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1 Machine Learning for Genetic Prediction of Psychiatric Disorders: A  
2 Systematic Review

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18 *Short/Running Title*

19 Review of ML for Genetic Prediction in Psychiatry

20

21 *Keywords*

22 Machine learning, systematic review, SNPs, polygenic risk score, AUC, psychiatric disorder

23

24 **Abstract**

25 Machine learning methods have been employed to make predictions in psychiatry from  
26 genotypes, with the potential to bring improved prediction of outcomes in psychiatric  
27 genetics; however, their current performance is unclear. We aim to systematically review  
28 machine learning methods for predicting psychiatric disorders from genetics alone and  
29 evaluate their discrimination, bias and implementation. Medline, PsychInfo, Web of Science  
30 and Scopus were searched for terms relating to genetics, psychiatric disorders and machine  
31 learning, including neural networks, random forests, support vector machines and boosting,  
32 on 10 September 2019. Following PRISMA guidelines, articles were screened for inclusion  
33 independently by two authors, extracted, and assessed for risk of bias. 63 full texts were  
34 assessed from a pool of 652 abstracts. Data were extracted for 77 models of schizophrenia,  
35 bipolar, autism or anorexia across 13 studies. Performance of machine learning methods  
36 was highly varied (0.48-0.95 AUC) and differed between schizophrenia (0.54-0.95 AUC),  
37 bipolar (0.48-0.65 AUC), autism (0.52-0.81 AUC) and anorexia (0.62-0.69 AUC). This is likely  
38 due to the high risk of bias identified in the study designs and analysis for reported results.  
39 Choices for predictor selection, hyperparameter search and validation methodology, and  
40 viewing of the test set during training were common causes of high risk of bias in analysis.  
41 Key steps in model development and validation were frequently not performed or  
42 unreported. Comparison of discrimination across studies was constrained by heterogeneity  
43 of predictors, outcome and measurement, in addition to sample overlap within and across  
44 studies. Given widespread high risk of bias and the small number of studies identified, it is  
45 important to ensure established analysis methods are adopted. We emphasise best  
46 practices in methodology and reporting for improving future studies.

47

## 48 **Introduction**

49 Machine learning represents a contrasting approach to traditional methods for genetic  
50 prediction. It has increased in popularity in recent years following breakthroughs in deep  
51 learning [1–4], and the scaling-up of datasets and computing power. The ability to function  
52 in high dimensions and detect interactions between loci [5] without assuming additivity  
53 makes such methods an attractive option in statistical genetics, where the effects of myriad  
54 factors on an outcome is difficult to pre-specify. Calls to address the complexity of disorders  
55 like schizophrenia with machine learning have also become more frequent [6–8]. However,  
56 the predictive performance of machine learning methods in psychiatric genetics is unclear,  
57 and a recent review of clinical prediction models across various outcomes and predictors  
58 found them to be no more accurate than logistic regression [9]; it is therefore timely to  
59 review their predictive performance in psychiatry.

60

61 Genome-wide association studies, genetic prediction and psychiatry have each been  
62 reviewed with respect to machine learning [10–16]. Recently, single nucleotide  
63 polymorphism (SNP)-based prediction has been reviewed across diseases [17]. However,  
64 psychiatry presents a distinct problem from somatic and neurological diseases as a result of  
65 genetic correlation between disorders [18] and the risk of class mislabelling due to biological  
66 heterogeneity that may underlie symptom-based diagnoses [19].

67

68 We systematically reviewed literature related to the question: what is the ability of machine  
69 learning (ML) methods to predict psychiatric disorders using only genetic data? We report  
70 discrimination, methodology and potential bias for diagnostic or prognostic models and  
71 compare to logistic regression (LR) and polygenic risk scores (PRS) where available.

72

## 73 **Materials and methods**

### 74 *Search Strategy*

75 Medline via Ovid, PsychInfo, Web of Science and Scopus were searched for journal articles  
76 matching terms for machine learning, psychiatric disorders and genetics on 10th September  
77 2019. Searches were broad, with terms for psychiatric disorders including schizophrenia,  
78 bipolar, depression, anxiety, anorexia and bulimia, attention-deficit hyperactivity disorder,  
79 obsessive compulsive disorder, Tourette's syndrome or autism. Terms for machine learning  
80 were also wide-ranging, including naïve Bayes, *k*-nearest neighbours (*k*-NN), penalised  
81 regression, decision trees, random forests, boosting, Bayesian networks, Gaussian  
82 processes, support vector machines and neural networks, but excluding regression methods  
83 without penalty terms, such as logistic regression. Searches were developed and conducted  
84 by MBS and were restricted to English language journal articles on humans, with no limits  
85 on search dates. Two authors (MBS, KC) independently reviewed all abstracts for inclusion.  
86 Full texts were assessed if either author had chosen to access them and independently  
87 screened against inclusion criteria. Where conflicts occurred a third author (VEP) was  
88 consulted as an arbiter. An example search for Medline (Ovid) is given in the supplementary  
89 (Table S1).

90

### 91 *Inclusion and Exclusion Criteria*

92 Studies were restricted to cohort, cross-sectional or case-control designs of individuals for  
93 binary classification of a single DSM or ICD-recognised psychiatric disorder compared to  
94 unaffected individuals, where only genotyping array, exome or whole-genome sequencing  
95 data were used as predictors. Studies based solely on gene expression were excluded, but

96 designs which made use of gene expression or functional annotations to inform models of  
97 genetic data were accepted. No further restriction was made on participants. Studies were  
98 excluded if they only predicted medication response, sub-groups within a psychiatric  
99 disorder or a psychiatric phenotype secondary to another disease. Studies were also  
100 considered ineligible if they had a clear primary aim of drawing inference at the expense of  
101 prediction, if they developed a novel statistical method or only made use of unsupervised or  
102 semi-supervised methods. The review was registered to PROSPERO in advance (registration  
103 number CRD42019128820).

104

#### 105 *Extraction and Analysis*

106 A data extraction form was developed through discussion between all authors; items from  
107 the critical appraisal and data extraction for systematic reviews of prediction modelling  
108 studies (CHARMS) checklist [20] were included as-is or modified, and additional items were  
109 included based on expert knowledge and relevance to the review topic, with reference to  
110 the genetic risk prediction studies (GRIPS) statement [21] for items pertaining to genetic  
111 prediction studies (Table S2). The form was piloted with five publications, containing 40  
112 extracted ML models between them, and updated before being applied to all texts.

113

114 The discrimination of machine learning methods was extracted independently by two  
115 authors (MBS, KC) as area under the receiver operating characteristic curve (AUC), or *c*-  
116 statistic. Model performance measures for classification by accuracy, sensitivity and  
117 specificity were also extracted. 95% confidence intervals for validation were estimated for  
118 AUC using Newcombe's method [22]. Results were not meta-analysed due to sample  
119 overlap, present in at least half of studies (see Table S3), which cannot easily be accounted

120 for in the meta-analysis. Information on participants, predictors and model development  
121 and validation were also obtained. LR or PRS models were also extracted when present.  
122 Though LR can be considered a machine learning approach, for the purpose of this review  
123 we regard it as a contrasting method due to its widespread use in classic statistical analysis.  
124 The presence of LR and PRS as comparators was not made a requirement due to their  
125 sparsity in the literature.

126

127 Risk of bias (ROB) and applicability were assessed using the prediction model risk of bias  
128 assessment tool (PROBAST) [23]. PROBAST consists of 20 questions designed to signal where  
129 ROB may be present in either the development or validation of a model across 4 categories:  
130 participants, predictors, outcome and analysis. These include, for instance, questions on  
131 how missingness or complexities in study design were handled. Information on handling of  
132 population structure, a common confound in genetic association studies, was also extracted  
133 to aid ROB assessment. Reporting of the systematic review follows the preferred reporting  
134 items for systematic reviews and meta-analyses (PRISMA) guidelines [24]. Extraction and  
135 ROB are detailed further in the supplementary.

136

## 137 **Results**

### 138 *Selection*

139 1,241 publications were identified through searches in Ovid Medline, PsychInfo, Scopus and  
140 Web of Science which included restrictions to English language journal articles (Figure S1).  
141 After merging and removing duplicates, 652 studies were assessed for inclusion. Of these,  
142 63 full texts were assessed to determine eligibility. 14 publications were selected, with two

143 merged as publications included the same models on the same dataset. A final total of 13  
144 studies were selected for inclusion, containing 77 distinct machine learning models.

145

#### 146 *Studies*

147 A wide range of machine learning methods were applied to schizophrenia (7 studies, 47% of  
148 models), bipolar disorder (5 studies, 39% of models), autism (3 studies, 10% of models) and  
149 anorexia (1 study, 4% of models) (Table 1), with no studies identified for the 6 remaining  
150 disorders. Single nucleotide polymorphisms (SNPs) were the most common source of  
151 genetic data. Copy number variants (CNVs) and PRs were each incorporated in models  
152 from a single study, and exome-sequencing data formed the basis of two studies. Datasets  
153 typically consisted of publicly-available genome-wide association studies (GWAS); potential  
154 sample overlap was established for at least 7 studies (Table S3). Briefly, 3 studies [25–27]  
155 included controls for the 1958 Birth Cohort [28] or the UK Blood Service [29], 4 studies  
156 included controls from Knowledge Networks [25, 30–32], 2 studies used a Swedish  
157 population-based sample [32, 33], and 3 studies used the same dataset, or provided a  
158 common reference for part of the dataset [25, 30, 31]. The remaining 6 studies [34–40]  
159 either gave unclear information, reported no previous reference for the dataset, or used  
160 datasets which appear to be separate from other studies. Where samples overlap, all  
161 models included in the review are distinct, using different predictors or modelling  
162 approaches. Additional overlap or cryptic relatedness may be present between studies.

163

164 Missingness was reported clearly in about half of all studies and models. When reported, it  
165 was most commonly handled by imputation after excluding genotypes with high

166 missingness. Studies also reported complete-case analysis and inclusion of missing values in  
167 coding of predictors (Table S4).

168

#### 169 *Machine Learning Methods*

170 Support vector machines (SVMs) and neural networks were the most popular, followed by  
171 random forests and boosting. SVMs were split roughly equally between using a linear kernel  
172 (3 studies, 7 models), a radial basis function (RBF) kernel (3 studies, 6 models), or an  
173 unreported kernel (3 studies, 6 models). Authors applying neural networks most commonly  
174 used multilayer perceptrons (3 studies, 6 models), an RBF network (2 studies, 5 models) or  
175 restricted Boltzmann machines (RBMs; 1 study, 9 models), with linear networks,  
176 convolutional neural networks (CNNs) and embedding layers each used once. Weak learners  
177 in boosted models were mainly decision trees, with the exception of a method which  
178 combined feature selection with the boosting of RBF-SVMs in AdaBoost [35]. Penalised  
179 regression was employed alongside linear and non-linear methods as least absolute  
180 shrinkage and selection operator (LASSO; 3 studies, 4 models) or ridge regression (1 study, 2  
181 models). 51% of all models were implemented in R or WEKA; Matlab and Python were  
182 preferred for neural networks (Table S5).

183

#### 184 *Risk of Bias*

185 Risk of bias was assessed for each model within each study (Figure S2). All models displayed  
186 risk of bias, mostly in relation to participants (study design and inclusion/exclusion criteria),  
187 outcome (standardised definition and assessment of outcomes) and analysis. Within-study  
188 ROB for participants was due to the use of case-control studies. Predictors were mostly  
189 rated to have unclear or low ROB; instances of high ROB were limited to predictors which

190 are unavailable at the point of model use. Outcome definitions or measurements often  
191 differed between cases and controls.

192

193 Models displayed high ROB during analysis. This was often traced to inappropriate or  
194 unjustified handling of missingness and removal of enrolled participants prior to analysis,  
195 predictor selection using univariable methods and failure to account for overfitting. No  
196 studies reported calibration measures. In addition to PROBAST, information on population  
197 structure within studies was extracted (Table S6). Most studies did not illustrate genetic  
198 ancestry across all observations in the current publication using dimensionality reduction,  
199 and none reported any evaluation of the final trained model for bias due to population  
200 structure. However, 2 studies (18% of models) visualised principal components for a  
201 subsample or showed a table of reported ancestry for participants [31, 39]. Where ancestry  
202 was not addressed in a study, it was most often visualised in a referenced publication (55%  
203 of all models). 2 studies (13% of models) had no details or references which addressed  
204 genetic ancestry.

205

206 Across-study ROB was not formally assessed. For schizophrenia, bipolar and autism, studies  
207 with smaller numbers of cases in the development set report AUC less often, instead  
208 preferring classification metrics such as accuracy, sensitivity and specificity.

209

210 PROBAST encourages assessment of studies for applicability to the review question as this is  
211 often narrower than inclusion criteria [23]. Concern was identified for models in three  
212 studies [30, 39, 41]. All others demonstrated either low concern or unclear applicability.

213 Reasons for concern were attributable to outcomes which combined closely-related

214 disorders, or the use of post-mortem gene expression data, whereas the review question  
215 focussed on models of single disorders with potential use in diagnosis or prognosis.

216

### 217 *Model Performance*

218 Over half of all models assessed discrimination using AUC (58% models). A wide range of  
219 classification metrics and measures of model fit were also reported (Table S7), with less  
220 than a quarter of models clearly reporting choosing a decision threshold *a priori* (Table S8).

221

222 Around 79% of models, from 12 studies, reported some form of internal validation (Table  
223 S9). The majority of these were *k*-fold cross-validation (57% of all models; 8 studies), a  
224 resampling approach which involves testing a model on each of *k* independent partitions of  
225 a dataset, every time training on the remaining *k*-1 folds. 10-fold cross-validation (CV) was  
226 most commonly used, with just below half of all cross-validated models invoking repeats  
227 with different random splits. The remainder of studies using internal validation created a  
228 random split between training and testing sets (21% of all models; 5 studies), or applied  
229 apparent validation, where training and testing are both done on the whole sample [31]. A  
230 minority reported external validation (26% of models; 2 studies). Use of internal validation  
231 was not reported for 16 models from a single study [25], but for which geographic and  
232 temporal external validation was given. External validation was reported for one other  
233 study, but with partly overlapping participants between development and validation sets  
234 [32].

235

236 Model performance varied by choice of statistical method, sample size and number of  
237 predictors within studies (Table S10). Discrimination for models of schizophrenia (Figure 1)

238 was extremely varied (0.541-0.95 AUC), with the highest AUC from exome data using  
239 XGBoost (0.95 AUC) [33]. In this study, Trakadis et al. (2019) used counts of variants in each  
240 gene, after annotation and predictor selection, on participants with part-Finnish or Swedish  
241 ancestry [42]. Similarly high AUC (0.905 AUC) made use of multiple schizophrenia-associated  
242 PRS [32]. However, the authors identify the presence of both the development and  
243 validation samples in the psychiatric genomics consortium (PGC) GWAS used to generate  
244 the schizophrenia PRS [43], in addition to having overlapping controls between internal  
245 validation (model development) and external validation (replication) samples. All other  
246 schizophrenia models involved learning from SNPs [27, 30, 34–36], with the exception of  
247 Wang et al. (2018) [39] where gene expression data from post-mortem samples informed  
248 the weights in a conditional RBM trained on genotypes.

249

250 Predictive ability for bipolar disorder (Figure 1) was consistently lower than for  
251 schizophrenia, frequently overlapping with chance (0.482-0.65 AUC). Models were trained  
252 on genotypes, excepting a study [38] using exome data to train a CNN as part of the Critical  
253 Assessment of Genome Interpretation (CAGI) competition [44], for which moderate  
254 discrimination was achieved (0.65 AUC).

255

256 Significantly fewer models were reported for autism (8 models, 3 studies) and anorexia (3  
257 models, 1 study) (Figure 1). Varying predictive performance was illustrated in autism (0.516-  
258 0.806 AUC). High AUC (0.806 AUC) was shown for a single prediction model [40], while  
259 models developed with a greater sample size by Engchuan et al. (2015) using CNVs were  
260 closer to or overlapping with chance (0.516-0.533 AUC) [37]. The only models predicting

261 anorexia nervosa had moderate discriminative ability between cases and controls (0.623-  
262 0.693 AUC) [26].

263

#### 264 *Logistic regression and polygenic risk scores*

265 Three studies reported AUC for either logistic regression (5 models) or polygenic risk scores  
266 (12 models) alongside machine learning methods. PRS were weighted by summary statistics  
267 from a GWAS on the same disorder as the outcome and used as the sole predictor in a  
268 logistic regression model. Though discrimination shows some difference between model  
269 types, the number of studies for comparison is low and results are clustered by study and  
270 type of validation (Figure S3).

271

#### 272 *Predictors*

273 Coding of predictors was mostly unclear or unreported (7 studies, 55% of models). Coding  
274 was unclear if it was implied through the description of the type of classifier or software but  
275 not clearly articulated for the reported study. PRS were continuous [32] while counts of  
276 variants-per-gene or genes-per-gene-set were used for exomes and CNVs respectively [33,  
277 37]. SNPs were coded under an additive model, a z-transformation of additive coding, or  
278 one-hot encoded (one predictor per genotype at a locus) (Table S11). GWAS summary  
279 statistics from external datasets were also used in the selection, weighting or combining of  
280 predictors (9 studies, 64% models; Table S12).

281

282 Predictor selection was adopted by most (12, 73% of models) and limited to filter-based  
283 selection, used prior to modelling, and embedded selection, an integral part of the  
284 prediction model (Table S13). The latter involved LASSO regression, or ensembles and

285 hybrids of decision trees and decision tables, in addition to a modified AdaBoost [35]. Filters  
286 were based on internal or external univariable association tests (GWAS). Embedded and  
287 wrapper-based methods, which typically 'wrap' a model in forward or backward-selection,  
288 were both also used prior to any predictive modelling. Modification of predictors using  
289 information from the test set was the most common cause of information 'leaking' from the  
290 test set to the training set, a source of inflation in performance measures (Table S14).

291

### 292 *Sample size*

293 Total sample size was generally low where a single sample had been used, but higher if  
294 genotypes from publicly-available amalgamated datasets used in a GWAS had been  
295 downloaded (median 3486, range 40-11853) (Table S10). Number of events in development  
296 followed a similar pattern (median 1341, range 20-5554) as class imbalance was minimal  
297 (median 1, range 0.65-2.93, calculated as non-events over events). Around half of studies  
298 gave sufficient information to calculate events per variable (EPV) (median 0.69, range  
299 0.00063-74.6). It could not be calculated where the number of candidate predictors were  
300 not reported for models in 2 studies [25, 39]; approximations are given in the  
301 supplementary where reporting was unclear in a further 5 studies [26, 32–34, 36, 38] (Table  
302 S10).

303

### 304 *Hyperparameter Search*

305 Hyperparameter search was mostly unreported or unclear (41 models, 9 studies), with some  
306 models reported as having been used with default settings. Ambiguous reporting resulted  
307 from description of search and tuning for a specific model, with no clarity as to whether  
308 these conditions applied to other models in the study. Only 19% of models clearly reported

309 attempting different hyperparameters for the extracted models (Table S15). Studies also  
310 report non-standard final hyperparameters, such as uneven batch size in neural networks,  
311 or showed good accuracy for a model which is highly sensitive to tuning of crucial  
312 hyperparameters, yet few reported tuning (Table S16). It is therefore likely that most  
313 studies evaluated several hyperparameter choices but did not report this.

314

### 315 ***Discussion***

316 All studies displayed high risk of bias in model development and validation with infrequent  
317 reporting of standard modelling steps. Performance measures consequently demonstrated  
318 a wide range of abilities to discriminate between cases and controls (0.482-0.95 AUC). These  
319 are likely optimistic owing to the high risk of bias identified through PROBAST and  
320 unaddressed sample overlap and population structure, as two studies showing the highest  
321 AUCs left these issues unresolved [32, 33]. Though potential bias and effective sample size  
322 limit overall interpretation of discrimination, low standards of model development,  
323 validation and reporting are a clear and consistent theme throughout all studies. Broad  
324 discrimination has also been observed for machine learning studies in cancer genomics [45];  
325 more established fields with clearer predictor-response relationships, such as medical  
326 imaging, are much more consistent [46].

327

328 Issues relating to ROB often rest on distinctions in methodology between clinical prediction  
329 modelling, machine learning and genetic association studies. For instance, genetic studies  
330 most commonly employ a case-control design. Such studies are extremely useful for  
331 identifying genetic risk factors for rare outcomes, but are considered inadequate for  
332 prediction modelling as absolute risks cannot be estimated; instead, case-cohort, nested

333 case-control, or prospective cohort designs are preferred [47]. Case-cohort and nested case-  
334 control designs involve sampling from an existing cohort and can be used for prediction  
335 models if the sampling fraction in controls is accounted for in analysis [48]. To project the  
336 prediction to the whole population in case-control studies, positive and negative predictive  
337 values should be corrected in accordance with the disease prevalence in the population and  
338 ratio of cases and controls in the sample [49]. Similarly, univariable tests of association are  
339 applied routinely in GWAS, and are often used in selection of predictors for genetic  
340 prediction models. Their application in prediction modelling though is usually discouraged,  
341 as predictors may differ in their importance when evaluated in isolation as compared to  
342 when considered concurrently with other variables [50].

343

344 Lack of adherence to appropriate procedures for machine learning are also a common cause  
345 of a model being assessed as at high risk of bias. Standard model validation procedures  
346 were followed by some researchers; however, many 'leaked' information between training  
347 and testing sets through not applying predictor manipulations or selection in only the  
348 training set/fold, or using the testing set/fold to adjust model hyperparameters, which can  
349 impose significant bias on estimates of prediction performance [51].

350

351 Most studies provided a measure of classification or discrimination for each model; none  
352 reported a measure of calibration. Model calibration compares observed and predicted  
353 probabilities of the outcome occurring, and is a crucial part of model development [52]  
354 which has been noted for its absence in genetic prediction literature [53]. Authors reporting  
355 only classification measures, such as accuracy, sensitivity or specificity, should also note that  
356 measures of discrimination are preferred as they use all the information over predicted

357 probabilities and delay any thresholding of risks to a more appropriate time. Of  
358 discrimination measures, the AUC is the most widely used in both machine learning and  
359 genetics [54, 55].

360

361 Hyperparameter optimisation is an essential part of developing machine learning models as  
362 it determines how they navigate the bias-variance trade-off and learn from data [56]. It is  
363 therefore surprising that it was so often unreported or subject to a small number of manual  
364 experiments. Hyperparameters should be systematically searched to ensure a model is not  
365 over or under-fit. Randomised search has been shown to be more effective than grid search  
366 where two or more such parameters require tuning [57], though grid search is also  
367 recommended by practitioners for SVMs, often with an initial 'coarse' search followed by a  
368 more thorough exploration of a finer grid of values [58]. The importance of search is  
369 particularly relevant in domains where there are a small number of events per candidate  
370 predictor [59], such as genomics, as appropriate hyperparameter choices can reduce  
371 overfitting.

372

373 Split-sample approaches were used by several studies, but should be avoided in favour of  
374 resampling methods such as bootstrapping or *k*-fold cross-validation [60]. The latter is an  
375 appropriate form of internal validation for traditional statistical methods; however,  
376 estimated prediction accuracies become overly-optimistic if done repeatedly, as when used  
377 for hyperparameter tuning through repeated rounds of CV. Nested cross-validation, where  
378 hyperparameters are optimised in an inner-fold and evaluated in the outer-fold, has been  
379 shown to give more realistic estimates [51, 61] but was not used in any studies. A single  
380 study presented both internal and external validation of models [32], for which a large drop

381 in performance is seen upon replication. Though partly due to sample overlap between the  
382 development set and the summary statistics used for generating a PRS, difficulty with  
383 replication is a wider issue in polygenic risk prediction. Risk scores for psychiatric disorders  
384 typically explain a small proportion of variance in a trait [62], with generalisation issues  
385 compounded by variants with small effect sizes and different allele frequencies between  
386 populations. Risk scores generated through machine learning methods have the potential to  
387 be more affected by these issues if appropriate modelling procedures are not followed.

388

389 A source of bias not explicitly covered in PROBAST is population structure. Genetic ancestry  
390 has the potential to bias both associations [63, 64] and predictions [65, 66] from genetic  
391 data. Supervised machine learning methods have proved particularly sensitive in detecting  
392 ancestry [67–69]. Few researchers discussed visualising ancestry or reported exclusions, and  
393 none reported modelling adjustments, even when previous association studies on the same  
394 datasets had demonstrated stratification and included principal components as covariates.  
395 The extent of the bias introduced in these studies is not clear: evidence mostly relates to  
396 deliberately predicting populations in humans using ML or looking at bias in complex trait  
397 prediction from PRS. While the potential for population stratification to impact predictions  
398 is apparent, the method for dealing with it when using machine learning methods is not.  
399 Several techniques have been proposed, including modifications to random forests [70];  
400 exclusions by, or inclusion of, principal components; and regressing-off the linear effects of  
401 principal components on SNPs before modelling (for example [71, 72]). Whether any  
402 combination of these is sufficient to reduce the effects of population stratification in non-  
403 linear machine learning predictions has not been demonstrated.

404

405 General reporting guidelines for machine learning prediction models are yet to be  
406 developed [73], though recommendations for undertaking [74, 75] evaluating [76] or  
407 reporting [77] exist for machine learning in omics data, psychiatry and medicine  
408 respectively, in addition to reporting guidelines outside of machine learning [21, 78]. We  
409 encourage authors to report on implementation, samples, predictors, missingness,  
410 hyperparameters and handling of potential information leakage, and consult guidelines  
411 where needed. Finally, we advocate for machine learning methods to be reported alongside  
412 polygenic risk scores as a standard baseline model for comparison. The potential for  
413 machine learning methods to provide improved prediction has received heightened  
414 attention in recent years. Any such outcome cannot occur without adherence to standards  
415 for the development, validation and reporting of models.

416

417

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422

423

424 **Conflict of Interest**

425 All authors report no potential conflicts of interest.

426

427

428 Supplementary information is available at MP's website.

429

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630

631 **Figure Legends**

632 **Figure 1:** discrimination for all models. *n*: number of cases in training set. Studies: a [35], b  
633 [40], c [34, 36], d [39], e [25], f [38], g [31], h [30], i [26], j [33], k [37], l [32], m [27].

634 \*Accuracy calculated from confusion matrix. \*\*SVM kernel not reported. †Modified  
635 architecture with intermediate phenotypes in training set only. ‡Modified architecture with  
636 intermediate phenotypes for training and test sets. ††Two-way MDR. †††Three-way MDR.

637 §Neural network embedding layer. <sup>1,2,3,4</sup>Internal and external validation are shown for study  
638 l, where validations for the same model are denoted with the same number. AB: AdaBoost,

639 BN: Bayesian networks, BFTree: best-first tree, CIF: conditional inference forest, cRBM:

640 conditional restricted Boltzmann machine, CI: confidence interval, CNN: convolutional

641 neural network, CNV: copy number variation, DTb: decision tables, DTNB: decision table

642 naïve Bayes, DT: decision tree, EC: evolutionary computation, GE: gene expression, GBM:

643 gradient boosting machine, *k*-NN: *k*-nearest neighbours, LASSO: least absolute shrinkage

644 and selection operator, LNN: linear neural network, MDR: multifactor dimensionality

645 reduction, MLP: multi-layer perceptron, NB: naïve Bayes, NN: neural network, PRS:

646 polygenic risk scores, RBF: radial basis function, RF: random forests, SNP: single nucleotide

647 polymorphisms, SVM: support vector machine, XGB: extreme gradient boosting.

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650 **Tables and Table Legends**

651

First Author (Year)	Disorder	Machine Learning Methods	Data	Models	Comparators
Aguiar-Pulido et al. (2010; 2013) <sup>1</sup>	Schizophrenia	AdaBoost, BFTree, DNTB, decision tables, SVM (kernel not reported), naïve Bayes, Bayesian networks, MDR, neural network (RBF, linear, perceptron), evolutionary computation	SNPs	12	
Yang et al. (2010)	Schizophrenia	AdaBoost (of SVM (RBF)), SVM (RBF)	SNPs	2	
Pirooznia et al. (2012)	Bipolar Disorder	Bayesian networks, random forest, neural network (RBF), SVM (kernel not reported)	SNPs	16	PRS, LR
Li et al. (2014)	Bipolar Disorder, Schizophrenia	LASSO, Ridge, SVM (linear)	SNPs	6	
Engchuan et al. (2015)	Autism	Neural network (perceptron), SVM (Linear), random forest, CIF	CNVs	4	
Acikel et al. (2016)	Bipolar Disorder	MDR, random forest, <i>k</i> -NN, naïve Bayes	SNPs	5	
Guo et al. (2016)	Anorexia nervosa	LASSO, SVM (RBF), GBM	SNPs	3	
Lakshman et al. (2017)	Bipolar Disorder	Decision tree, random forest, neural network (CNN)	Exomes	3	
Chen et al. (2018)	Schizophrenia	Neural network (perceptron)	PRS	4	PRS, LR
Wang et al. (2018)	Schizophrenia, Bipolar Disorder, Autism	Neural networks (cRBM)	SNPs, gene expression	9	LR
Ghafouri-Fard et al. (2019)	Autism	Neural network (with embedding layer)	SNPs	1	
Trakadis et al. (2019)	Schizophrenia	LASSO, random forest, SVM (kernel not reported), GBM (XGBoost)	Exomes	4	
Vivian-Griffiths et al. (2019)	Schizophrenia	SVM (linear, RBF)	SNPs	8	PRS

652

653 **Table 1:** overview of studies. <sup>1</sup>Merged in extraction [34, 36]. BFTree: best-first decision tree,

654 CIF: conditional inference forest, cRBM: conditional restricted Boltzmann machine, CNN:

655 convolutional neural network, DNTB: Decision table naïve Bayes, GBM: gradient boosting  
656 machine, *k*-NN: *k*-nearest neighbours, LASSO: least absolute shrinkage and selection  
657 operator, LR: logistic regression, MDR: multifactor dimensionality reduction, PRS: polygenic  
658 risk score, RBF: radial basis function, SVM: support vector machine.

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