Cardiometabolic prediction models for young people with psychosis spectrum disorders in the UK (PsyMetRiC 2.0): a retrospective, multicohort clinical prediction model study

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Summary

Background Young people with psychosis spectrum disorders are at a high risk of cardiometabolic morbidity and subsequent premature mortality, but there are no accurate clinic-ready prediction models for this group. We aimed to collaboratively refine, extend, and validate the Psychosis Metabolic Risk Calculator (PsyMetRiC) prediction models for accuracy, clinical usefulness, and acceptability, and to translate the models into a regulated, clinically available medical device.

Methods In this retrospective, multicohort clinical prediction model study, we used primary care (Clinical Practice Research Datalink and QResearch) and secondary care (South London and Maudsley NHS Foundation Trust) datasets. Individuals from primary care sources were aged 16–35 years when they received a first recorded diagnosis of a psychosis-spectrum disorder between Jan 1, 2005, and Dec 31, 2015, with follow-up to Dec 31, 2020. Individuals from the secondary care source were enrolled in the psychosis early intervention service between Jan 1, 2012, and Dec 31, 2024. We developed models for a binary outcome of metabolic syndrome within 1–6 years using logistic regression; a time-to-event outcome of type 2 diabetes within 10 years using Weibull regression; and a binary outcome of clinically significant weight gain within 1 year using logistic regression. We revised existing predictors (hereafter referred to as the PsyMetRiC1 models) for finer detail and added new predictors: a family history of cardiometabolic disorder, antidepressant prescription, systolic blood pressure, and HbA_{1c} (hereafter PsyMetRiC2 models). Refinement and external validation were performed for metabolic syndrome models (PsyMetRiC1-MetS and PsyMetRiC2-MetS), and development and external validation were performed for the type 2 diabetes model (PsyMetRiC2-T2D). Development and internal validation were performed for the clinically significant weight gain model (PsyMetRiC2-WG), but external validation was not possible due to data availability. Partial versions without biochemical results were also developed for weight gain and metabolic syndrome models. We involved stakeholders including people with lived experience; and implemented the models in a web application compliant with regulatory standards in Great Britain.

Findings In total, we included 25 850 individuals (male, n=13 614 [52·7%]; female, n=12 236 [47·3%]; White European, 16 445 [63·6%]; Black African or Caribbean, south Asian, mixed, and east Asian or other n=9405 [36·3%]; and mean age 26·7 years [SD=5·4]). For primary care, we included 3989 individuals for development and 4347 individuals for external validation of metabolic syndrome outcomes; and 9181 individuals for development and 7487 individuals for external validation of type 2 diabetes outcomes. For secondary care, we included 846 individuals for development and internal validation of weight gain outcomes. For metabolic syndrome, the performance of PsyMetRiC2-MetS at external validation was C=0·81 (95% CI 0·77–0·84) for the full model (with biochemical predictors) and C=0·79 (0·76–0·83) for the partial model (without biochemical predictors). For type 2 diabetes, discriminative performance at internal validation of PsyMetRiC2-T2D was C=0·86 (0·76–0·95) for the full model, and at external validation it was C=0·81 (0·71–0·88). For weight gain, discriminative performance at internal validation of PsyMetRiC2-WG was C=0·78 (0·73–0·82) for the full model and C=0·77 (0·72–0·80) for the partial model. Calibration plots were acceptable for all models. All models displayed evidence of clinical usefulness at all plausible thresholds. The PsyMetRiC web application is available at https://psymetric.app.

Interpretation We developed prediction models for incident cardiometabolic disorders in young people with psychosis. The PsyMetRiC models are among the first in psychiatry to be available for routine clinical use. PsyMetRiC can support a shift toward collaborative, preventive physical health care for young people with psychosis.

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See **Online** for appendix 1

Introduction

Psychosis spectrum disorders are associated with a 15-year shortened lifespan on average.[1] This excess mortality is predominantly driven by physical comorbidities, including type 2 diabetes and obesity, which increase the risk of later cardiovascular disease.[2] This increase in comorbidities is recognised as a target in NHS England's Core20PLUS5 approach to reducing health inequalities;[3] is frequently cited as important by people with these disorders;[4] and inflates health-care costs.[5] Cardiometabolic dysfunction is detectable by the first episode of psychosis[6] and occurs years earlier than in the rest of the population.[7] This earlier onset, alongside propagating factors including health behaviours and psychotropic adverse effects,[8] contributes to the poor performance of population-based cardiometabolic prediction models in this group.[9]

The Psychosis Metabolic Risk Calculator (PsyMetRiC) is a clinical prediction model developed and externally validated in 2021, predicting the risk of metabolic syndrome up to 6 years after the first episode of psychosis.[10] It has since been externally validated in multiple international settings, demonstrating generalisability and flexibility for setting-specific adaptation.[11,12] Yet, despite growing interest in clinical prediction model research across biomedicine, the field suffers from a dearth of clinical translation.[13] Barriers include unclear positioning within care pathways and the availability or acceptability of downstream interventions; additionally, prediction models intended for clinical use are regulated as medical devices, necessitating a range of pre-market and post-market technical and infrastructural requirements beyond development and validation before they can reach clinical practice.

Furthermore, methodological advances and stakeholder feedback provide opportunities to improve accuracy, usefulness, and acceptability. The need to consider equity in predictive performance for people from ethnic minority and other underserved backgrounds[14] is important for PsyMetRiC, given that psychosis disproportionately affects individuals from these groups.[15]

Research in context

Evidence before this study

Clinical prediction models are used routinely in the general population to support primary prevention of adverse cardiometabolic outcomes. Yet, prospective studies and systematic reviews of existing cardiometabolic prediction models developed for either the general or psychiatric populations have found that none are likely to be suitable for young people with early psychosis spectrum disorders. This group is at a high risk of cardiometabolic morbidity, with earlier metabolic abnormalities contributing to later cardiovascular events. Notably, signs of cardiometabolic dysfunction can be detectable from psychosis onset in young adults. With stakeholder input, the Psychosis Metabolic Risk Calculator (PsyMetRiC) prediction model was first developed and externally validated in the UK in 2021, predicting up to 6-year risk of metabolic syndrome in people aged 16–35 years with psychosis spectrum disorders. A systematic search (done from June 1, 2021, to Oct 3, 2025, searching Pubmed, Web of Science, and Google Scholar with no language restrictions) identified published external validation studies of PsyMetRiC in populations in Spain, Switzerland, Australia, Finland, Hong Kong, and Canada. Overall, the results suggested that PsyMetRiC is broadly generalisable in terms of discriminating those with and without risk of metabolic syndrome, with varying differences in calibration that were addressed with setting-specific recalibration in each study. However, prediction models designed for clinical use, including PsyMetRiC, fall under the remit of medical device regulations in most global territories, necessitating a range of requirements beyond model development and validation before they can be used in clinical practice. Further stakeholder feedback has also encouraged expanding the outcome set (to type 2 diabetes and weight gain) and refining the predictors (ie, finer detail for ethnicity and psychotropic medications, and incorporating family history of cardiometabolic disorders).

Added value of this study

We collaboratively developed, refined, and externally validated the first clinically available cardiometabolic clinical prediction models tailored for young people with psychosis spectrum disorders. Meaningful stakeholder involvement focused on maximising acceptability, usefulness, and real-world impact. Externally validated PsyMetRiC models separately predicted the future risk of metabolic syndrome and type 2 diabetes—key antecedents of longer term cardiovascular disease—in young people with psychosis spectrum disorders. An internally validated model predicting clinically significant weight gain shows promise but requires external validation. The accompanying web application, currently supporting the metabolic syndrome and type 2 diabetes models, is registered as class 1 software as a medical device in Great Britain under UK Medical Devices Regulations 2002 (as amended).

Implications of the available evidence

The PsyMetRiC models are among the first clinical prediction models available for routine clinical use in psychiatry. They can help shift cardiometabolic care in early psychosis from reactive management—which is associated with persistently poor outcomes—to earlier, proactive prevention supported by shared decision making. This work provides a translational template for moving prediction models from statistical equations to regulated medical devices trusted by clinicians and patients. Ongoing work will evaluate health economic and implementation outcomes and support international deployment beyond Great Britain.

Following TRIPOD-AI guidelines[16] (appendix 1 pp 56–58), we revised and extended the original PsyMetRiC models, and conducted their first external validations in large primary care datasets; we developed and externally validated a new PsyMetRiC version predicting type 2 diabetes risk within 10 years; and we developed and internally validated a new version predicting clinically significant weight gain within 1 year. We prioritised clinical usefulness and acceptability via stakeholder input, considered equity in performance, and produced a web application compliant with regulatory standards under UK Medical Devices Regulations 2002 (as amended),[17] enabling registration as a class 1 medical device.

Methods

Study design

This was a retrospective, multicohort clinical prediction model study using routinely collected primary and secondary care data to revise and extend existing PsyMetRiC models and to develop and validate new models.

We recruited eight people aged 16–25 years with experience of psychosis through the national networks of The McPin Foundation and Centre for Mental Health to form a lived experience advisory panel for the broader PsyMetRiC project. The lived experience advisory panel met on five occasions and completed ad-hoc work during the conduct of this study (appendix 1 pp 20–21).

We held research development focus groups with stakeholders (two focus groups with young people with experience of psychosis [n=9 in total across both groups]; one group of carers [n=4]; one group of clinicians [n=3]; one group with clinical academics [n=3]; and one group with clinical prediction model methodologists [n=6]). Focus groups considered health risk communication informed by existing evidence, implementation, and real-world impact (appendix 1 pp 17–19, 25–27). Findings were used to co-develop a health risk communication guide (appendix 2).

We implemented PsyMetRiC models with sufficient evidence of generalisability at external validation into a stakeholder-informed web application for use by health professionals. The application is configured to accept either manual inputs via the user interface or structured predictor data via an application programming interface mechanism. This mechanism supports automated pre-population of inputs from local electronic health records that are automatically extracted, with clinicians required to review and confirm inputs before generating risk estimates. We produced the necessary documentation and evidence for pre-market and post-market requirements to permit registration as a class 1 medical device in Great Britain under UK Medical Devices Regulations 2002 (as amended),[17] including technical documentation, risk management evidence, and a proportionate post-market surveillance system (appendix 1 pp 22–24).

Data sources

For primary care, we used two large electronic databases: Clinical Practice Research Datalink (CPRD) Gold (approved project 22_002104) and QResearch (approved project OX154; ethical approval completed by the East Midlands-Derby Research Ethics Committee; reference number 18/EM/0400). Both databases are based on routine anonymised health records from UK primary care practices that use different health record software. We excluded potentially overlapping primary care practices (eg, practices that switched software during the study period) by applying a CPRD-supplied migrators file. We used data from English practices due to the availability of Townsend deprivation scores, alongside linkage with Hospital Episode Statistics and Office for National Statistics records. These databases have previously been used together for the development and external validation of population-based prediction models.[18]

For secondary care, we used the Clinical Records Interactive Search resource to capture routine anonymised health record data from South London and Maudsley NHS Foundation Trust psychosis early intervention service (National Institute for Health and Care Research [NIHR] Biomedical Research Centre Clinical Records Interactive Search Oversight Committee reference number 23-068).

Study population

For primary care data, we included individuals aged 16–35 years when they received a first recorded diagnosis of a psychosis-spectrum disorder between Jan 1, 2005, and Dec 31, 2015, from primary care records from the aforementioned electronic databases or Hospital Episode Statistics, with a follow-up period of up to Dec 31, 2020. We included individuals who would be eligible for care within early intervention services in the UK, broadly comprising individuals experiencing psychotic symptoms for the first time (ICD codes F06.0-2, F20-F31, F32.3, F33.3, and F53.1) as per previous PsyMetRiC studies.[10–12] We intentionally included a diagnostically heterogeneous sample to reflect real-world eligibility for early intervention services, which is defined by the presence of psychotic symptoms rather than a single diagnosis. We created separate cohorts for each outcome (ie, separate cohorts for the analysis of metabolic syndrome and type 2 diabetes; inclusion and exclusion criteria were the same across cohorts, but because we developed models for different outcomes, this led to different cohorts for each outcome). For secondary care data from South London and Maudsley NHS Foundation Trust, we included participants aged 16–35 years who were enrolled in the early intervention service between Jan 1, 2012, and Dec 31, 2024.

See Online for appendix 2

We excluded individuals with complete missing data on either exposure or outcome variables, or who met outcome criteria at baseline. Appendix 1 (pp 34) presents

a flowchart of individuals assessed throughout the study for each outcome.

Outcomes

The harmonised definition of metabolic syndrome,[19] representing a number of different cardiometabolic abnormalities including central adiposity with elevated blood pressure, dysglycaemia, increased triglycerides, and reduced high-density lipoprotein cholesterol, within 1–6 years, was used as a binary outcome, as per previous PsyMetRiC studies.[10–12] We defined a time-to-event type 2 diabetes outcome assessed within 20 years, but we reported predictive accuracy at 10 years based on stakeholder feedback. We defined a binary outcome on clinically significant weight gain (hereafter referred to as weight gain) as an increase to a less healthy BMI category within 1 year based on stakeholder feedback (appendix 1 pp 2–3).

The PsyMetRiC models

PsyMetRiC was originally developed using shrinkage-applied logistic regression to predict the risk of metabolic syndrome up to 6 years after the first episode of psychosis, comprising versions with (full model) and without (partial model) biochemical predictors.[10] In this study, we revised the original PsyMetRiC models (hereafter PsyMetRiC1 models; eg, for metabolic syndrome [PsyMetRiC1-MetS]) using finer predictor coding; we extended them with additional predictors (a family history of cardiometabolic disorder, antidepressant prescription, systolic blood pressure, and HbA_{1c}; hereafter referred to as PsyMetRiC2); and we developed and validated new PsyMetRiC models predicting the risk of weight gain (PsyMetRiC2-WG) and type 2 diabetes (PsyMetRiC2-T2D). Appendix 1 (p 35) outlines the developmental lineage and translational trajectory of PsyMetRiC models, from initial development to clinical availability.

Original PsyMetRiC predictors were included based on clinical knowledge, previous research, clinical usefulness, and acceptability.[10] For PsyMetRiC1-MetS, two predictors were adjusted for finer predictor coding (table 1; appendix 1 pp 4–5). PsyMetRiC2-MetS extended these with four additional predictors, and the same extended predictor set was applied for the new models PsyMetRiC2-WG and PsyMetRiC2-T2D (table 1; appendix 1 pp 6–7). Time-varying predictors were ascertained within windows around the index record (the first recorded diagnosis of a psychosis-spectrum disorder; from −365 to +100 days for type 2 diabetes and metabolic syndrome; from −100 to +30 days for weight gain), choosing the measurement closest to the index record date when multiple records were available; time-invariant predictors were assessed at any point (appendix 1 p 8). Published code lists were used where possible.[21] For continuous predictors we recoded extreme outlier values (more than three IQR below the first quartile or more than the third quartile) as missing.

	Predictors* for PsyMetRiC1 model for metabolic syndrome	Predictors* for PsyMetRiC2 models†
Original predictors		
Age, years	Predictor unchanged	Predictor unchanged
Sex,‡ male *vs* female	Predictor unchanged	Predictor unchanged
Ethnicity,§ White European, Black African or Caribbean, and Asian or other	Ethnicity,§ White European, Black African or Caribbean, south Asian, mixed, and east Asian or other	Ethnicity,§ White European, Black African or Caribbean, south Asian, mixed, and east Asian or other
Smoking, yes *vs* no	Predictor unchanged	Predictor unchanged
BMI, kg/m^2	Predictor unchanged	Predictor unchanged
Antipsychotic prescription: metabolically active,¶ yes *vs* no	Antipsychotic prescription: four classes,‖ based on receptor affinities[20]	Antipsychotic prescription: four classes,‖ based on receptor affinities[20]
HDL cholesterol, mmol/L**	Predictor unchanged	Predictor unchanged
Triglycerides, mmol/L**	Predictor unchanged	Predictor unchanged
New predictors		
Systolic blood pressure, mm Hg	Not used	Predictor added
Antidepressant prescription, yes *vs* no	Not used	Predictor added
Family history of cardiometabolic disorders, yes *vs* no	Not used	Predictor added
HbA_{1c}, mmol/mol**	Not used	Predictor added

PsyMetRiC=Psychosis Metabolic Risk Calculator. *Further details are provided in the appendix (pp 4–7). †Comprising PsyMetRiC2 models for metabolic syndrome, type 2 diabetes, and weight gain. ‡Sex was obtained from routine health records. Gender identity was not available. §Ethnicity was recorded on the basis of self-assigned ethnicity recorded in primary care (QResearch) using standard NHS categories; in Clinical Practice Research Datalink, a single derived ethnicity category per participant was used, drawing on primary care and linked Hospital Episode Statistics where available. ¶See original PsyMetRiC manuscript for details.[10] ‖Comprising muscarinic antagonists (eg, olanzapine); dopamine partial agonists or adrenergic antagonists (eg, aripiprazole); serotonergic and dopaminergic antagonists (eg, risperidone); and dopaminergic antagonists (eg, amisulpride). See appendix 1 (pp 4–5) for the complete list and rationale. **Not included in the partial model versions.

Table 1: **PsyMetRiC predictor refinement**

Statistical analysis

We performed missing sample analysis to explore selection bias, and tests of analytical precision using recommended statistical equations[22,23] (appendix 1 pp 9–11). As done previously,[10] we did not examine non-linear terms or interactions because the added variable complexity would increase overfitting risk and potentially reduce generalisability; this parsimonious strategy is supported by contemporary sample size guidance for prediction modelling and the consistent external performance of the original PsyMetRiC across multiple validations.[11,12]

For metabolic syndrome, we first externally validated the original PsyMetRiC full and partial models in CPRD. Then, to create PsyMetRiC1-MetS, we used CPRD to perform model revision and recalibration, and for PsyMetRiC2-MetS we extended PsyMetRiC1-MetS with four new predictors (table 1). External validation of PsyMetRiC1-MetS and PsyMetRiC2-MetS was conducted in QResearch (appendix 1 pp 12–14). For weight gain (PsyMetRiC2-WG), we used logistic regression with intercepts stratified by baseline BMI category, hypothesising that individuals already overweight at

baseline would have a differential baseline risk of weight gain. Full and partial models were developed using secondary care data, and they were internally validated (appendix 1 pp 12–14). We could not perform external validation of PsyMetRiC2-WG due to the unavailability of a sufficient validation sample. For example, the available sample in primary care sources was insufficient possibly because clinical guidelines recommended that physical health checks were initially completed within secondary care. For type 2 diabetes (PsyMetRiC2-T2D), we used Weibull regression and performed internal validation in CPRD, and external validation in QResearch (appendix 1 pp 12–14). We did not consider a partial model version for PsyMetRiC2-T2D due to the importance of blood markers in making accurate predictions.

We conducted multiple imputation using chained equations for missing data and performed visual posterior-predictive imputation checks. Numerical estimates were pooled using Rubin's rules (appendix 1 pp 12–16). Where possible, for newly developed models we derived prediction, calibration, classification, and decision curve instability plots.

We derived distributions of linear predictors and outcome probabilities and drew standardised predictor contribution plots. Predictive performance was assessed using measures of discrimination, calibration, and clinical usefulness, as recommended.[24] For models developed using logistic regression (PsyMetRiC1-MetS, PsyMetRiC2-MetS, and PsyMetRiC2-WG), we report pooled estimates of C-statistic, calibration intercept, and calibration slope with 95% CIs; pooled calibration plots;[25] and decision curve metrics (net benefit, defined as true positives minus weighted false positives; standardised net benefit, defined as net benefit divided by outcome prevalence, across a range of plausible thresholds; and decision curve plots). For PsyMetRiC2-T2D, we report pooled numerical estimates of Harrell's C-statistic, calibration metrics (mean [Eavg], 50th [E50] and 90th [E90] percentile, and maximum [Emax] calibration error; and a summary-based global estimated calibration index [ECI]) with 95% CIs, decision curve metrics, calibration, and decision curve plots (appendix 1 pp 12–14).

We conducted external validation stratified by sex (administratively recorded) and ethnic background (self-assigned) for the new metabolic syndrome (PsyMetRiC2-MetS) and type 2 diabetes (PsyMetRiC2-T2D) models to appraise equity. We consider these analyses exploratory due to the limited subgroup sample sizes. We could not conduct such analyses for PsyMetRiC2-WG or stratify on other potentially relevant factors (eg, Townsend deprivation index or year of baseline assessment) due to sample size constraints.

Aligned to the guidance for unbiased predictive information for health-care decision-making and equity framework,[26] for PsyMetRiC2-T2D we assessed whether including ethnicity as a predictor might more likely lessen or widen health inequities by comparing the ethnicity-stratified calibration and net benefit of the a priori-defined model (ethnicity aware) with a version excluding ethnicity (ethnicity blind). We could not conduct similar analyses with models for metabolic syndrome (predictors already adjusted for ethnicity) or weight gain (insufficient sample size) models, so we used the results for PsyMetRiC2-T2D as the basis for reconsidering the inclusion of ethnicity across all models. Equations for all PsyMetRiC models are available online under an academic use licence.[27]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In total, we included 25 850 individuals from all three databases (male, n=13 614 [52·7%]; female n=12 236 [47·3%]; White European, 16 445 [63·6%]; Black African or Caribbean, south Asian, mixed, and east Asian or other n=9405 [36·3%]; and mean age 26·7 years [SD=5·4]). For primary care, we included 3989 individuals for development and 4347 individuals for external validation of metabolic syndrome outcomes; and 9181 individuals for development and 7487 individuals for external validation of type 2 diabetes outcomes, representing 121 202 person-years of follow-up. For secondary care, we included 846 individuals for development and internal validation of weight gain outcomes (table 2; appendix 1 p 36). Missing sample analyses showed that the included samples had higher ethnic diversity and were younger compared with the excluded samples (appendix 1 pp 28–29).

For metabolic syndrome, the appendix 1 (pp 29, 37–38) reports the distributions of linear predictors and predicted probabilities for the metabolic syndrome models (PsyMetRiC1-MetS and PsyMetRiC2-MetS). Figure 1 outlines standardised predictor contributions. The pooled external validation results of the original PsyMetRiC models in CPRD for the full model were C=0·78 (95% CI 0·76 to 0·81), calibration intercept=0·16 (0·02 to 0·09), and calibration slope=1·12 (0·91 to 1·14); for the partial model they were C=0·77 (0·74 to 0·79), calibration intercept=–0·07 (–0·14 to 0·01), and calibration slope=0·92 (0·82 to 1·01). Calibration plots showed good agreement between predicted risk and observed proportions in the full model, but systematic over-prediction in the partial model (appendix 1 p 39). Performance improved incrementally at each stage, after revising predictor coding (PsyMetRiC1-MetS) and after adding new predictors (PsyMetRiC2-MetS; appendix 1 pp 29, 39). At external validation of PsyMetRiC2-MetS in QResearch, the pooled results for the full model were C=0·81 (0·77 to 0·84), calibration intercept=–0·04 (–0·25 to 0·11), and calibration slope=1·22 (0·93 to 1·45); and for

the partial model, they were C=0·79 (0·76 to 0·83), calibration intercept=–0·11 (–0·33 to 0·12), and calibration slope=1·14 (0·97 to 1·28). Calibration plots showed acceptable agreement between predicted risk and observed proportions in the full model, and mild miscalibration in the partial model (figure 2A, B). External validation decision curve analysis suggested that at a cutoff value of more than 0·05, PsyMetRiC2-MetS full and partial models provided a greater net benefit than intervening in all or none of the sample, with preference for the full model particularly at higher risk thresholds (figure 2C). For example, at a threshold of 0·20, the full and partial models would provide net benefits of 0·10 and 0·09, equivalent to an additional 50% and 48% of metabolic syndrome cases that could be identified, respectively (appendix 1 pp 30–31).

For type 2 diabetes, appendix 1 (pp 31, 40) reports distributions of linear predictors and predicted probabilities for PsyMetRiC2-T2D. Figure 1 reports

	Metabolic syndrome		Type 2 diabetes		Weight gain: early intervention service*
	CPRD	QResearch	CPRD	QResearch	
Total	3989	4347	9181	7487	846
Sex†					
Male	2060 (51·6%)	2220 (51·1%)	4689 (51·1%)	4107 (54·9%)	538 (63·6%)
Female	1929 (48·4%)	2127 (48·9%)	4492 (48·9%)	3380 (45·1%)	308 (36·4%)
Age	26·2 (5·5)	27·5 (5·6)	26·1 (5·5)	27·4 (5·5)	25·8 (4·9)
Ethnic group‡					
White European	2408 (60·4%)	2980 (68·6%)	5638 (61·4%)	5205 (69·5%)	214 (25·3%)
Black African or Caribbean	404 (10·1%)	438 (10·1%)	1151 (12·5%)	768 (10·3%)	452 (53·4%)
South Asian	422 (10·6%)	510 (11·7%)	954 (10·4%)	736 (9·8%)	98 (11·6%)
East Asian or other	452 (11·3%)	419 (9·6%)	901 (9·8%)	778 (10·4%)	39 (4·6%)
Mixed§	303 (7·6%)	0	537 (5·8%)	0	43 (5·1%)
BMI baseline, kg/m²	24·4 (5·9)	24·7 (5·8)	24·5 (5·9)	24·6 (5·8)	23·8 (3·0)
HDL baseline, mean mmol/L	1·3 (0·4)	1·3 (0·4)	1·4 (0·4)	1·3 (0·4)	1·4 (0·4)
Triglycerides baseline, mean mmol/L	1·3 (0·7)	1·2 (0·7)	1·3 (0·8)	1·3 (0·8)	1·1 (0·5)
HbA_{1c} baseline, mean mmol/L	35·0 (5·6)	37·2 (9·5)	34·1 (4·1)	35·6 (4·4)	35·3 (5·6)
Systolic blood pressure baseline, mean mmol/mol	119·3 (13·3)	118·9 (13·5)	119·0 (13·6)	118·9 (13·9)	121·2 (12·1)
Antidepressant at baseline	1105 (27·7%)	1360 (31·3%)	2451 (26·7%)	2019 (27·0%)	132 (15·6%)
Antipsychotic at baseline¶					
Muscarinic antagonist	1810 (45·4%)	2034 (46·8%)	4036 (44·0%)	2938 (39·2%)	410 (48·5%)
Dopamine partial agonist or adrenergic antagonist	821 (20·6%)	780 (17·9%)	1543 (16·8%)	1721 (23·0%)	204 (24·1%)
Serotonergic and dopaminergic antagonist	599 (15·0%)	896 (20·6%)	1020 (11·1%)	1349 (18·0%)	137 (16·2%)
Dopaminergic antagonist	353 (8·8%)	455 (10·5%)	891 (9·7%)	805 (10·8%)	95 (11·2%)
Family history of cardiometabolic disorders	1643 (41·2%)	1836 (42·2%)	3892 (42·4%)	2935 (39·2%)	NA
Smoking at baseline	2185 (54·8%)	3039 (69·9%)	5138 (56·0%)	4252 (56·8%)	522 (61·7%)
Metabolic syndrome at baseline‖	62/4051 (1·5%)	119/4466 (2·7%)	NC	NC	NC
Metabolic syndrome at follow-up	841 (21·1%)	930 (21·4%)	NC	NC	NC
Type 2 diabetes at baseline‖	NC	NC	48/9229 (0·5%)	32/7519 (0·4%)	NC
Type 2 diabetes at follow-up	NC	NC	348 (3·8%)	297 (4·0%)	NC
Obesity at baseline‖**	NC	NC	NC	NC	196/1042 (18·8%)
Obesity at follow-up**	NC	NC	NC	NC	244 (28·8%)
Mean follow-up, years	3·8 (1·4)	3·4 (1·6)	7·4 (4·7)	7·5 (4·5)	0·43 (0·28)

Data are n (%) or mean (SD). CRPD=Clinical Practice Research Datalink. NA=not available. NC=not computed. *South London and Maudsley NHS Foundation Trust psychosis early intervention service. †Sex was obtained from routine health records. Gender identity was not available. ‡Ethnicity was recorded based on self-assigned ethnicity recorded in primary care (QResearch) using standard NHS categories; in CRPD, a single derived ethnicity category per individual was used, drawing on primary care and linked Hospital Episode Statistics where available. §Differences in the proportion of people with a mixed ethnic background in primary care sources are related to differences in data provision. ¶Classification from McCutcheon and colleagues,[20] see appendix (pp 4–5). ‖Participants who met the outcome criteria at baseline were excluded, so these individuals were not included in the total number, hence the denominators in the outcomes at baseline rows are higher. **≥29·9 kg/m² for White Europeans and ≥27·5 kg/m² for all other ethnic groups (appendix pp 2–3).

Table 2: **Characteristics of included samples**

predictor contributions. At internal validation, the pooled performance statistics were C=0·86 (95% CI 0·76 to 0·95); and the calibration metrics were Eavg=0·01 (0·01 to 0·02), E50=0·01 (0·00 to 0·01), E90=0·02 (0·01 to 0·03), Emax=0·10 (0·08 to 0·14), and ECI=0·04 (0·03 to 0·06). The internal validation calibration plot revealed good agreement between the predicted risk and observed proportions, but some overprediction at higher risk probabilities (appendix 1 p 41). At external validation, pooled results were C=0·81 (0·71 to 0·88); and the calibration metrics were Eavg=0·01 (0·00 to 0·03), E50=0·01 (0·00 to 0·03), E90=0·02 (–0·01 to 0·06),

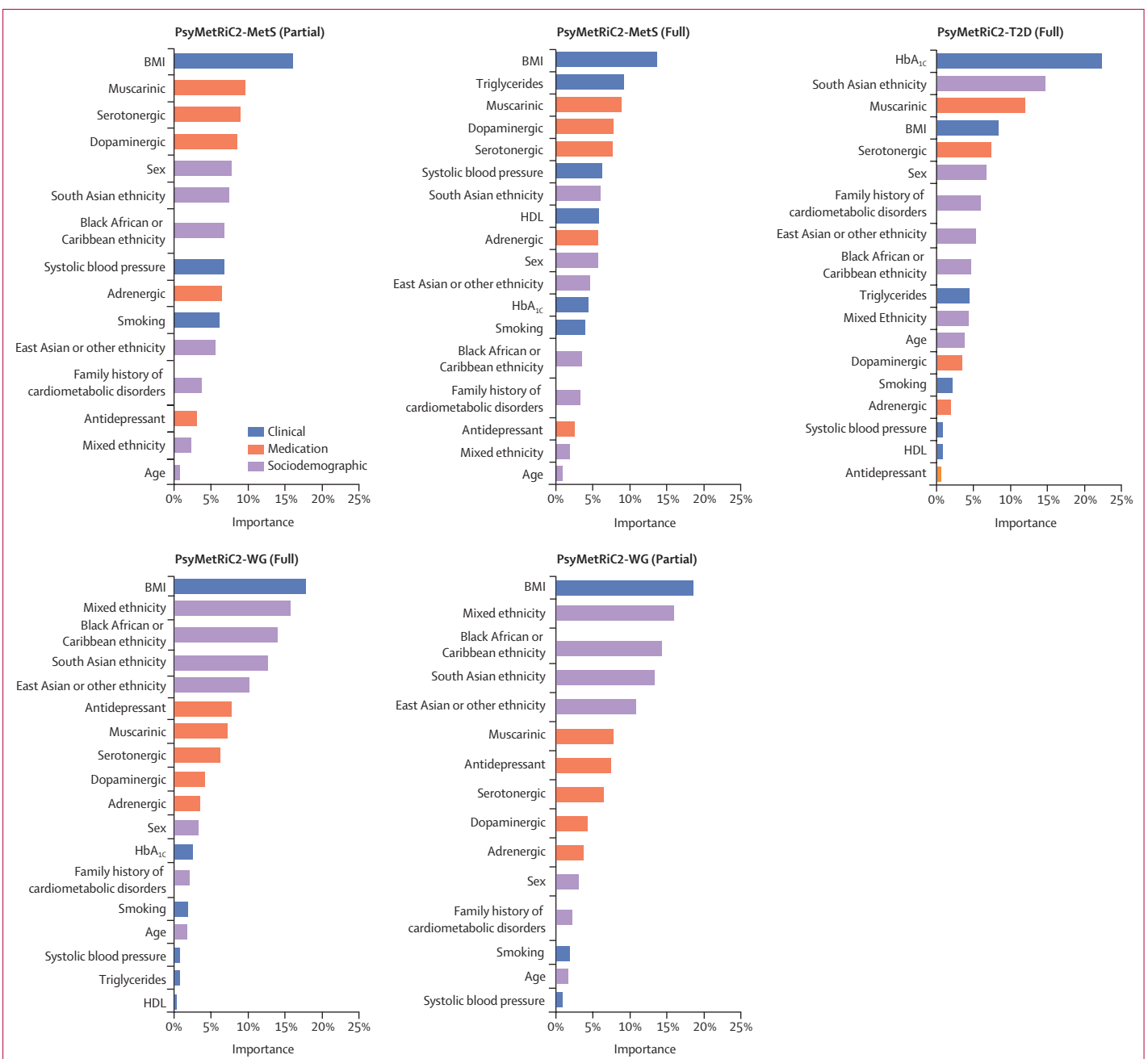
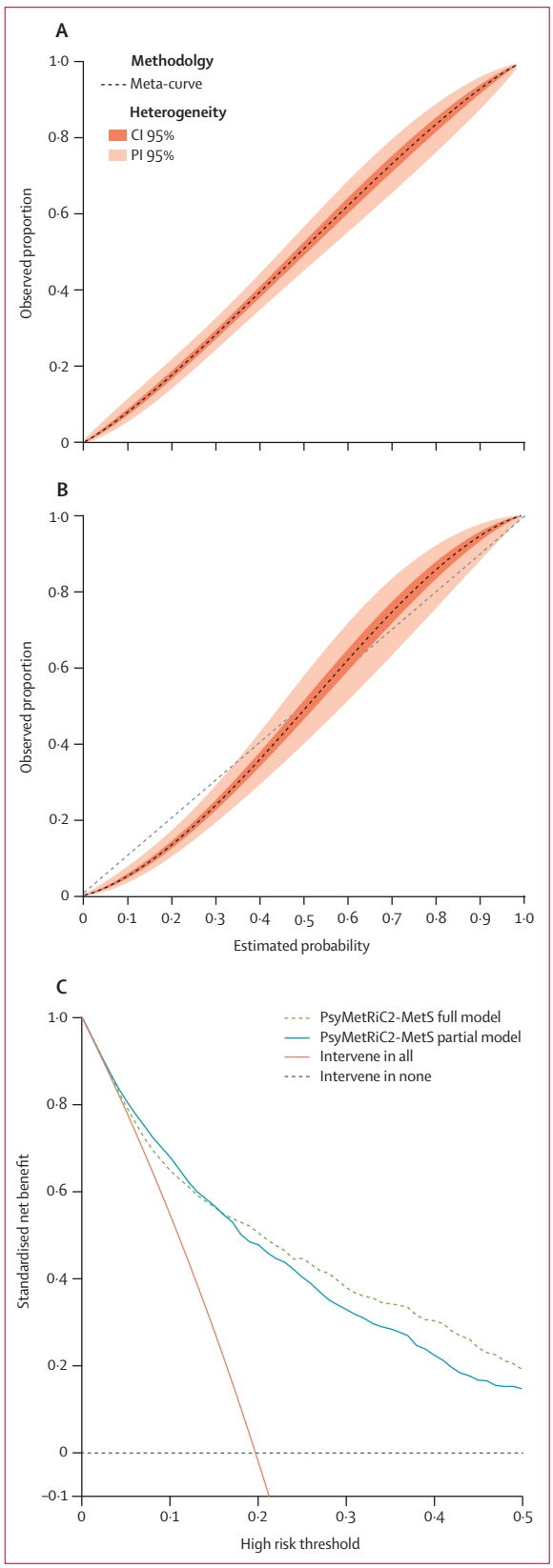


Figure 1: **Standardised relative predictor importance of PsyMetRiC2 models**
Partial indicates the models without biochemical predictors, and full indicates the models with biochemical predictors. Muscarinic refers to antipsychotics of the muscarinic antagonist class, serotonergic refers to antipsychotics of the serotonergic and dopaminergic antagonist class, dopaminergic refers to antipsychotics of the dopaminergic antagonist class, and adrenergic refers to antipsychotics of the adrenergic antagonist or dopamine partial agonist class (appendix pp 4–5). We did not consider a partial model version for PsyMetRiC2-T2D due to the perceived importance of blood markers in making accurate predictions. PsyMetRiC2-MetS=Psychosis Metabolic Risk Calculator 2 model predicting metabolic syndrome. PsyMetRiC2-T2D=Psychosis Metabolic Risk Calculator 2 model predicting type 2 diabetes. PsyMetRiC2-WG=Psychosis Metabolic Risk Calculator 2 model predicting clinically significant weight gain.



Emax=0·09 (–0·13 to 0·31), and ECI=0·04 (–0·13 to 0·22). The calibration plot showed good agreement between predicted risk and observed proportions (figure 3A). External validation decision curve analysis suggested that at the cutoff value of more than 0·03, PsyMetRiC2-T2D provided greater net benefit than intervening in all or none of the samples (figure 3B). For example, at a threshold of 0·10 the model would provide a net benefit of 0·04, equivalent to an additional 47% of T2D cases that could be identified (appendix 1 pp 31–32).

For weight gain, appendix 1 (pp 42–43) reports distributions of predicted probabilities and prediction stability results for PsyMetRiC2-WG. At internal validation, pooled results for the full model were C=0·78 and calibration slope=0·88; and for the partial model they were C=0·77 and calibration slope=0·87. Internal validation calibration plots revealed acceptable agreement between predicted risk and observed proportions (appendix 1 p 44). Decision curve analysis suggested that at a cutoff value of more than 0·03, both PsyMetRiC2-WG model provided greater net benefit than intervening in all or none of the samples (appendix 1 p 45). For example, at a threshold of 0·30, the full and partial models would provide net benefits of 0·12 and 0·11, equivalent to an additional 43% and 39% of weight gain cases that could be identified, respectively (appendix 1 pp 32–33).

For PsyMetRiC2-MetS, we found no meaningful difference in discrimination performance by demographic group but identified some differences in calibration performance (appendix 1 pp 46–48). This led to some differences between ethnic groups in clinical usefulness, particularly for people of Black African or Caribbean backgrounds (appendix 1 p 49). Despite that, for all subgroups across the range of plausible thresholds, PsyMetRiC2-MetS retained clinical usefulness (appendix 1 p 49).

For PsyMetRiC2-T2D, we found no meaningful difference in discrimination, calibration, or decision curve performance by demographic group (appendix 1 pp 50–52). For White Europeans, there was a negligible effect of including ethnicity as a predictor. For all other ethnic groups, the ethnicity aware model improved the calibration performance and clinical usefulness (appendix 1 pp 53–54).

Figure 2: **External validation plots of PsyMetRiC2 model for metabolic syndrome in QResearch**
(A) Full model for calibration. (B) Partial model for calibration. (C) Decision curve plot of full and partial models. Calibration plots, pooled across imputed datasets,[25] show agreement between observed proportions and estimated risk. The decision curve plot shows the standardised net benefit across high-risk thresholds, alongside competing strategies of intervening in all or none of the sample. Clinical usefulness is indicated where the model yields higher net benefit than both competing strategies across thresholds likely to be considered in practice. The orange line represents intervening in all. The grey dashed line (along the X axis at Y=0) represents intervening in none. PsyMetRiC=Psychosis Metabolic Risk Calculator.

Discussion

In our development of cardiometabolic prediction models for people aged 16–35 years with psychosis spectrum disorders, our primary analysis refined the original PsyMetRiC models and developed new versions predicting stakeholder-preferred shorter term weight gain and longer term type 2 diabetes. A priori-defined refinements improved PsyMetRiC1-MetS discrimination by 0·03 (4%) and yielded an external validation excellent performance for PsyMetRiC2-MetS and PsyMetRiC2-T2D. Internal validation results for PsyMetRiC2-WG were promising, but we identified prediction instability, which warranted caution in assuming generalisability. To maximise usefulness and reflect that PsyMetRiC outcomes might be correlated with shared risk factors, we used the same baseline predictors for all models. However, given the prominence of blood-based markers for PsyMetRiC2-T2D, a partial version was not feasible. Furthermore, consistent with other validations,[10–12] the full model outperformed the partial model versions across measures. This underscores the importance of biochemical assessment in early psychosis. Where possible, we implemented models in a web application compliant with regulatory standards in Great Britain, enabling registration as a class 1 medical device. This enables clinical use in Great Britain. To our knowledge, these are among the first prediction models in psychiatry to obtain this status.

We performed sensitivity analyses to assess equity. Clinical usefulness was maintained across strata, and including ethnicity was more likely to reduce than exacerbate inequalities. However, we identified some demographic performance differences for PsyMetRiC2-MetS. Ethnicity recording reflected self-assigned categories and should be interpreted as a sociocultural construct. Observed differences might reflect unmeasured structural and socioeconomic drivers. For instance, despite NHS England's Core20Plus5 prioritising physical health checks for severe mental illness,[3] disparities in recording persist.[28] Unequal physical health check access might create ascertainment bias[29] that could affect models such as PsyMetRiC, but this is difficult to quantify or address using routine data.[30] We intend to address this within the implementation process, informed by further research and stakeholder consultation.

Stakeholder involvement also addressed effective risk communication. Patients and health professionals might misinterpret risk estimates,[31] impeding health risk communication, and this might help to explain the low impact on behavior change.[32] We used several approaches to address this. For example, the web application presents risk information in various graphical and numerical formats (appendix 1 p 55),[33] represents uncertainty,[34] and includes an adaptation of the heart age score, an approach that shows promise in positively affecting behaviour change motivation.[35] We co-produced a risk communication guide with stakeholders that will undergo further development.

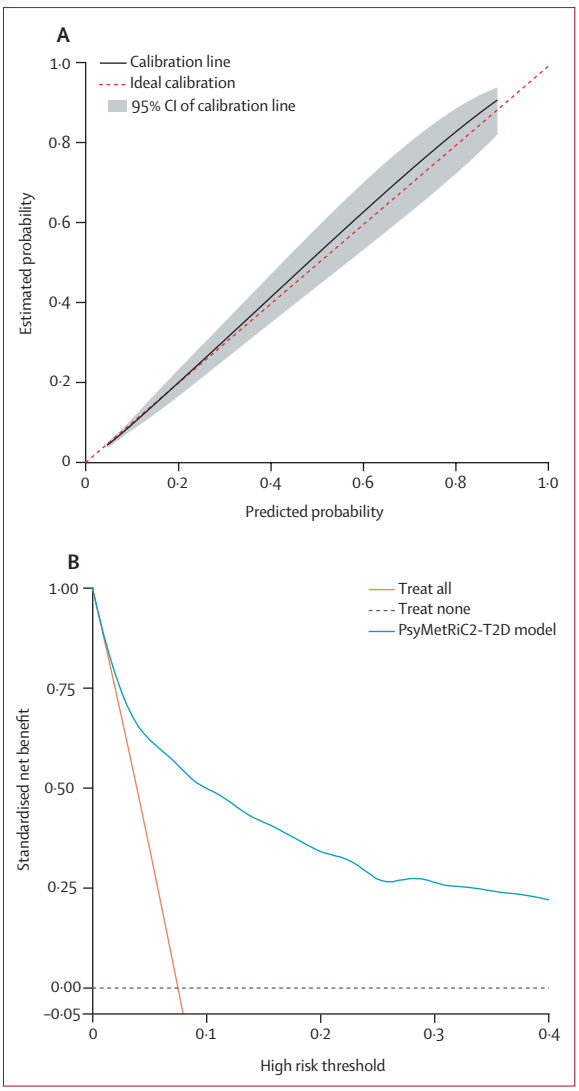


Figure 3: **External validation plots of PsyMetRiC2 for type 2 diabetes in QResearch**

(A) Calibration plot. (B) Decision curve plot. The calibration plot shows the agreement between observed proportions and estimated risk. The decision curve plot shows the standardised net benefit across high-risk thresholds, alongside competing strategies of intervening in all or none of the sample. Clinical usefulness is indicated where the model yields higher net benefit than both competing strategies across thresholds likely to be considered in practice. PsyMetRiC=Psychosis Metabolic Risk Calculator.

For instance, stakeholder discussions highlighted that PsyMetRiC could increase the risk of medication non-adherence, which the co-produced risk communication guide addresses, and will be monitored closely as part of ongoing research and post-market surveillance.

The web application does not currently define risk thresholds. Threshold preferences varied among stakeholder groups, and our analyses underscored the need to consider equity in setting thresholds. Planned qualitative and health economic work will explore this further. However, implementing thresholds within the

application could shift it from informing care to driving care—probably prompting higher regulatory classification in many jurisdictions. Global regulatory classification for prediction models is tightening, with costs and infrastructure requirements scaling accordingly. To pragmatically preserve availability and sustainability, we chose to retain the informing role, and we will develop and evaluate thresholds outside the web application, informed by future research and stakeholder engagement.

The web application does not recommend specific interventions. Future work will test whether PsyMetRiC-guided interventions (eg, antipsychotic selection, enhanced monitoring, and adjunctive treatments) improve outcomes and are cost-effective. Nevertheless, our consultations with people who have lived experience of psychosis and carers suggested that blanket recommendations at specific risk thresholds might not be appropriate or feasible. For example, the blanket recommendation of metformin or other pharmaceutical treatments is not helpful for individuals who do not wish to take more medication; similarly, advising physical activity might be unhelpful for those who cannot afford appropriate exercise clothing or footwear; and promoting healthy eating might be impractical for individuals without a suitable living environment in which to prepare nutritious meals. Instead, clinicians should contextualise risk scores within individual circumstances to support tailored, holistic intervention. This patient-centred approach aligns with the COM-B model,[36] in which behaviour results from capability, opportunity, and motivation. Stakeholders favoured this model, and we are exploring its usefulness in ongoing qualitative work.

The PsyMetRiC web application will receive iterative updates over time. Updates will reflect qualitative research, economic modelling, PsyMetRiC2-WG external validation, and trial-based effect evaluation. Prediction model impact studies are rare[13] but are crucial to assess implementation and unintended consequences, such as medication non-adherence. Other updates will arise from user feedback and post-market surveillance. Finally, PsyMetRiC will require ongoing external validation to monitor temporal shifts in cardiometabolic risk.

Validated and regulatory certified general population models for type 2 diabetes exist, but evidence suggests these are unsuitable for young people with psychosis and might underpredict risk.[37] A key explanation is that cardiometabolic risk in the general population accumulates with age,[7] so age strongly drives risk estimates. In contrast, cardiometabolic risk is detectable in many young people from the onset of psychosis.[6] QDiabetes,[38] a guideline-recommended population-based prediction model, is not intended for use in individuals younger than 25 years. Similarly, PRIMROSE, a cardiovascular prediction model tailored for people with severe mental illness, was developed for adults older than 30 years but is not certified for clinical use.[39] Given that psychosis incidence peaks in the early 20s, delaying risk estimation until individuals meet age eligibility risks missing a crucial preventive window in this high-risk group.

Although PsyMetRiC prioritised scalability using routine predictors, future iterations might incorporate additional risk factors. These include social and behavioural determinants (eg, loneliness,[40] physical activity, and diet[2]) and emerging biomarkers such as metabolomics, genetic liability,[41] and dual-energy x-ray absorptiometry scans. These might offer incremental value for cardiometabolic outcomes, beyond the variance already captured in routine markers. The feasibility of integrating these measures within early psychosis pathways warrants evaluation. Future iterations might also consider other psychotropic and non-psychotropic medications that could alter cardiometabolic risk trajectories.

Limitations include the exploratory nature of sensitivity analyses; larger, more diverse studies are needed. Substantial exclusion due to missing baseline or follow-up data, or both, might have introduced selection bias, potentially influencing outcome prevalence and net benefit because imputation was limited to included participants without weighting. The absence of a suitable validation sample for PsyMetRiC2-WG has precluded its current inclusion in the web application. Where performance differences are identified, heterogeneity should be examined before recalibration or revision. Clinical availability of the PsyMetRiC web application applies only to Great Britain, although we hope to expand this in future. We did not explore potential non-linear relationships or interactions in model building; although this might have limited development sample optimisation, it was a deliberate design choice to reduce model complexity and support transportability, and future studies with larger datasets could examine prespecified interactions. The psychotropic medication predictors are unable to capture the effect of adherence over time and might reflect prescriber bias. Although the PsyMetRiC2-T2D model accommodates longer follow-up, we reported and emphasised performance at 10 years based on stakeholder priorities and the available follow-up distribution. Future work in larger datasets could examine prespecified diagnostic subgroup performance and, where appropriate, explore diagnosis-stratified recalibration or extensions. Finally, the web application implementation, which requires manual predictor inputs, might not be optimal for clinical use. Manual calculation is time-consuming. Integration within electronic health records would improve ease and speed of use but would probably require buy-in from providers willing to register as medical device manufacturers. Conversely, the web application implementation encourages purposeful, conscientious use—potentially promoting deeper health risk communication, which might be less likely with automated health record alerts—and our application programming interface integration, if implemented locally, would remove the burden of manual data input.

In conclusion, the PsyMetRiC models are among the first in psychiatry to be available for routine clinical use. PsyMetRiC can support a shift toward collaborative, preventive physical health care for young people with psychosis. Ongoing and future work will encompass health economic modelling to explore cost-effectiveness, qualitative research to explore implementation strategies, and a trial-based evaluation to explore impact.

Contributors

BIP led the conceptualisation, funding acquisition, study design, data curation, formal analysis, methodology, software development, investigation, validation, visualisation, and wrote the original draft. EFO contributed to data curation, formal analysis, investigation, and writing: review and editing. SS and CL contributed to visualisation, software development, and writing: review and editing. KVBH contributed to data curation, investigation, visualisation, and writing: review and editing. GMK, PBJ, and RU co-led on conceptualisation, supervision, and writing: review and editing. BL, GKM, DS, CAC-G, AKD, MB, SJ, SJG, and RIGH contributed to supervision and writing: review and editing. JE contributed to study design, investigation, methodology, software, supervision, validation, visualisation and writing: review and editing. AELW and SA contributed to project administration, resources, supervision, investigation, and writing: review and editing. TF contributed to software, visualisation, and writing: review and editing. TP and RAM contributed to writing: review and editing. SH, MR, and KW contributed to investigation, project administration, resources, supervision, and writing: review and editing. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. BIP and EFO had full access to and verified the data.

Declaration of interests

DS is an expert advisor for the National Institute for Health and Care Excellence (NICE) Centre for Guidelines. BIP is a NICE topic advisor for Severe and Enduring Mental Illness. The views expressed are the authors and not those of NICE. RAM has received speaker and consultancy fees from Boehringer Ingelheim, Bristol Myers Squibb, Janssen, Karuna, Lundbeck, Newron, Otsuka, Angelini Pharma, and Viatris; and co-directs a company that designs digital resources to support treatment of mental ill health. GKM and BIP received grants paid to the institution from the Evelyn Trust and the Wellcome Trust to pay research costs associated with this project. BIP additionally received grants for the conduct of this work paid to their institution from the National Institute for Health and Care Research (NIHR) and the BMA Foundation. SJG receives salary support paid to his institution from NHS East of England and has received honoraria from AstraZeneca for contributing to postgraduate educational meetings. GMK has received grant funding in the past 36 months from Medical Research Council, National Institute for Health and Care Research, and Wellcome Trust; has received book royalties from Cambridge University Press; and consulting and speaker fees from the Danish Research Fund and Neuroimmune Foundation. RU has received consulting and speaker fees from Bristol Myers Squibb, TEVA, Viatris, and Springer Healthcare; was honorary general secretary (unpaid) for the British Association of Psychopharmacology (2021–25) and is a current member of the Clinical Advisory Group for Rethink Mental Illness. TP has received speaker and consultancy fees from Bristol Myers Squibb, Boehringer Ingelheim, CNX Therapeutics, Janssen, Lecturing Minds Stockholm AB, Lundbeck, Otsuka, Recordati, Teva Pharmaceuticals, ROVI Biotech, Schwabe Pharma, and Sunovion. BIP, EFO, and JE are part of the PsyMetRiC Operating Division in partnership with University of Birmingham Enterprise, but do not derive any financial benefit. All other authors declare no competing interests.

Data sharing

The Psychosis Metabolic Risk Calculator (PsyMetRiC)1 metabolic syndrome model, PsyMetRiC2 metabolic syndrome model, and PsyMetRiC2 type 2 diabetes model are available for clinical use in Great Britain at https://psymetric.app/. The underlying equations for all PsyMetRiC models are available under an academic use licence at https://licensing.micragateway.org/product/psymetric-algorithm. The co-produced risk communication guide (appendix 2) is also available for download on the web application (https://psymetric.app/). Data sources are available on application to QResearch, Clinical Practice Research Datalink, and South London and Maudsley NHS Foundation Trust.

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