 (UK). We acknowledge Lesley Bates, Catherine Bresner and Lucinda Hopkins, at Cardiff
368 University, for laboratory sample management.

369 We would like to acknowledge funding for BDRN from the Wellcome Trust and Stanley
370 Medical Research Institute, all members of BDRN, and especially the participants who
371 have kindly given their time to participate in our research.

372
373 Generation Scotland (GS) received core support from the Chief Scientist Office of the
374 Scottish Government Health Directorates [CZD/16/6] and the Scottish Funding Council
375 [HR03006]. Genotyping of the GS:SFHS samples was carried out by the Genetics Core
376 Laboratory at the Wellcome Trust Clinical Research Facility, Edinburgh, Scotland and
377 was funded by the Medical Research Council UK and the Wellcome Trust (Wellcome
378 Trust Strategic Award "STratifying Resilience and Depression Longitudinally" (STRADL)
379 Reference 104036/Z/14/Z)

380
381 The Type 1 Diabetes Genetics Consortium (T1DGC; EGA dataset EGAS00000000038) is
382 a collaborative clinical study sponsored by the National Institute of Diabetes and
383 Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious
384 Diseases (NIAID), National Human Genome Research Institute (NHGRI), National
385 Institute of Child Health and Human Development (NICHD), and JDRF. Venous blood
386 collection for the 1958 Birth Cohort (NCDS) was funded by the UK's Medical Research
387 Council (MRC) grant G0000934, peripheral blood lymphocyte preparation by Juvenile
388 Diabetes Research Foundation (JDRF) and WT and the cell-line production, DNA
389 extraction and processing by WT grant 06854/Z/02/Z. Genotyping was supported by
390 WT (083270) and the European Union (EU; ENGAGE: HEALTH-F4-2007- 201413).

391
392 The funders have had no role in the design and conduct of the study; collection,
393 management, analysis, and interpretation of the data; preparation, review, or approval
394 of the manuscript; and decision to submit the manuscript for publication

395
396 V Escott-Price had full access to all the data in the study and takes responsibility for the
397 integrity of the data and the accuracy of the data analysis.

398 J. Allardyce, G. Leonenko, A F J. Pardiñas, M. Hamshere and V. Escott-Price, all from MRC
399 Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine
400 and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, UK conducted
401 and are responsible for the data analysis.

402
403 Conflict of interest Disclosures: M.C. O'Donovan received a consultancy fee from Roche
404 in July 2015. No other disclosures are reported

405

406 Reference List

- 407 1. *ICD-10 Classification of Mental and Behavioural Disorder: Clinical Descriptions and Diagnostic*
408 *Guidelines*. Geneva: World Health Organisation 1992.
- 409 2. *Diagnostic and Statistical Manual of Mental Disorders* 5th ed. Arlington: American
410 Psychiatric Association; 2013.
- 411 3. Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability.
412 *Archives of general psychiatry*. 1978;35(6):773-782.
- 413 4. Allardyce J, McCreddie RG, Morrison G, van Os J. Do symptom dimensions or categorical
414 diagnoses best discriminate between known risk factors for psychosis? *Social psychiatry and*
415 *psychiatric epidemiology*. 2007;42(6):429-437.
- 416 5. Derks EM, Allardyce J, Boks MP, Vermunt JK, Hijman R, Ophoff RA. Kraepelin was right: a
417 latent class analysis of symptom dimensions in patients and controls. *Schizophrenia bulletin*.
418 2012;38(3):495-505.
- 419 6. Dikeos DG, Wickham H, McDONALD C, et al. Distribution of symptom dimensions across
420 Kraepelinian divisions. *The British Journal of Psychiatry*. 2006;189(4):346-353.
- 421 7. Kitamura T, Okazaki Y, Fujinawa A, Yoshino M, Kasahara Y. Symptoms of psychoses. A factor-
422 analytic study. *The British Journal of Psychiatry*. 1995;166(2):236-240.
- 423 8. Lindenmayer J-P, Brown E, Baker RW, et al. An excitement subscale of the Positive and
424 Negative Syndrome Scale. *Schizophrenia research*. 2004;68(2):331-337.
- 425 9. McGorry P, Bell R, Dudgeon P, Jackson H. The dimensional structure of first episode
426 psychosis: an exploratory factor analysis. *Psychological medicine*. 1998;28(04):935-947.
- 427 10. McIntosh A, Forrester A, Lawrie S, et al. A factor model of the functional psychoses and the
428 relationship of factors to clinical variables and brain morphology. *Psychological medicine*.
429 2001;31(01):159-171.
- 430 11. Murray V, McKee I, Miller P, et al. Dimensions and classes of psychosis in a population
431 cohort: a four-class, four-dimension model of schizophrenia and affective psychoses.
432 *Psychological medicine*. 2005;35(04):499-510.
- 433 12. Ratakonda S, Gorman JM, Yale SA, Amador XF. Characterization of psychotic conditions: Use
434 of the domains of psychopathology model. *Archives of General Psychiatry*. 1998;55(1):75-81.
- 435 13. Serretti A, Olgiati P. Dimensions of major psychoses: a confirmatory factor analysis of six
436 competing models. *Psychiatry research*. 2004;127(1):101-109.
- 437 14. Alastair G. Cardno, Frühling V. Rijsdijk, Pak C. Sham, Robin M. Murray, Peter McGuffin. A
438 Twin Study of Genetic Relationships Between Psychotic Symptoms. *American Journal of*
439 *Psychiatry*. 2002;159(4):539-545.
- 440 15. Charney AW, Ruderfer DM, Stahl EA, et al. Evidence for genetic heterogeneity between
441 clinical subtypes of bipolar disorder. *Transl Psychiatry*. 2017;7:e993.
- 442 16. Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH. Genetic relationship between
443 five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet*. 2013;45:984-994.
- 444 17. Lichtenstein P, Yip BH, Bjork C, Pawitan Y, Cannon TD, Sullivan PF. Common genetic
445 determinants of schizophrenia and bipolar disorder in Swedish families: a population-based
446 study. *Lancet*. 2009;373:234-239.
- 447 18. Maier W, Lichtermann D, Franke P, Heun R, Falkai P, Rietschel M. The dichotomy of
448 schizophrenia and affective disorders in extended pedigrees. *Schizophrenia*
449 *Research*. 57(2):259-266.
- 450 19. Mortensen P, Pedersen CB, Melbye MM, Mors OO, Ewald HH. Individual and familial risk
451 factors for bipolar affective disorders in denmark. *Archives of General Psychiatry*.
452 2003;60(12):1209-1215.
- 453 20. Purcell SM, Wray NR, Stone JL, et al. Common polygenic variation contributes to risk of
454 schizophrenia and bipolar disorder. *Nature*. 2009;460(7256):748-752.

- 455 21. Consortium SWGotPG. Biological insights from 108 schizophrenia-associated genetic loci.
456 *Nature*. 2014;511:421-427.
- 457 22. Ruderfer D, Fanous A, Ripke S, McQuillin A, Amdur R. Cross-Disorder Working Group of
458 Psychiatric Genomics Consortium, et al. Polygenic dissection of diagnosis and clinical
459 dimensions of bipolar disorder and schizophrenia. *Mol Psychiatry*. 2014;19(9):1017-1024.
- 460 23. Ford JM, Morris SE, Hoffman RE, et al. Studying hallucinations within the NIMH RDoC
461 framework. *Schizophrenia bulletin*. 2014:sbu011.
- 462 24. Manchia M, Cullis J, Turecki G, Rouleau GA, Uher R, Alda M. The impact of phenotypic and
463 genetic heterogeneity on results of genome wide association studies of complex diseases.
464 *PloS one*. 2013;8(10):e76295.
- 465 25. Wray NR, Maier R. Genetic basis of complex genetic disease: the contribution of disease
466 heterogeneity to missing heritability. *Current Epidemiology Reports*. 2014;1(4):220-227.
- 467 26. Diefendorf AR, Kraepelin E. Clinical psychiatry: A textbook for students and physicians,
468 abstracted and adapted from the 7th German edition of Kraepelin's Lehrbuch der Psychiatrie
469 In:1907:562.
- 470 27. Organization WH. Report of the international pilot study of schizophrenia. 1973.
- 471 28. Azorin JM, Akiskal H, Hantouche E. The mood-instability hypothesis in the origin of mood-
472 congruent versus mood-incongruent psychotic distinction in mania: validation in a French
473 National Study of 1090 patients. *Journal of affective disorders*. 2006;96(3):215-223.
- 474 29. Black DW, Nasrallah A. Hallucinations and delusions in 1,715 patients with unipolar and
475 bipolar affective disorders. *Psychopathology*. 1989;22(1):28-34.
- 476 30. Goes FS, Zandi PP, Miao K, et al. Mood-incongruent psychotic features in bipolar disorder:
477 familial aggregation and suggestive linkage to 2p11-q14 and 13q21-33. *American Journal of*
478 *Psychiatry*. 2007;164(2):236-247.
- 479 31. Tohen M, Tsuang MT, Goodwin DC. Prediction of outcome in mania by mood-congruent or
480 mood-incongruent psychotic features. *American Journal of Psychiatry*. 1992;149:1580-1580.
- 481 32. Toni C, Perugi G, Mata B, Madaro D, Marenmani I, Akiskal HS. Is mood-incongruent manic
482 psychosis a distinct subtype? *European archives of psychiatry and clinical neuroscience*.
483 2001;251(1):12-17.
- 484 33. Green EK, Raybould R, Macgregor S, et al. Operation of the schizophrenia susceptibility gene,
485 neuregulin 1, across traditional diagnostic boundaries to increase risk for bipolar disorder.
486 *Archives of General Psychiatry*. 2005;62(6):642-648.
- 487 34. Park N, Juo SH, Cheng R, et al. Linkage analysis of psychosis in bipolar pedigrees suggests
488 novel putative loci for bipolar disorder and shared susceptibility with schizophrenia. *Mol*
489 *Psychiatry*. 2004;9(12):1091-1099.
- 490 35. Potash JB, Zandi PP, Willour VL, et al. Suggestive linkage to chromosomal regions 13q31 and
491 22q12 in families with psychotic bipolar disorder. *American Journal of Psychiatry*.
492 2003;160(4):680-686.
- 493 36. Raybould R, Green EK, MacGregor S, et al. Bipolar disorder and polymorphisms in the
494 dysbindin gene (DTNBP1). *Biological psychiatry*. 2005;57(7):696-701.
- 495 37. Dudbridge F. Polygenic Epidemiology. *Genetic Epidemiology*. 2016;40(4):268-272.
- 496 38. Pasaniuc B, Price AL. Dissecting the genetics of complex traits using summary association
497 statistics. *Nature Reviews Genetics*. 2016.
- 498 39. Wray NR, Lee SH, Mehta D, Vinkhuyzen AA, Dudbridge F, Middeldorp CM. Research review:
499 Polygenic methods and their application to psychiatric traits. *Journal of child psychology and*
500 *psychiatry, and allied disciplines*. 2014;55(10):1068-1087.
- 501 40. Consortium C-DGotPG. Genetic relationship between five psychiatric disorders estimated
502 from genome-wide SNPs. *Nature genetics*. 2013;45(9):984-994.
- 503 41. Hamshere ML, O'Donovan MC, Jones IR, et al. Polygenic dissection of the bipolar phenotype.
504 *The British Journal of Psychiatry*. 2011;198(4):284-288.

- 505 42. Green EK, Hamshere M, Forty L, Gordon-Smith K, Fraser C, Russell E. Replication of bipolar
506 disorder susceptibility alleles and identification of two novel genome-wide significant
507 associations in a new bipolar disorder case-control sample. *Mol Psychiatry*. 2013;18:1302-
508 1307.
- 509 43. Green EK, Rees E, Walters JTR, et al. Copy number variation in bipolar disorder. *Mol*
510 *Psychiatry*. 2016;21(1):89-93.
- 511 44. Wing JK, Babor TT, Brugha TT, et al. Scan: Schedules four clinical assessment in
512 neuropsychiatry. *Archives of General Psychiatry*. 1990;47(6):589-593.
- 513 45. Jones L, Scott J, Haque S, et al. Cognitive style in bipolar disorder. *The British Journal of*
514 *Psychiatry*. 2005;187(5):431-437.
- 515 46. McGuffin P, Farmer A, Harvey I. A polydiagnostic application of operational criteria in studies
516 of psychotic illness: Development and reliability of the opcrit system. *Archives of General*
517 *Psychiatry*. 1991;48(8):764-770.
- 518 47. Leckman JF, Sholomskas D, Thompson D, Belanger A, Weissman MM. Best estimate of
519 lifetime psychiatric diagnosis: a methodological study. *Archives of General Psychiatry*.
520 1982;39(8):879-883.
- 521 48. Pardiñas AF, Holmans P, Pocklington AJ, et al. Common schizophrenia alleles are enriched in
522 mutation-intolerant genes and maintained by background selection. *bioRxiv*. 2016.
- 523 49. Hilner JE, Perdue LH, Sides EG, et al. Designing and implementing sample and data collection
524 for an international genetics study: the Type 1 Diabetes Genetics Consortium (T1DGC).
525 *Clinical trials*. 2010;7(1_suppl):S5-S32.
- 526 50. Amador C, Huffman J, Trochet H, et al. Recent genomic heritage in Scotland. *BMC genomics*.
527 2015;16(1):437.
- 528 51. Zuvich RL, Armstrong LL, Bielinski SJ, et al. Pitfalls of merging GWAS data: lessons learned in
529 the eMERGE network and quality control procedures to maintain high data quality. *Genetic*
530 *epidemiology*. 2011;35(8):887-898.
- 531 52. Delaneau O, Zagury J-F, Marchini J. Improved whole-chromosome phasing for disease and
532 population genetic studies. *Nature methods*. 2013;10(1):5-6.
- 533 53. Howie B, Fuchsberger C, Stephens M, Marchini J, Abecasis GR. Fast and accurate genotype
534 imputation in genome-wide association studies through pre-phasing. *Nature genetics*.
535 2012;44(8):955-959.
- 536 54. McClellan J, McCurry C. Early onset psychotic disorders: diagnostic stability and clinical
537 characteristics. *European child & adolescent psychiatry*. 1999;8(1):S13-S19.
- 538 55. Vieta E, Gasto C, Otero A, Nieto E, Vallejo J. Differential features between bipolar I and
539 bipolar II disorder. *Comprehensive psychiatry*. 1997;38(2):98-101.
- 540 56. Craddock N, Jones I, Kirov G, Jones L. The Bipolar Affective Disorder Dimension Scale
541 (BADDs)—a dimensional scale for rating lifetime psychopathology in bipolar spectrum
542 disorders. *BMC psychiatry*. 2004;4(1):19.
- 543 57. Scott-Long JFJ. Models for nominal outcomes with case-specific data. In: *Regression Models*
544 *for Categorical Dependent Variables Using STATA*. Texas 77845: Stata Press; 2006:252-254.
- 545 58. Westfall PHY, S.S., *Resampling-based multiple testing: examples and methods for p-value*
546 *adjustment*. New Jersey: John Wiley & Sons; 1993.
- 547 59. Large-scale genome-wide association analysis of bipolar disorder identifies a new
548 susceptibility locus near ODZ4. *Nat Genet*. 2011;43:977-983.
- 549 60. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising
550 to the challenge of larger and richer datasets. *Gigascience*. 2015;4(1):7.
- 551 61. Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with
552 shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet*.
553 2013;381:1371-1379.

- 554 62. Ruderfer DM, Fanous AH, Ripke S, McQuillin A, Amdur RL. Polygenic dissection of diagnosis
555 and clinical dimensions of bipolar disorder and schizophrenia. *Mol Psychiatry*. 2014;19:1017-
556 1024.
- 557 63. Dudbridge F. Power and predictive accuracy of polygenic risk scores. *PLoS Genet*.
558 2013;9(3):e1003348.
- 559 64. Caspi A, Houts RM, Belsky DW, et al. The p Factor: One General Psychopathology Factor in
560 the Structure of Psychiatric Disorders? *Clinical psychological science : a journal of the*
561 *Association for Psychological Science*. 2014;2(2):119-137.
- 562 65. Keshavan MS, Morris DW, Sweeney JA, et al. A dimensional approach to the psychosis
563 spectrum between bipolar disorder and schizophrenia: the Schizo-Bipolar Scale.
564 *Schizophrenia research*. 2011;133(1):250-254.
- 565 66. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new
566 classification framework for research on mental disorders. In: Am Psychiatric Assoc; 2010.
- 567 67. Insel TR. The NIMH research domain criteria (RDoC) project: precision medicine for
568 psychiatry. *American Journal of Psychiatry*. 2014;171(4):395-397.
- 569 68. Schumann G, Binder EB, Holte A, et al. Stratified medicine for mental disorders. *European*
570 *Neuropsychopharmacology*. 2014;24(1):5-50.
- 571 69. Insel TR, Cuthbert BN. Brain disorders? Precisely. *Science*. 2015;348(6234):499-500.
- 572 70. Joyce DW, Kehagia AA, Tracy DK, Proctor J, Shergill SS. Realising stratified psychiatry using
573 multidimensional signatures and trajectories. *Journal of Translational Medicine*.
574 2017;15(1):15.
- 575 71. Allardyce J, Morrison G, Van Os J, Kelly J, Murray RM, McCreadie RG. Schizophrenia is not
576 disappearing in south-west Scotland. *The British journal of psychiatry : the journal of mental*
577 *science*. 2000;177:38-41.
- 578 72. Van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and
579 meta-analysis of the psychosis continuum: evidence for a psychosis proneness–persistence–
580 impairment model of psychotic disorder. *Psychological medicine*. 2009;39(02):179-195.

581

Table 1: Differential Association of PRS across variously defined BD strata (controls as comparator category)

	N (subsample)	RR	Bootstrapped p-value	Bonferroni Corrected p-value	Bootstrapped 95% confidence intervals
CLOZUK	4,976	1.94	< .001	< .001	1.86, 2.01
A) Bipolar Disorder cases stratified by RDC defined subtypes					
SABD	356	1.37	< .001	< .001	1.22, 1.54
BD I	2,775	1.30	< .001	< .001	1.24, 1.36
BD II	1,268	1.04	0.26	0.26	0.97, 1.11
B) Bipolar Disorder cases stratified by lifetime occurrence of psychosis					
No LEP	2,079	1.09	0.001	0.004	1.04, 1.15
LEP	2,296	1.36	< .001	< .001	1.29, 1.43
C) Psychotic Bipolar Disorder cases stratified by level of mood incongruence					
Low LMI	1,126	1.24	< .001	< .001	1.17, 1.33
High LMI	981	1.46	< .001	< .001	1.36, 1.57
D) Sensitivity Analysis: Psychotic Bipolar Disorder cases stratified by levels of mood incongruence (excluding SABD cases)					
Low LMI	1,068	1.25	< .001	< .001	1.16, 1.33
High LMI	699	1.49	< .001	< .001	1.37, 1.62

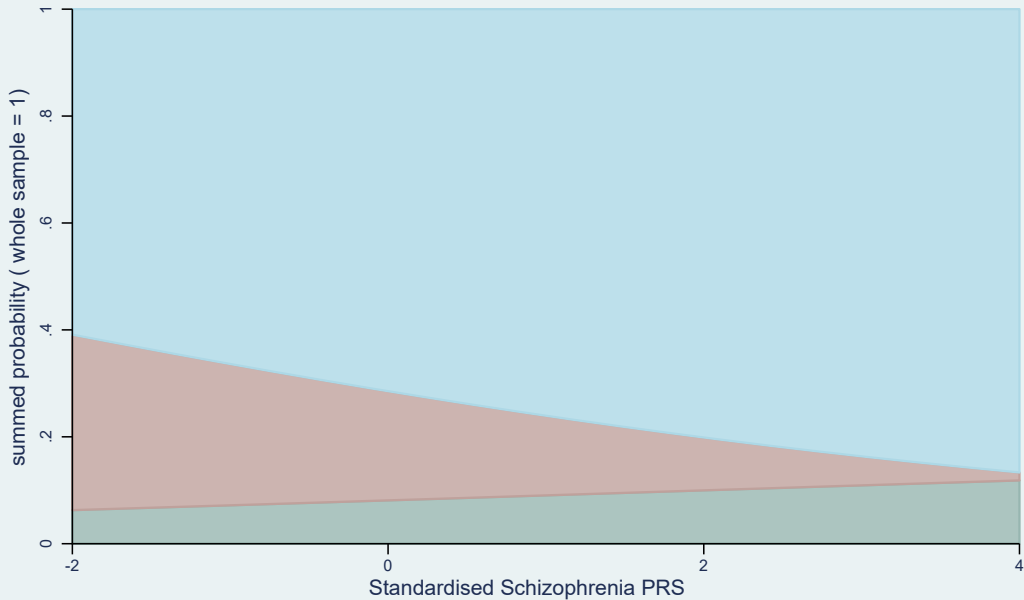
CLOZUK - Treatment resistant Schizophrenia, treated with clozapine, BD I - RDC bipolar disorder subtype I, BD II - RDC bipolar disorder type II, SABD-RDC bipolar schizoaffective disorder, LEP - lifetime ever occurrence of psychotic symptoms, LMI - lifetime pattern of low/high mood incongruent psychotic features RR - relative risk ratio PRS adjusted for 1st 10 PCs and genotyping platform

Table 2: PRS-SCZ associations among cases

	RR	Bootstrapped p-value	Bonferroni corrected p-value	Bootstrapped 95% C.I.
SABD compared to TRS	0.71	< .001	< .001	0.63, 0.80
BD I compared to TRS	0.67	< .001	< .001	0.64, 0.71
BD II compared to TRS	0.54	< .001	< .001	0.50, 0.57
SABD compared to BD II	1.32	< .001	< .001	1.16, 1.50
BP I compared to BD II	1.25	< .001	< .001	1.16, 1.35
SABD compared to BD I	1.05	0.41	0.41	0.93, 1.18

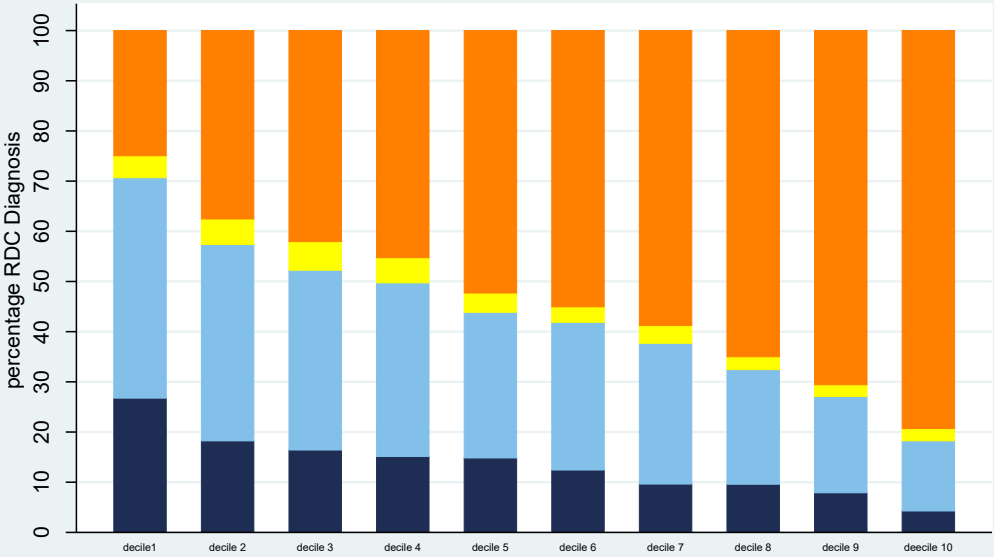
TRS - treatment resistant schizophrenia, treated with clozapine, BD I - RDC bipolar disorder subtype I, BD II - RDC bipolar disorder type II, SABD-RDC bipolar schizoaffective disorder, RR - relative risk ratio PRS adjusted for 1st 10 PCs and genotyping platform 95% bootstrapped C.I. - 95% confidence intervals.

Figure 1. Probability of RDC bipolar subtype as a function of polygenic risk scores (PRS) for schizophrenia



x-axis - standardised PRS in standard deviation units, SABD - schizoaffective bipolar type, BD I - bipolar disorder type I, BD II - bipolar type II

Figure 2: Percentage of bipolar subtype as a function of PRS for schizophrenia - grouped by decile



x-axis deciles of PRS, SABD - schizoaffective bipolar type, BD I - bipolar disorder type 1, BD II - bipolar disorder type II

BD II BD I SABD CLOZUK

Figure 2. Relative Risk Ratio of PRS with subtypes of BD compared with controls (CLOZUK included for comparison)

