Perry, B. I., Upthegrove, R., Crawford, O., Jang, S., Lau, E., McGill, I., Carver, E., Jones, P. B., & Khandaker, G. M. (2020). Cardiometabolic risk prediction algorithms for young people with psychosis: a systematic review and exploratory analysis. *Acta Psychiatrica Scandinavica, 142*(3), 215-232. https://doi.org/10.1111/acps.13212

Publisher's PDF, also known as Version of record

License (if available):
CC BY

Link to published version (if available):
10.1111/acps.13212

Link to publication record in Explore Bristol Research

PDF-document

This is the final published version of the article (version of record). It first appeared online via John Wiley and Sons at https://doi.org/10.1111/acps.13212. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/
Cardiometabolic risk prediction algorithms for young people with psychosis: a systematic review and exploratory analysis

Perry BI, Upthegrove R, Crawford O, Jang S, Lau E, McGill I, Carver E, Jones PB, Khandaker GM. Cardiometabolic risk prediction algorithms for young people with psychosis: a systematic review and exploratory analysis.

Objective: Cardiometabolic risk prediction algorithms are common in clinical practice. Young people with psychosis are at high risk for developing cardiometabolic disorders. We aimed to examine whether existing cardiometabolic risk prediction algorithms are suitable for young people with psychosis.

Methods: We conducted a systematic review and narrative synthesis of studies reporting the development and validation of cardiometabolic risk prediction algorithms for general or psychiatric populations. Furthermore, we used data from 505 participants with or at risk of psychosis at age 18 years in the ALSPAC birth cohort, to explore the performance of three algorithms (QDiabetes, QRISK3 and PRIMROSE) highlighted as potentially suitable. We repeated analyses after artificially increasing participant age to the mean age of the original algorithm studies to examine the impact of age on predictive performance.

Results: We screened 7820 results, including 110 studies. All algorithms were developed in relatively older participants, and most were at high risk of bias. Three studies (QDiabetes, QRISK3 and PRIMROSE) featured psychiatric predictors. Age was more strongly weighted than other risk factors in each algorithm. In our exploratory analysis, calibration plots for all three algorithms implied a consistent systematic underprediction of cardiometabolic risk in the younger sample. After increasing participant age, calibration plots were markedly improved.

Conclusion: Existing cardiometabolic risk prediction algorithms cannot be recommended for young people with or at risk of psychosis. Existing algorithms may underpredict risk in young people, even in the face of other high-risk features. Recalibration of existing algorithms or a new tailored algorithm for the population is required.

Summations

- A large number of cardiometabolic risk prediction algorithms have been developed, but only three algorithms (QRISK3, QDiabetes and PRIMROSE) included psychiatric predictors. All three algorithms were developed and validated in large samples of relatively older participants.
- From our exploratory analysis, we show that all three algorithms may underpredict cardiometabolic risk in young adults with or at risk of developing psychosis, which may be a function of the way age is modelled in the algorithms.
- No existing cardiometabolic risk prediction algorithm can be recommended for use in young adults with or at risk of developing psychosis, yet the population remains at higher risk of cardiometabolic disorders than their age-matched peers.
Introduction

Cardiometabolic disorders broadly include cardiovascular diseases (CVD), disorders of adiposity such as obesity and disorders of glucose-insulin homeostasis such as type 2 diabetes mellitus (T2DM) (1). They impose a huge societal burden costing an estimated £30 billion and accounting for over 190 000 deaths each year in the UK alone (2). A particularly high-risk group for the development of cardiometabolic disorders are people with psychotic disorders such as schizophrenia, who make up around 0.8% of the population (3) and have up to a 30% increased incidence of cardiometabolic disorders than the general population (4). Indeed, increased physical comorbidity is a leading cause for significantly increased mortality rates and reduced life expectancy for people with schizophrenia compared with the general population (5–7). We therefore need clinical tools to predict cardiometabolic risk in this group in order to optimize care and improve long-term outcomes. Yet, a recent report of a small sample of people with chronic schizophrenia suggests that some commonly used cardiometabolic risk prediction algorithms return differing risk prediction scores when tested on the same participants. This calls into question the reliability and suitability of such algorithms for relatively older people with chronic schizophrenia, let alone young people with or at risk of psychosis (8).

Recent evidence suggests that the physical comorbidity associated with schizophrenia starts early. Markers of developing cardiometabolic disorders are a feature that distinguish cases of first-episode psychosis from matched general population controls (9, 10) and are associated with young adults at risk of developing psychosis (11). The field of early intervention in psychosis rests on a premise that intervening early could improve longer-term outcomes, and this premise applies equally to the treatment of cardiometabolic disorders. Therefore, cardiometabolic risk prediction algorithms may be a useful tool for healthcare professionals to help tailor treatment plans for young people with psychosis that could help to reduce both long-term physical and psychiatric morbidity. However, such a tool could only be clinically useful if the predictions it makes are accurate. It is unclear as to whether this may or may not be the case.

Aims of the study

We conducted a systematic review to identify and compare existing cardiometabolic risk prediction algorithms developed for the general or psychiatric populations and consider their suitability for young people with psychosis. Next, we performed an exploratory analysis using data from a large UK birth cohort to examine the predictive ability of any algorithms highlighted as potentially suitable by the review, in a sample of young adults with or at risk of psychosis. To explore the impact of age on risk estimates, we reassessed model performance after artificially increasing the age of participants to the mean age of the original algorithm development study, leaving all other predictors unchanged.

Method

Systematic review

Literature search. We conducted a systematic literature search of EMBASE (1947-present), Ovid MEDLINE (1946-present), PsychINFO (1806-present), Web of Science (from inception) and the first twenty pages of Google Scholar (12) to 1 December 2019. We also searched the references of included studies. Our search strategy is presented below. MeSH headings (denoted with *) and text terms were used:

Group 1: metabolism* (OR) metabolic* (OR) diabetes mellitus* (OR) cardiovascular diseases* (OR) obesity* (OR) cardiometabolic

(AND)

Group 2: risk assessment* (OR) risk* (OR) outcome assessment* (OR) patient outcome assessment* (OR) prognosis*

(AND)

Group 3: calculator (OR) computers* (OR) algorithms* (OR) software* (OR) tool.
We applied the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) guidelines (13). The systematic review was registered on PROSPERO (CRD42019150377).

**Study selection.** The inclusion criteria were as follows: (i) studies reporting the development and/or validation of cardiometabolic risk algorithms designed for either the general or psychiatric populations; (ii) studies which reported in combination the development and validation (internal or external) of an original algorithm; reported the development but not validation of an algorithm; reported the first validation of a previously developed but not validated algorithm; or reported a new recalibration of a previously developed algorithm; (iii) cardiometabolic risk was defined as CVD (stroke, myocardial infarction, hypertension, unstable angina) and its common predeterminants including T2DM, prediabetes, obesity or dyslipidaemia; (iv) studies reported in any language; (v) published and unpublished research, conference proceedings and academic theses. The exclusion criteria were as follows: (i) algorithms designed specifically for other defined health groups (i.e. postoperative patients or patients with any physical health diagnoses at baseline) and (ii) studies reporting validation without recalibration of previously validated algorithms.

Titles and abstracts were screened independently by four authors (BIP, EL, IM and EC) prior to full-text screening. Any discrepancies were resolved in consultation with a senior author (GMK). Data were extracted by three authors (BIP, OC and SJ) from studies that met the inclusion criteria. Searches were re-run immediately (BIP, OC and SJ) from studies that met the inclusion criteria. Searches were re-run immediately after recalibration of previously validated algorithms.

**Data extraction and synthesis.** We extracted data on general characteristics (e.g. population, location, study type, type of risk predicted), the characteristics of included participants (e.g. age, sex, ethnicity) and characteristics of the developed/validated algorithms (e.g. included predictors, algorithm performance). Risk of bias was assessed using the ‘Prediction model Risk Of Bias Assessment Tool’ (PROBAST) (14), which aims to identify shortcomings in study design, conduct or analysis that could lead to systematically distorted estimates of model predictive performance. PROBAST includes four domains for potential sources of bias in prediction model studies (participants, predictors, outcome and analysis) which are then summarized by an overall judgement, either low risk, high risk or unclear risk of bias (14). We plotted the range and frequency of predictors included in studies. We illustrated the relative weighting of different predictors in one included study which featured psychiatric predictors. Algorithm performance was compared using statistics relating to model discrimination (how well an algorithm discriminates people at higher risk from people at lower risk, e.g. Harrell’s C Statistic, where a score of 1.0 indicates perfect discrimination, and a score of 0.5 indicates the model is no better than chance) and model calibration (the accuracy of absolute risk estimates, e.g. calibration plots) (15). We also examined the events-per-variable ratio (EPV) (the ratio of outcome events; predictors considered in algorithm development) of each study to assess the potential risk of model overfitting (16). An EPV of 10 or more had previously been considered satisfactory (17), though higher ratios have more recently been advised (18). Where an EPV ratio was not reported, we calculated it where possible from the information available in the study. Finally, we considered the likely suitability of all included algorithms for young people with psychosis. We summarized and compared studies with a narrative synthesis (19).

**Exploratory analysis.** The Avon Longitudinal Study of Parents And Children (ALSPAC) birth cohort initially recruited 14 541 pregnant women resident in a geographically defined region in southwest of England, with expected dates of delivery 1 April 1991 to 31 December 1992, resulting in 14 062 live births (20–22). Following further periods of recruitment over time, 913 additional participants were recruited. See http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/ for a fully searchable data dictionary. Study data were collected and managed using REDCap electronic data capture tools hosted at University of Bristol (23,24). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and Local Research Ethics Committees. All participants provided informed consent.

**Study sample.** We included participants who at age 18 or 24 years were identified as experiencing definite psychotic symptoms or psychotic disorder. In ALSPAC, psychotic symptoms were identified through the face-to-face, semi-structured Psychosis-Like Symptom Interview (PLIKS) conducted by trained psychology graduates and coded according to the definitions in the Schedules for Clinical Assessment in Neuropsychiatry, version 217.
Perry et al.

2.0. See Supplementary Data for further information. We excluded participants who already met the outcome criteria at age 18 years and participants who had missing data on all included variables. Additionally, we conducted a post hoc sensitivity analysis to examine the potential impact of sample size; we performed the analysis again including all participants from the total ALSPAC sample at age 18 years who did not meet the criteria for the outcome at age 18 years and who did not have missing data on all included variables. See Figures S1–S2 for flow charts of included participants.

Outcome. We used the harmonized definition (25) of the metabolic syndrome measured at age 24y as the outcome, in which it is an established precursor of T2DM (26) and CVD (27). Metabolic syndrome is a more appropriate outcome for a sample of relatively young participants. The follow-up period was six years. The binary outcome was coded present for participants meeting ≥3 factors from the following: ethnicity-specific waist circumference (≥94 cm in males and ≥80 cm in females for Caucasians; ≥90 cm in males and ≥80 cm in females for other ethnic groups (25)); elevated triglycerides (≥1.7 mmol/L); reduced high-density lipoprotein (HDL) (<1.0 mmol/L in males and <1.3 mmol/L in females); elevated seated blood pressure (systolic ≥130 mmHg); and elevated fasting plasma glucose (FPG) (≥5.7 mmol/L). See Supplementary Methods for further detail on biochemical measurements.

Predictors. We included all available predictors from QDiabetes, QDiabetes and PRIMROSE, which were the three algorithms highlighted as being potentially the most suitable for young people with psychosis. These included age, Townsend deprivation score, body mass index (BMI), ethnicity, smoking, antipsychotic medication use, antidepressant use, corticosteroid use, psychosis, depression, family history of cardiovascular disease or type 2 diabetes, hypertension, FPG, cholesterol:HDL ratio, systolic blood pressure, total cholesterol, HDL, alcohol intake and year of assessment. For a full list of predictors for each algorithm and details on how they were measured, see Table S1 and Methods S1.

Statistical analysis. Estimated six-year risk estimates for metabolic syndrome were calculated for QDiabetes (28), QDiabetes (29) and PRIMROSE (30), by applying the published fully specified algorithms to our sample. QDiabetes and PRIMROSE comprise different models depending on the availability of blood test results; thus, we used the model which performed best in the original model development studies (28, 30). For QDiabetes, the best performing model included FPG; for PRIMROSE, the best performing model included lipids. QDiabetes and QRISK3 estimate risk separately for males and females. We used multiple imputation using chained equations (31) to address the impact of missing predictor data. See Methods S1 for further details. Algorithm performance was assessed using measures of discrimination (Harrell’s C statistic and $R^2$) and a measure of calibration (calibration plots). Calibration plots included grouped observations, which were split at each 0.2 of predicted risk. First, we calculated model performance using actual participant age (18 years). To assess the impact of age on model performance, we artificially substituted every participants’ age in ALSPAC to the mean age from the original algorithm development study (QDiabetes = 44.9 years; QRISK3 = 42.9 years; and PRIMROSE = 49.5 years), leaving all other predictors unchanged. We re-ran each algorithm and compared the model performance statistics described above. Statistical analysis was carried out in R version 3.6.0 (32).

Results

Systematic review

Study selection and quality assessment. The literature search returned 7744 results after removing duplicates. We reviewed 362 full texts, of which 110 studies met inclusion criteria (28-30, 33-138). See Fig. 1 for the PRISMA diagram. Three studies were not contained within peer-reviewed journals and were published either as conference proceedings (108), a thesis (93) or a preprint (106). Reporting quality was relatively poor across the majority of studies, with 108 studies (98%) either at unclear or high risk of bias following assessment with the PROBAST tool (14). See Table S2.

Study characteristics. Table S3 reports the characteristics of included studies. All studies were conducted on general population samples of healthy adults, except one which was conducted on patients with severe mental illness, defined as either schizophrenia, other psychotic disorder or bipolar disorder (30). The majority of included studies were conducted in high-income or upper-middle-income countries, with the UK, USA and China best represented. Eleven studies were conducted in lower- or middle-income countries. Sample sizes were highly variable in both development ($n = 100$).
participants (120) to \( n = 8\,136\,705 \) participants (28) and validation cohorts \( n = 90 \) participants (104) to \( n = 2\,671\,298 \) participants (29)). Sixty-one studies (55%) assessed the risk of fatal or non-fatal CVD; 31 studies (28%) assessed the risk of T2DM; five studies (5%) assessed the risk of either prediabetes or T2DM; three studies (3%) assessed the risk of metabolic syndrome or obesity; and three studies (3%) assessed the risk of stroke or transient ischaemic attack.

Lengths of predicted risks ranged from one (119) to 30 (80, 123) years. The most common risk prediction timeframes were either ten-year risk (38 studies, 35%) or five-year risk (14 studies, 13%). Thirty-nine studies (35%) performed external validation of an original algorithm. Forty studies (36%) performed internal validation, either by subsetting the initial cohort or by bootstrap methods. All algorithms were designed using either Cox proportional hazards or logistic regression analysis. Most studies selected variables for inclusion from previous research or clinical importance (50 studies, 45%), or using statistical methods, that is forward or backward selection (31 studies, 28%). Seventeen studies (15%) used simple univariable analysis of each considered predictor, which is least preferable since it cannot assess interactions between two or more variables. Eleven studies (10%) used machine learning techniques.

**Participant characteristics.** All studies were conducted in adults. The mean age of participants based on the 76 studies that reported mean age was 50.50 years (SD 9.31). No studies included a mean age of participants below 35 years. Eighty-nine studies (81%) reported the sex distribution of
Perry et al.

the derivation cohort (mean 55.29% male (SD 17.27)), and 42 studies (38%) reported for the validation cohort (mean 52.25% male (SD 14.44)). The majority of studies included roughly equal sex distribution, apart from nine studies which included only (121, 127) or mostly females (82, 83, 85, 98, 120, 122, 128) and 12 studies which included only (41, 71, 94, 102,103,112,119,132,136) or mostly males (69,80,81). Thirty-three studies (30%) reported the ethnic makeup of their sample, where samples ranged from being ethnically completely homogenous in 18 studies (16%) to relatively heterogeneous, with less than 66% of participants falling into the most common ethnic group (63,72,84,125). See Table S3.

Algorithm characteristics. Predictors included in existing algorithms. Figure 2 shows the frequency of different predictors included in studies. The most common predictors were age (98 studies, 89%), smoking (83 studies, 75%) and systolic blood pressure (55 studies, 50%). Inflammatory markers such as CRP or IL-6 were included as predictors in 15 studies (14%). The number of predictors considered for each algorithm varied between four (44, 52, 53, 79) and 473 predictors (86). EPV varied between 2.1 (55) and 5,075.4 (29). Twenty studies featured EPV ratios that were likely < 10. See Table S4.

Performance of existing algorithms. Discrimination statistics were presented in 93 studies (85%), and calibration statistics were presented in 62 studies (56%). From the 80 studies that included both model development and validation analysis, 35 (44%) reported performance statistics from both development and validation cohorts, 27 (34%) reported only validation cohort statistics, and ten (13%) reported development only statistics. Most commonly overall, studies reported both discrimination and calibration statistics (35 studies, 32%). Next most commonly, studies reported measures for discrimination, calibration and sensitivity/specificity (23 studies, 21%). Eleven studies (10%) reported no model performance statistics. Discrimination was mostly assessed with area under the curve (AUC/Harrell’s C statistics). AUC ranged between 0.61 (100) and 0.97 (120) though notably the latter was at risk of model overfit, with a sample size of \( n = 100 \) and an EPV ratio of 3.1. The

![Fig. 2. Range and frequency of different predictors used in current algorithms. ALT, Alanine Aminotransferase; ApoA/ApoB, Apolipoprotein A/B Levels; Atyp Antipsych, Prescribed Antipsychotic Medication; BP Meds, Prescribed Antihypertensive Medication; Chol:HDLC, Cholesterol:HDLC Ratio; Chron Dis, Personal History of Chronic Disease; CVD Event, Personal History of Cardiovascular Disease; DBP, Diastolic Blood Pressure; ECG, Electrocardiogram Findings; eGFR, Glomerular Filtration Rate; ETOH, Alcohol Use; FHx CVD, Family History Cardiovascular Disease; FHx T2DM, Family History of Type 2 Diabetes Mellitus; FPG, Fasting Plasma Glucose; Genetic, Genotype Data; Gest DM, Gestational Diabetes Mellitus; HbA1C, Glycated Haemoglobin; HDL, High-Density Lipoprotein; HR, Heart Rate; HTN, Diagnosis of Hypertension; IFG, Impaired Fasting Glucose; LDL, Low-Density Lipoprotein; Phys Act, Physical Activity; RA, Rheumatoid Arthritis; Renal Dis, Renal Disorders; SMI, Diagnosis of Serious Mental Illness; SysBP, Systolic Blood Pressure; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; Tot Chol, Total Cholesterol; Tri, Triglycerides; WC, Waist Circumference; WCC, White Cell Count; WHR, Waist:Hip Ratio. *not counted as a predictor in studies that developed sex-specific algorithms. [Colour figure can be viewed at wileyonlinelibrary.com]
Potential applicability of existing cardiometabolic risk algorithms for young people with psychosis. Psychiatric illness and treatment were taken into account in three studies (28–30) predicting risk of CVD (29, 30) or T2DM (28). Two of these studies (QRISK3 and QDiabetes (28, 29)) were conducted on large general population samples, and one (PRIMROSE) was conducted in people with severe mental illness (30). QRISK3 and QDiabetes (28, 29) included diagnosis of severe mental illness as a single predictor, whereas PRIMROSE included separate predictors for bipolar disorder and psychosis (30). QRISK3 and QDiabetes included the presence of any atypical antipsychotic as a predictor (28, 29); PRIMROSE included first- or second-generation antipsychotics as separate predictors, along with antidepressants as another predictor (30). All three studies were conducted on middle-aged adults (mean ages QDiabetes: 42.9 years (28), QRISK3: 44.9 years (29), PRIMROSE: 49.5 years (30)). In PRIMROSE, age was applied as a non-linear term with a log transformation and was weighted heavily in comparison to other risk factors. See Figure S3. In both QRISK3 and QDiabetes, age was applied as a fractional polynomial, also implying a non-linear impact on risk. QRISK3 and QDiabetes both included a number of interactions between age and other predictors, further amplifying the relative importance of age in the algorithms.

QRISK3, QDiabetes and PRIMROSE were taken forward for the exploratory analysis, on the basis of the following: large samples used in development and validation; strong performance statistics; low risk of bias in three domains; and inclusion of psychiatric predictors/development in a psychiatric sample.

Exploratory analysis

Baseline characteristics. The six-year observed risk of metabolic syndrome at age 24 years in our sample of participants with or at risk of psychosis was 14.21% in females and 11.88% in males. In our sensitivity analysis (all available ALSPAC participants), the six-year observed risk was 7.54% for females and 5.76% for males. In our primary analysis, we included 3030 person-years of observation.

In our sensitivity analysis, we included 19 020 person-years of observation. Characteristics of included participants for both the primary and sensitivity analyses are presented in Table 1 and Table S6 respectively. Associations between algorithm predictors and outcome are reported in Table S7.

Primary analysis – psychosis sample. Discrimination. At age 18 years, Harrell’s C Statistics were as follows: QDiabetes males \( C = 0.75 \) (95% CI, 0.72–0.78) and females \( C = 0.78 \) (95% CI, 0.73–0.84); QRISK3 males \( C = 0.58 \) (95% CI, 0.52–0.65) and females \( C = 0.61 \) (95% CI, 0.55–0.66); and PRIMROSE \( C = 0.73 \) (95% CI, 0.70–0.78). After substituting participant ages to the mean age of the original studies, Harrell’s C Statistics mildly improved for each algorithm. Similarly, at age 18 years, \( R^2 \) statistics were marginally higher in females than males in QDiabetes and QRISK3 and improved mildly after substituting participant ages to the mean age of the original studies. See Table 2.

Calibration. At age 18 years, calibration was poor across all three algorithms, with observed risk estimates consistently higher than predicted risk estimates. After substituting participant ages to the mean age of the original studies, calibration improved markedly in all three algorithms. See Figure 3.

Sensitivity analysis – whole ALSPAC sample. Discrimination. QDiabetes and QRISK3 performed better in the overall sample than the psychosis sample. PRIMROSE performed better in the psychosis sample. Harrell’s C Statistics were as

| Characteristic | Females | Males |
|---------------|---------|-------|
| Number of participants | 323 (63.9) | 182 (36.1) |
| Total person-years of observation | 1938 | 1092 |
| Ethnicity – White/Not-recorded | 315 (67.5) | 176 (86.7) |
| Systolic BP (mmHg), Mean (SD) | 104.88 (8.28) | 118.90 (9.67) |
| HDL (mmol/L), Mean (SD) | 1.29 (0.36) | 1.18 (0.33) |
| FPG (mmol/L), Mean (SD) | 4.98 (0.36) | 5.19 (0.68) |
| Total cholesterol (mmol/L), Mean (SD) | 3.86 (0.68) | 3.55 (0.63) |
| Chol:HDL ratio, ratio SD | 3.04 (0.85) | 3.00 (0.85) |
| BMI (kg/m²), Mean (SD) | 23.75 (3.55) | 23.62 (4.50) |
| Family history cardiometabolic/Cardiovascular disorders | 194 (60.1) | 117 (64.3) |
| Smoking ≥1 cigarette daily | 173 (53.6) | 100 (54.9) |
| Depression | 91 (27.9) | 28 (15.4) |
| Alcohol use | 47 (15.4) | 31 (16.7) |
| Antidepressant medication | 45 (14.7) | 16 (8.6) |
| Antipsychotic medication | 12 (3.7) | 6 (2.1) |
Perry et al.

Table 2. Discrimination statistics for algorithms tested on psychosis risk group at age 18 years and mean age of original study

| Algorithm     | Age 18 years | Mean age original study |
|---------------|--------------|-------------------------|
|               | Male         | Female                  | Male         | Female                  |
| QDiabetes FPG | C = 0.70 (0.65–0.74) | C = 0.78 (0.73–0.84) | C = 0.78 (0.75–0.80) | C = 0.83 (0.80–0.87) |
|               | $R^2$ = 0.13 (0.09–0.19) | $R^2$ = 0.16 (0.10–0.24) | $R^2$ = 0.21 (0.14–0.27) | $R^2$ = 0.25 (0.19–0.31) |
| QRISK3        | C = 0.58 (0.52–0.65) | C = 0.61 (0.56–0.66) | C = 0.63 (0.58–0.69) | C = 0.66 (0.59–0.72) |
|               | $R^2$ = 0.09 (0.05–0.16) | $R^2$ = 0.10 (0.03–0.18) | $R^2$ = 0.11 (0.07–0.16) | $R^2$ = 0.13 (0.05–0.20) |
| PRIMROSE Lipid | 0.73 (0.70–0.78) | 0.75 (0.69–0.79) | 0.75 (0.69–0.79) | 0.80 (0.75–0.83) |
|               | $R^2$ = 0.13 (0.10–0.17) | $R^2$ = 0.16 (0.12–0.22) | $R^2$ = 0.16 (0.12–0.22) | $R^2$ = 0.18 (0.15–0.21) |

Calibration. In a similar pattern to the psychosis sample, at age 18 years, calibration was poor across all three algorithms, with observed risk estimates consistently higher than predicted risk estimates. After substituting participant ages to the mean age of the original studies, calibration improved markedly in all three algorithms. See Table S8.

Discussion

Main findings

We performed a systematic review of cardiometabolic risk prediction algorithms developed either for the general or psychiatric populations and considered their potential suitability for young people with psychosis. We also used data from a sample of relatively young adults to first explore whether existing cardiometabolic risk prediction algorithms may be suitable for young people with or at risk of psychosis and second to explore the impact of the manner in which age is weighted in existing cardiometabolic risk prediction algorithms. We do not present the results of our exploratory analysis as an external validation of the three algorithms, since the algorithms we tested were not developed to predict metabolic syndrome. Rather, we present our findings as a means to explore the likely suitability of these algorithms for a population of individuals who may be at higher cardiometabolic risk compared with the general population. It should be made clear from the outset that the three algorithms we tested, as we show in the results of our systematic review, were developed and validated on large samples and perform well in the populations they were designed for.

Systematic review

We identified a substantial number of cardiometabolic risk prediction algorithms, yet most have not been integrated into clinical practice. Predicted outcomes ranged from prediabetes and T2DM, CVD or transient ischaemic attack and stroke. The five most commonly included predictors across all algorithms were age, smoking, systolic blood pressure, sex and BMI. One included algorithm (PRIMROSE) was developed in a population of people with severe mental illness (30), which predicted risk of CVD. Two (QRISK3 and QDIabetes) were developed in the general population and included psychiatric predictors (28, 29) such as a diagnosis of schizophrenia.

All included algorithms were developed in samples of middle- to older-age adults. One might traditionally consider this proportionate, since cardiometabolic disorders are traditionally considered diseases of advancing age. Yet, cardiometabolic risk still exists in the absence of advancing age; even in the general population, there is an increasing prevalence of early-onset T2DM (140) and childhood obesity (141), likely related to the shift towards a more sedentary lifestyle and unhealthy diet in recent decades. The absence of an algorithm developed for younger populations is an important finding, since early intervention may reduce the risk of young people forming part of a future generation of patients with chronic cardiovascular diseases (142). This finding suggests the need for either new or recalibrated versions of currently existing cardiometabolic risk algorithms tailored to the younger generations.
Primary prevention is the best means with which to address the personal and societal burden attributed to T2DM, CVD and its complications (143).

Whilst this message is important for the general population, it is particularly important for young people with/at risk of psychosis, who are at a
higher risk of precipitant cardiometabolic disorders. This population may be more likely to smoke (144), exercise less (145) and eat a more unhealthy diet (145) than their peers and yet may also be prescribed medication that in itself can adversely and severely impact cardiometabolic indices (146). Further, they may be faced with inappropriate barriers to accessing healthcare (147), diagnostic overshadowing (148) and may have an intrinsic biological propensity for altered cardiometabolic function (149). Meta-analyses featuring mostly antipsychotic-naive young people with first-episode psychosis have consistently reported an increased incidence of insulin resistance, impaired glucose tolerance (9, 10) and dyslipidaemia (9, 150, 151) compared with matched controls from the general population, after adjusting for anthropometric and sociodemographic factors. Each is predeterminants of cardiometabolic disorders such as T2DM and obesity. These factors may not be adequately captured by currently existing algorithms. Additionally, meta-analyses of cross-sectional studies suggest that psychosis is associated with higher levels of circulating inflammatory markers (152–155), and evidence from some longitudinal studies suggests an association between inflammatory markers at baseline and psychosis at follow-up (156–158), although other longitudinal studies have reported negative findings (159). Inflammatory states are also associated with cardiometabolic disorders (160–163). Whilst 15 relatively newer algorithms from our systematic review did include inflammatory predictors, none also included psychiatric predictors.

Each of the three algorithms that did include psychiatric factors featured an antipsychotic-related predictor. Antipsychotic-associated weight gain can occur relatively quickly after initiation (164) and is associated with altered eating behaviours (165) and sedentariness (166). However, whilst there are some efficacy differences between antipsychotics, these are gradual rather than discrete (167). Differences in side-effects are more marked, and each has an inherently different impact upon cardiometabolic risk (168). This may be explained by differing affinities to receptors other than the dopamine-2 (D2) receptor, for example the histamine-1 (H1) receptor, serotonin-2c (5-HT2c) and adrenergic receptors (a2 and b3) (169), which may have a role in the regulation of food intake (170). The varied impact upon cardiometabolic risk by different antipsychotics does not abide by the traditional distinctions of either typical/atypical or first/second generation, which were the binary distinctions of the included algorithms. A more appropriate antipsychotic predictor may instead model antipsychotics based on their relative cardiometabolic risk.

We used the PROBAST tool (14) to examine the risk of bias of included studies in our systematic review. Only two studies were rated as low risk of bias, with all others rated as either unclear or high risk of bias. This may be a reflection of the relatively recent introduction of the ‘Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis’ (TRIPOD) guidelines for prediction model studies (139). Nevertheless, the results suggest that the reported performance statistics and therefore clinical validity of the majority of included studies should be accepted with extreme caution.

The EPV ratio also varied widely between studies. A low EPV ratio can be an indicator of model overfit (17) which can bias results. We identified 20 studies with an EPV ratio of likely <10, and therefore, the performance reported in those studies should be interpreted with caution. Finally, it is striking that whilst many included studies promoted the use of their algorithms in clinical practice, there appears to have been relatively little follow-up to assess either clinical or economic impact. A notable exception was PRIMROSE (30), which was the only algorithm developed and validated on a sample of people with mental illness. A cost-effectiveness analysis (171) found it improved quality of life and reduced healthcare-related costs in comparison with using no algorithm.

A previously published systematic review (172) examining cardiovascular risk prediction algorithms in the general population also identified a very large number of studies. The review similarly concluded the methodological shortcomings of most risk prediction algorithms likely limit their suitability for clinical practice. The previous review differs from our own since we were interested in identifying original or recalibrated algorithms and assessing their suitability for young people with psychosis. Therefore, we did not include studies reporting new validations in a similar population to already validated algorithms. The previous review also presented sex-stratified algorithms as distinct entities, increasing the apparent number of algorithms they reported. For ease of simplicity and in consideration of our overarching research question, we did not take this step. Finally, a large number of new algorithms have been developed since the previous review, which we were able to include in our own.

Exploratory analysis

We considered three algorithms for exploratory analysis: QRISK3, QDiabetes and PRIMROSE.
These were selected due to the large sample sizes in model development and validation, model performance statistics, relatively low risk of bias and the inclusion of psychiatric predictors/development in a psychiatric population.

We found that discrimination statistics were relatively good at age 18 years for QDiabetes and PRIMROSE and improved further when substituting to the mean age of original studies. This means that QDiabetes and PRIMROSE were able to predict higher risks in ‘cases’ than ‘non-cases’, even in relatively young adults. This did not apply to QRISK3, particularly in males, where the algorithm was little better than chance at discriminating higher and lower cardiometabolic risk in young adults with or at risk of psychosis.

For all three algorithms, however, the discriminative ability in our sample was attenuated compared with the original published studies (28–30). This may be because our sample included younger participants than the original studies. For example, both QRISK3 and QDiabetes were developed and validated in participants aged 25 and over, and PRIMROSE was developed and validated in participants aged 30 and over. QDiabetes and QDiabetes set a minimum age of 25 when using their online calculators, although PRIMROSE sets a minimum of age 18 years. Additionally, in our primary analysis, we tested a sample of participants with or at risk of psychosis, whereas QDiabetes and QRISK3 were designed for use in the general population. Furthermore, we tested a different outcome compared with the original algorithms. We tested metabolic syndrome since it is an established precursor of both T2DM and CVD (26, 27) and is a more suitable outcome for younger populations. The improvement in discrimination statistics after substituting age provides some face validity to our chosen outcome.

However, discriminative ability is only half the story, since discrimination statistics cannot assess the accuracy of the amount of risk apportioned by a model; this represents a test of absolute risk estimates and is examined with a measure of calibration. Our calibration plots at 18 years showed that observed risk was systematically greater than predicted risk in all models, suggesting a notable underprediction of risk in younger participants. Calibration plots improved markedly in all algorithms when we artificially substituted age to the mean age of the original studies. This suggests that the manner with which age is modelled in current algorithms is a major limiting factor in applying them to younger populations. This is likely because many cardiometabolic risk factors are cumulative over time (173); thus, age becomes increasingly important with regard to cardiometabolic risk as one gets older. This notion is elegantly painted by all three algorithms, which modelled age as either a non-linear function, included interactions between age and other predictors, or both.

Strengths and limitations

Strengths of this systematic review include following PRISMA reporting guidelines (13), as would be expected for a high-quality review. Alongside the review, we were able to complement our findings with an exploratory analysis using data from a large birth cohort of young adults. We were able to test three validated cardiometabolic risk prediction algorithms which are commonly used in clinical medicine in the UK, on a different population who are in clear and crucial need of a suitable tool.

Limitations of the study first and foremost relate to the exploratory analysis. The three algorithms we tested were not designed for use in young adults, though this in itself should not be a barrier to explore potential suitability in a different population. Nevertheless, our results should not be seen to cast doubt on the predictive ability of such algorithms when applied to the populations intended by the authors. We were unable to include every predictor from the algorithms we tested, which may have impacted upon performance statistics. That said, the impact of this limitation on our results may not have been uniform for each predictor we could not include. For example, even if we had the data, it is unlikely that many participants in our relatively young cohort would have diagnosed CVD or chronic kidney disease, a history of gestational diabetes or be prescribed statins. Also, our measured outcome differed from the outcome of the algorithms we tested. Whilst three algorithms included in the systematic review did aim to predict risk of metabolic syndrome, we did not consider them for our exploratory analysis since they did not include psychiatric predictors, were at relatively high risk of bias, and study authors did not publish their fully specified algorithm equations. Nevertheless, metabolic syndrome is a precursor of T2DM (26) and CVD (27), and the relatively good performance of the algorithm when we artificially substituted age to the mean age of the original study suggests face validity to our chosen outcome. Our sample size was relatively small compared with the original studies. However, by testing a more encompassing outcome, we were able to include a greater number of cases and reduce the impact of model overfit.

Other limitations relate to the systematic review. We were unable to follow a meta-analytic approach to the synthesis of results due to study...
heterogeneity. The lack of meta-analytic approach meant we were unable to examine the risk of publication bias, which may have played a part in the configuration of studies we included in our synthesis, since only three included studies were not published in peer-reviewed journals.

In conclusion, young people who are at higher risk than the general population of developing psychosis are also at higher risk of developing cardiometabolic disorders. A suitable cardiometabolic risk prediction algorithm for this population would be highly beneficial to general and psychiatric practitioners to help them to tailor treatment plans with the aim of reducing long-term physical and psychiatric morbidity. Existing cardiometabolic risk algorithms cannot be recommended for this purpose since they likely underestimate the cardiometabolic risk of all young people, let alone a group already at significantly higher risk than the general population. Existing algorithms require recalibration to suit younger populations, and, better still, a new cardiometabolic risk prediction algorithm is required which is specifically developed for young people with psychosis. A well-designed algorithm may include a more appropriate distinction of metabolically active antipsychotics; should more appropriately weight the predictors for the specific characteristics of young people with psychosis; and may include a more age-appropriate outcome, such as metabolic syndrome. Further, particular attention should be paid to patient acceptability, to ensure the algorithm is actually used in clinical practice rather than simply buried in a research database. In lieu of a suitable algorithm, simple lifestyle interventions such as smoking cessation, encouraging a healthy diet and increasing physical activity must be offered to all young people with or at risk of psychosis. Indeed, encouraging results are emerging from studies of primary prevention in this population (174, 175), who may not have yet developed chronic and pervasive lifestyle behaviours which are associated with chronic illness.

Acknowledgements

This report is independent research supported by the National Institute for Health Research (NIHR Doctoral Research Fellowship, Dr Benjamin Ian Perry, DRF-2018-11-ST2-018). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care. GMK acknowledges funding support from the Welcome Trust (Intermediate Clinical Fellowship; grant code: 201486/Z/16/2); the BMA Foundation (J Moulton Grant 2019); the MQ: Transforming Mental Health (grant code: MQDS17/40 [with PBJ]); the Medical Research Council (grant code: MC_PC_17213) and the Medical Research Council (grant code: MR/S037675/1 [with RU]). PBJ receives grant support from the NIHR Applied Research Collaboration East of England. This publication is the work of the authors who will serve as guarantors for the contents of this paper. The authors report no conflicts of interest.

Conflict of Interest

The authors declare no conflicts of interest.

Peer Review

The peer review history for this article is available at https://publons.com/publon/10.1111/acps.13212.

Data availability statement

Access to anonymized data from ALSPAC is subjected to formal application processes. Please see http://www.bristol.ac.uk/alspac/researchers/ for more information.

References

1. Masood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. Lancet 2014;383:999–1008.
2. Scarborough P, Bhattacharyya P, Wickramasinghe K, Smelina K, Mitchell C, Rayner M eds. Heart Disease Statistics. British Heart Foundation, London; 2010.
3. Simons JC, Ward AJ, Rotella P, Collins J, Wodrich R. An evaluation of variation in published estimates of schizophrenia prevalence from 1990 horizontal line 2013: a systematic literature review. BMC Psychiatry. 2015;12:193.
4. Holt RI, Peveler RC, Byrne CD. Schizophrenia, the metabolic syndrome and diabetes. Diabet Med. 2004;21:515–523.
5. Laursen TM, Plana-Ripoll O, Andersen PK et al. Cause-specific life years lost among persons diagnosed with schizophrenia: Is it getting better or worse? Schizophrenia Res. 2019;206:284–290.
6. Plana-Ripoll O, Pedersen CB, Aggerbo E et al. A comprehensive analysis of mortality-related health metrics associated with mental disorders: a nationwide, register-based cohort study. Lancet 2019;394:1827–1835.
7. Plana-Ripoll O, Weeye N, Mømen NC et al. Changes Over Time in the Differential Mortality Gap in Individuals With Mental Disorders. JAMA Psychiatry 2020.
8. Berry A, Drake RJ, Webb RT, Ashcroft DM, Carr MJ, Yung AR. Investigating the agreement between cardiovascular disease risk calculators among people diagnosed with Schizophrenia. Front Psychiatry 2018;9:685.
9. Perry BI, McIntosh G, Wierich S, Singh S, Rees K. The association between first-episode psychosis and abnormal glycaemic control: systematic review and meta-analysis. Lancet Psychiatry. 2016;3:1049–1058.
10. Pilling NG, Bux K, Gobula C, Donohue JS, Rees K. Impaired glucose homeostasis in first-episode schizophrenia: a systematic review and meta-analysis. JAMA Psychiatry 2017;74:261–269.
11. Perry BI, Upthegrove R, Thompson A, Marwaha S, Zammitt S, Khan Z, Khandaker G. Relationships between dysglycaemia,
immune activation and psychotic experiences: findings from the U.K. ALSPAC Birth Cohort. In preparation.

12. HARDWAY NR, COLLINS AM, COUGHLIN D, KIRK S. The role of google scholar in evidence reviews and its applicability to grey literature searching. PLoS One 2015;10:e0138237.

13. MOHER D, LIBRATY A, TETTALF J, ALTMAN DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine 2009;6:e1000097.

14. WOLFF RF, MOONS KGM, RIDLEY RD et al. PROBAST: a tool to assess the risk of bias and applicability of prediction model studies. Ann Intern Med. 2019;170:51–58.

15. ALBA AC, AGORITAS T, WALSH M et al. Discrimination and calibration of clinical prediction models: Users’ guides to the medical literature. JAMA 2017;318:1377–1384.

16. PEDUZI P, CONCATO J, KEMPER E, HOLFORD TR, FEINSTEIN AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49:1373–1379.

17. PAYLOR M, AMBLER G, SEAMAN SR et al. How to develop a more accurate risk prediction model when there are few events. BMJ 2015;351:h3868.

18. GUNDUMU EO, ALTMAN DG, COLLINS GS. Adequate sample size for developing prediction models is not simply related to events per variable. J Clin Epidemiol. 2016;76:175–182.

19. RODGERS M, SOWDEN A, PETTICREW M et al. Testing methodological guidance on the conduct of narrative synthesis in systematic reviews: effectiveness of interventions to promote smoke alarm ownership and function. Evaluation 2009;15:47–61.

20. BOND A, GOLDING J, MACLEOD J et al. Cohort Profile: The ‘Children of the 90s’–the index offspring of the Avon Longitudinal Study of Parents and Children. Int J Epidemiol 2013;42:111–127.

21. FRASER A, MACDONALD-WALLIS C, TILLING K et al. Cohort profile: the avon longitudinal study of parents and children: ALSPAC mothers cohort. Int J Epidemiol 2013;42:97–110.

22. NORTHSTONE K, LEWCOCK M, GROOM A et al. The Avon Longitudinal Study of Parents and Children (ALSPAC): an update on the enrolled sample of index children in 2019. Wellcome Open Res. 2019;4:51.

23. HARRIS PA, TAYLOR R, MINOR BL et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.

24. HARRIS PA, TAYLOR R, THELIER R, PAYNE J, GONZALEZ N, CONDE JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–381.

25. ALBERT KG, ECKER RH, GRUNDY SM et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity, Circulation 2009;120:1640–1645.

26. SUN JA, LEE JH, LIM SY et al. Metabolic syndrome as a predictor of type 2 diabetes, and its clinical interpretations and usefulness. J Diabetes Invest 2013;4:334–343.

27. WILSON PW, D’AGOSTINO RB, PARSEH H, SULLIVAN L, MERG JD. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 2005;112:3066–3072.

28. HEPWORTH-COX J, COUPLAND C. Development and validation of QDiabetes-2018 risk prediction algorithm to estimate future risk of type 2 diabetes: cohort study. BMJ 2017;359:j5019.

29. HEPWORTH-COX J, COUPLAND C, BRINDLE P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ 2017;357:j2099.

30. OSBORN DP, HARDISON S, OMAR RZ et al. Cardiovascular risk prediction models for people with severe mental illness: results from the prediction and management of cardiovascular risk in people with severe mental illnesses (PRIMROSE) research program. JAMA Psychiatry. 2015;72:143–151.

31. BUURSEN SV, GROOTHUIS-OUDSHOORN K. MICE: multivariate imputation by chained equations in R. J Stat Softw 2011;45:1–67.

32. R COVEY Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing, 2017.

33. ABDUL-GHANI MA, ABDUL-GHANI T, STERN MP et al. Two-step approach for the prediction of future type 2 diabetes risk. Diabetes Care 2011;34:2108–2112.

34. ADDA D, EDWARDS MK, LORENZI PD. Predictive validity of a medical-related cardiorespiratory fitness algorithm in predicting cardiovascular disease- and all-cause mortality: implications for integration into clinical practice. Mayo Clin Proc. 2016;91:1320–1321.

35. AERPLAKREN W, BUSNAG P, WOODWARD M et al. A risk score for predicting incident diabetes in the Thai population. Diabetes Care 2006;29:1872–1877.

36. ALQPOORI A, ALGHADIR A, AWAD H. The Arab Risk (ARA-BRISK): Translation and Validation. Biomed Res Int 2014;25:271–275.

37. ALSSIMA MA, NEWSON RS, BAKER SJL et al. One risk assessment tool for cardiovascular disease, type 2 diabetes, and chronic kidney disease. Diabetes Care 2012;35:741–748.

38. ALSSIMA MA, VISTSEN D, HEYMANS MW et al. The Evaluation of Screening and Early Detection Strategies for Type 2 Diabetes and Impaired Glucose Tolerance (DETECT-2) update of the Finnish diabetes risk score for prediction of incident type 2 diabetes. Diabetologia 2011;54:1004–1012.

39. ARNETO EG, JACKSON AS, SOX X et al. Longitudinal algorithms to estimate cardiorespiratory fitness: associations with nonfatal cardiovascular disease and disease-specific mortality. J Am Coll Cardiol 2014;63:2289–2296.

40. ARTIGAS-RODENAS LM, CABRERO-HERENCIA JA, DIVISION-GARROTE JA et al. Framingham risk score for prediction of cardiovascular diseases: a population-based study from southern Europe. PLoS One 2013;8:e73529.

41. ASSMANN G, CULLEN P, SCHULTE H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. Circulation 2002;105:310–315.

42. BACKHOFER K, HIRAKAWA Y, TONKIN A et al. Development of an Australian cardiovascular disease mortality risk score using multiple imputation and recalibration from national statistics. BMC Cardiovasc Disord. 2017;17:17.

43. CHEN L, MAGLIANO DJ, BALKAU B et al. AUSTRISK: an Australian Type 2 Diabetes Risk Assessment Tool based on demographic, lifestyle and simple anthropometric measures. Med J Aust. 2010;192:197–202.

44. CHEN L, TONKIN AM, MOOS L et al. Recalibration and validation of the SCORE risk chart in the Australian population: the AusSCORE chart. Eur J Cardiovasc Prev Rehabil 2009;16:562–570.
Perry et al.

45. CHEN X, WU Z, CHEN Y et al. Risk score model of type 2 diabetes prediction for rural Chinese adults: the Rural Deqing Cohort Study. J Endocrinol Invest 2017;40:1115–1123.

46. CHEN K, CAI T, Hsu H et al. A prediction model for type 2 diabetes risk among Chinese people. Diabetologia 2009;52:443–450.

47. D’AGOSTINO RB, GRIFFIN S, SULLIVAN LM, WILSON P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001;286:180–187.

48. D’AGOSTINO RB, VASAS RS, PENCINA MJ et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743–753.

49. de BAQUEL D, de BAKKER G. Predictive ability of the SCORE Belgium risk chart for cardiovascular mortality. Int J Cardiol 2010;143:385–390.

50. DUGGE O, JANCHY O, JOSHI LAMT P et al. Adapting existing diabetes risk scores for an Asian population: a risk score for detecting undiagnosed diabetes in the Mongolian population. BMC Public Health 2015;15:938.

51. GABRIEL R, BROTONS C, TORMO MJ et al. The ERICE-score: the new native cardiovascular score for the low-risk and aged Mediterranean population of Spain. Rev Esp Cardiol (Engl Ed) 2015;68:205–215.

52. GAO WG, DONG YH, PANG ZC et al. A simple Chinese risk score for undiagnosed diabetes. Diabet Med 2010;27:274–281.

53. GAO WG, Qiao Q, PITKANENI J et al. Risk prediction models for the development of diabetes in Mauritian Indians. Diabet Med 2009;26:1966–1992.

54. GUMER C, CARSTENSSEN B, SANDBAEK A et al. A Danish diabetes risk score for targeted screening: the Inter99 study. Diabetes Care 2004;27:727–733.

55. GRIFFIN SJ, LITTLE PS, HALES CN, KINMONTH AL, WAREHAM NJ. Diabetes risk score: towards earlier detection of type 2 diabetes in general practice. Diabetes Metab Rev 2000;16:164–171.

56. HEIANZA Y, ARASE Y, SATO K et al. Development of a screening score for undiagnosed diabetes and its application in estimating absolute risk of future type 2 diabetes in Japan: Toranomon Hospital Health Management Center Study 10 (TOPICS 10). J Clin Endocrinol Metab. 2013;98:1051–1060.

57. HERKES KE, EDDY DM, ARONDEKAR B, SCHLESSINGER L. Diabetes Risk Calculator: a simple tool for detecting undiagnosed diabetes and pre-diabetes. Diabetes Care 2008;31:1040–1045.

58. HIPPISLEY-COX J, COULPEL C, BRENDLE P. Derivation and validation of QStroke score for predicting risk of ischaemic stroke in primary care and comparison with other risk scores: a prospective open cohort study. BMJ 2013;346:f2573.

59. HIPPISLEY-COX J, COULPEL C, ROBINSON J, BRENDLE P. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. BMJ 2010;341:c6624.

60. HIPPISLEY-COX J, COULPEL C, ROBINSON J, SHIRES A, BRENDLE P. Predicting risk of type 2 diabetes in England and Wales: prospective derivation and validation of QDScore. BMJ 2009;338:b880.

61. HIPPISLEY-COX J, COULPEL C, VINOGRADOVA Y, ROBINSON J, MAY M, BRENDLE P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. BMJ 2007;335:136.

62. HIPPISLEY-COX J, COULPEL C, VINOGRADOVA Y et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ 2008;336:1475–1482.

63. HA KH, LEE YH, SONG SO et al. Development and validation of the Korean QRISK risk score: a 10-year national cohort study. Diabetes Metab J 2018;42:402–414.

64. KATUERANDA P, HILL NR, STRATTON I, SHERIFF R, DE SILVA SDN, MATTHEWS DR. Development and validation of a Diabetes Risk Score for screening undiagnosed diabetes in Sri Lanka (SLDRISK). BMC Endocr Disord. 2016;16:42.

65. KO G, SO W, TONG P et al. A simple risk score to identify Southern Chinese at high risk for diabetes. Diabet Med. 2010;27:644–649.

66. LINDESTRÖM J, TUOMILEHTO J. The diabetes risk score: a practical tool to predict type 2 diabetes risk. Diabetes Care 2003;26:725–731.

67. MÜHLEBRÜCK K, LUDWIG T, JEFFESEN C et al. Update of the German Diabetes Risk Score and external validation in the German MONICA/KORA study. Diabetes Res Clin Pract 2014;104:459–466.

68. MÜHLEBRÜCK K, PAPROTT R, JOOST HG, BOEHM H, HEIDEMANN C, SCHULZE MB. Derivation and external validation of a clinical version of the German Diabetes Risk Score (GDRS) including measures of HbA1c. BMJ Open Diabetes Res Care. 2018;6:e000524.

69. NÄNNI A, NAKAGAWA T, KUWHARA K et al. Development of risk score for predicting 3-year incidence of type 2 diabetes: japan epidemiology collaboration on occupational health study. PLoS One 2015;10:e0142779.

70. PANAGIOTAKOS DB, GREGOUREPPOULOU EN, FITZGERALD AP, PETSAVOS C, STEFANADIS C. Validation of the Helsinki SCORE (a Calibration of the ESC SCORE Project) regarding 10-year risk of fatal cardiovascular disease in Greece. Hellenic J Cardiol 2015;56:302–328.

71. RIDKER PM, PAYNTER NP, RIFAI N, GAZIANO JM, COOK NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. Circulation 2008;118:2243–2251.

72. ROBINSON CA, AGARWAL G, NERENBERG K. Validating the CANRISK prognostic model for assessing diabetes risk in Canada’s multi-ethnic population. Chronic Dis Can 2011;32:19–31.

73. ROSELLA LC, MANUEL DG, BURCHILL C, STUKEL TA. A population-based risk algorithm for the development of diabetes: development and validation of the Diabetes Population Risk Tool (DiPoRT). J Epidemiol Community Health 2011;65:613–620.

74. SARAFIZADEGAN N, HASSENEJAD R, MARATEB HR et al. PARS risk charts: A 10-year study of risk assessment for cardiovascular diseases in Eastern Mediterranean Region. PLoS One 2017;12:e0189389.

75. SCHULZE MB, HOFMANN K, BOEHM H et al. An accurate risk score based on anthropometric, dietary, and lifestyle factors to predict the development of type 2 diabetes. Diabetes Care 2007;30:510–515.

76. SELMER R, ISLAND J, ARIANSEN I et al. NORRISK 2: A Norwegian risk model for acute cerebral stroke and myocardial infarction. Eur J Prev Cardiol 2017;24:773–782.

77. SUN F, TAO Q, ZHANG A. An accurate risk score for estimating 5-year risk of type 2 diabetes based on a health screening population in Taiwan. Diabetes Res Clin Pract. 2009;85:228–234.

78. TABARI BP, ENGELGAU MM, HERMAN WH. A multivariate logistic regression equation to screen for dysglycaemia: development and validation. Diabet Med. 2005;22:599–605.

79. WEN J, HAO J, LIANG Y et al. A non-invasive risk score for predicting incident diabetes among rural Chinese people:
A village-based cohort study. PLoS One 2017;12: e0186172.  

80. Wickramasinghe CD, Ayers CR, Das S, de Lemos JA, Willis BL, Breslow MJ. Prediction of 30-year risk for cardiovascular mortality by fitness and risk factor levels: the Cooper Center Longitudinal Study. Circ Cardiovasc Qual Outcomes 2014;7:597–602.  

81. Wong CK, Siu SC, Wan EY et al. Simple non-laboratory- and laboratory-based risk assessment algorithms and nomogram for detecting undiagnosed diabetes mellitus. J Diabetes. 2016;8:414–421.  

82. Yatsuya H, Ito Y, Yamagishi K et al. Development of a point-based prediction model for the incidence of total stroke: Japanese public health center study. Stroke 2013;44:1295–1302.  

83. Anderson JP, Parkh JR, Shenfeld DK et al. Reverse engineering and evaluation of prediction models for progression to type 2 diabetes: an application of machine learning using electronic health records. J Diabetes Sci Technol 2015;10:6–18.  

84. Aboel-Wahab EW, Shatat HZ, Chai F. Adapting a prediction rule for metabolic syndrome risk assessment suitable for developing countries. J Prim Care Community Health. 2019;2019:215013729882760.  

85. Alaa AM, Bolton T, di Angelantonio E, Reud JHF, van der Schouw YT. Cardiovascular disease risk prediction using automated machine learning: A prospective study of 423,604 UK Biobank participants. PLoS One 2019;14: e0213653.  

86. Arima H, Yoshimoto K, Ooi Y et al. Development and validation of a cardiovascular risk prediction model for Japanese: the Hisayama study. Hypertens Res 2009;32:1119–1122.  

87. Aslibekyan S, Campos H, Loucks EB et al. Development of a cardiovascular risk score for use in low-and middle-income countries. J Nutr. 2011;141:1375–1380.  

88. Balkar B, Hu G, Qiao Q et al. Prediction of the risk of cardiovascular mortality using a score that includes glucose as a risk factor. The DECODE Study. Diabetologia 2004;47:2118–2128.  

89. Barazzoni R, Gortan Cappellari G, Semolic Aet al. Central adiposity markers, plasma lipid profile and cardiometabolic risk prediction in overweight-obese individuals. Clin Nutr. 2019;38:1171–1179.  

90. Bell K, Hayen A, McGeechan K, Neal B, Irwig L. Effects of additional blood pressure and lipid measurements on the prediction of cardiovascular risk. Eur J Prev Cardiol 2012;19:1474–1485.  

91. Bolano B, de Meylder R, Goderis G et al. Cardiovascular prevention in general practice: development and validation of an algorithm. Acta Cardiol 2004;59:598–605.  

92. Boucher H. Exploring the Utility of MUAC in Classifying Adult Metabolic Syndrome Using NHANES 2015–2016. William Honors College: Honors Research Projects, University of Akron; 2019.  

93. Brand RJ, Rosenman RH, Sholutz RI, Friedman M. Multivariate prediction of coronary heart disease in the western collaborative group study compared to the findings of the Framingham study. Circulation 1976;53:348–355.  

94. Brautbar A, Ballantyne CM, Lawson K et al. Impact of adding a single allele in the 9p21 locus to traditional risk factors on reclassification of coronary heart disease risk and implications for lipid-modifying therapy in the Atherosclerosis Risk in Communities study. Circ Cardiovasc Genet 2009;2:279–285.  

95. Chambless LE, Folsom AR, Sharrett AR et al. Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) study. J Clin Epidemiol 2003;56:880–890.  

96. Chen KL, Hsu HC, Su TC et al. Constructing a point-based prediction model for the risk of coronary artery disease in a Chinese community: a report from a cohort study in Taiwan. Int J Cardiol. 2012;157:263–268.  

97. Choe EK, Rhee H, Lee S et al. Metabolic syndrome prediction using machine learning models with genetic and clinical information from a nonobese healthy population. Genomics Inform. 2018;16:e31.  

98. Cross DS, McCarthy CA, Htupovelos E et al. Coronary risk assessment among intermediate risk patients using a clinical and biomarker based algorithm developed and validated in two population cohorts. Curr Med Res Opin 2012;28:1819–1830.  

99. Davies RW, Dandona S, Stewart AF et al. Improved prediction of cardiovascular disease based on a panel of single nucleotide polymorphisms identified through genome-wide association studies. Circ Cardiovasc Genet 2010;3:468–474.  

100. Demopoulos AC, Nikolaidou M, Caballero FF et al. Machine learning methodologies versus cardiovascular risk scores, in predicting disease risk. BMC Med Res Methodol 2018;12:179.  

101. Dunder K, Lind L, Zethelius B, Berglund L, Lithell H. Evaluation of a scoring scheme, including proinsulin and the apolipoprotein B/apolipoprotein AI ratio, for the risk of acute coronary events in middle-aged men: Uppsala Longitudinal Study of Adult Men (ULSAM). Am Heart J. 2004;148:596–601.  

102. Ferrario M, Chiodoni P, Chambless LE et al. Prediction of coronary events in a low incidence population. Assessing accuracy of the CUORE Cohort Study prediction equation. Int J Epidemiol 2005;34:413–421.  

103. Fiedland DR, Cembrer C, Tarima S. Audiometric pattern as a predictor of cardiovascular status: development of a model for assessment of risk. Laryngoscope. 2009;119:473–486.  

104. Gaziano TA, Young CR, Fitzmaurice G, Atwood S, Gaziano JM. Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. Lancet 2008;371:923–931.  

105. Gupta P, Prieto-Merino D, Alay VS. Cardiovascular risk prediction in India: comparison of the original and recalibrated Framingham prognostic models in Urban populations. [Version 1; peer review : 2 approved with reservations]. Wellcome Open Research 2019:4:1–14.  

106. Hamer M, Chida Y, Stamatakis E. Utility of C-reactive protein for cardiovascular risk stratification across three age groups in subjects without existing cardiovascular diseases. Am J Cardiol 2009;104:538–542.  

107. Hassain R, Mahmud SMH, Hossen MA. Predicting risk factor of obesity among middle-aged people using data mining techniques. Procedia Computer Sci 2018;132:1068–1076.  

108. Insuile M, Abraham G, Nelson CP et al. Genomic risk prediction of coronary artery disease in 480,000 adults: implications for primary prevention. J Am Coll Cardiol 2018;10:1883–1893.  

109. Kang HM, Kim DJ. Metabolic syndrome versus Framingham risk score for association of self-reported coronary
heart disease: The 2005 Korean Health and Nutrition Examination Survey. Diabetes Metab J 2012;36:237–244.

111. Knuiman MW, Vu HT, Bartholomew HC. Multivariate risk estimation for coronary heart disease: the Busselton Health Study. Aust N Z J Public Health 1998;22:747–753.

112. L’Italien G, Ford I, Norrie J et al. The cardiovascular event reduction tool (CERT)–a simplified cardiac risk prediction model developed from the West of Scotland Coronary Prevention Study (WOSCOPS). Am J Cardiol. 2000;85:720–724.

113. Launer D, Chau NP, Cazelles B, Segond P. Estimation of CHD risk in a French working population using a modified Framingham model. The PCV-METRA Group. J Clin Epidemiol 1994;47:1353–1364.

114. Lees JS, Welsh CE, Celis-Morales CA et al. Glomerular filtration rate by differing measures, albuminuria and prediction of cardiovascular disease, mortality and end-stage kidney disease. Nat Med 2019;25:1753–1760.

115. Liao X, Kerr D, Morales J, Duncan I. Application of machine learning to identify clustering of cardiometabolic risk factors in U.S. adults. Diabetes Technology Ther 2019;21:2535–2543.

116. Menotti A, Lanti M, Agarita-Rosell E et al. New tools for prediction of cardiovascular disease risk derived from Italian population studies. Nutr Metab Cardiovasc Dis 2005;2005:426–440.

117. Merry AH, Boer JM, Schouten LJ et al. Risk prediction of incident coronary heart disease in The Netherlands: re-estimation and improvement of the SCORE risk function. Eur J Prev Cardiol 2012;19:840–848.

118. Mohammedreza B, Farzad H, Davoud K, Fereidoun Prosaff AF. Prognostic significance of the complex "Vascular Adiposity Index" vs. simple anthropometric measures: Tehran lipid and glucose study. Cardiovascular Diabetol 2012;11:20.

119. Nooh H, Maruyama K, Iso H et al. Prediction of myocardial infarction using coronary risk scores among Japanese male workers: 3M Study. J Atheroscler Thromb 2010;17:452–459.

120. Park Y, Lim J, Lee J, Kim SG. Erythrocyte fatty acid profiles can predict acute non-fatal myocardial infarction. Br J Nutr 2009;102:1355–1361.

121. Paynter NP, Chasan-Taber L, Burke JD, Shipman D, Cook NR, Ridker PM. Cardiovascular disease risk prediction with and without knowledge of genetic variation at chromosome 9p21.3. Ann Intern Med 2009;150:65–72.

122. Paynter NP, Mazer NA, Pradhan AD, Gaziano JM, Ridker PM, Cook NR. Cardiovascular risk prediction in diabetic men and women using hemoglobin A1c vs diabetes as a high-risk equivalent. Arch Intern Med 2011;171:1712–1718.

123. Pencina MJ, D’Agostino RB, Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the Framingham heart study. Circulation 2009;119:3078–3084.

124. Pocock SJ, McCormack V, Gueyffier F, Boutitie F, Fagard RH, Bossel JP. A score for predicting risk of death from cardiovascular disease in adults with raised blood pressure, based on individual patient data from randomised controlled trials. BMJ 2001;323:75–81.

125. Pylypchuk R, Wels S, Kerr A et al. Cardiovascular disease risk prediction equations in 400 000 primary care patients in New Zealand: a derivation and validation study. Lancet 2018;05:1897–1907.

126. Rana JS, Cote M, Despres JP et al. Inflammatory biomarkers and the prediction of coronary events among people at intermediate risk: the EPIC-Norfolk prospective population study. Heart 2009;95:1682–1687.

127. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA 2007;297:611–619.

128. Ayala Solares JR, Canoy D, Raymond FED et al. Long-term exposure to elevated systolic blood pressure in predicting incident cardiovascular disease: evidence from large-scale routine electronic health records. J Am Heart Assoc 2019;08:e012129.

129. Steren MP, Williams K, Gonzalez-Villafando C, Hunt KJ, Haefner SM. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? Diabetes Care 2004;27:2676–2681.

130. Tanabe N, Iso H, Okada K et al. Serum total and non-high-density lipoprotein cholesterol and the risk prediction of cardiovascular events – the JALS-ECC -. Circ J 2010;74:1346–1356.

131. Tohid F, Hadaeghi F, Harati H, Azizi F. C-reactive protein in risk prediction of cardiovascular outcomes: Tehran Lipid and Glucose Study. Int J Cardiol 2009;132:369–374.

132. Voss R, Cullen P, Schultz H, Assmann G. Prediction of risk of coronary events in middle-aged men in the Prospective Cardiovascular Münster Study (PROCAM) using neural networks. Int J Epidemiol 2002;31:1253–1262; discussion 62–64.

133. GROUP WCRCW. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. Lancet Glob Health 2019;7:e1332–e1345.

134. Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). Heart 2007;93:172–176.

135. Wu Y, Liu X, Li X et al. Estimation of 10-year risk of fatal and nonfatal ischemic cardiovascular diseases in Chinese adults. Circulation 2006;114:2217–25.

136. Zhang XF, Atta J, D’Este C, Yu XH, Wu XG. A risk score predicted coronary heart disease and stroke in a Chinese cohort. J Clin Epidemiol 2005;58:951–958.

137. Zou X, Qiao Q, Jr L et al. Nonlaboratory-based risk assessment algorithm for undiagnosed type 2 diabetes developed on a nation-wide diabetes survey. Diabetes Care 2013;36:3944–3952.

138. Moons KG, Bots ML, Salonen JT et al. Prediction of stroke in the general population in Europe (EUROTROSE): Is there a role for fibrinogen and electrocardiography? J Epidemiol Community Health. 2002;56 (Suppl 1):S0–S16.

139. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ 2015;350:g7594.

140. Wilmot E, Ikram I. Early onset type 2 diabetes: risk factors, clinical impact and management. Ther Adv Chronic Dis 2014;5:234–244.

141. Skinner AC, Perrin EM, Skefton JA, Prevalence of obesity and severe obesity in US children, 1999–2014. Obesity (Silver Spring) 2016;24:1116–1123.

142. Chryssant SG. A new paradigm in the treatment of the cardiovascular disease continuum: focus on prevention. Hippokratia 2011;15:7–11.
Cardiometabolic Risk Prediction in Early Psychosis

162. Hermesdorff HH, Zuleit MA, Puchau B, Martinez JA. Central adiposity rather than total adiposity measurements are specifically involved in the inflammatory status from healthy young adults. Inflammation 2011; 34:161–170.

163. Calabro P, Yin ET. Intra-abdominal adiposity, inflammation, and cardiovascular risk: new insight into global cardiometabolic risk. Curr Hypertens Rep 2008; 10:32–38.

164. Spertus J, Horvitz-Lennon M, Aring H, Normand S-L. Risk of weight gain for specific antipsychotic drugs: a meta-analysis. NPJ Schizophr 2018; 4:12.

165. Sertissi O, Viala A, Bourdel MC et al. Impact of antipsychotic treatments on the motivation to eat: preliminary results in 153 schizophrenic patients. Int Clin Psychopharmacol 2009; 24:257–264.

166. Vancampfort D, Firth J, Schuch FB et al. Sedentary behavior and physical activity levels in people with schizophrenia, bipolar disorder and major depressive disorder: a global systematic review and meta-analysis. World Psychiatry 2017; 16:308–315.

167. Heim M, Nikolakopoulou A, Schneider-Thoma J et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet 2019; 394:939–951.

168. Vancampfort D, Stubbs B, Mitchell AJ et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry. 2015; 14:339–347.

169. Starrenburg FC, Bouwers JP. How can antipsychotics cause Diabetes Mellitus? Insights based on receptor-binding profiles, humoral factors and transporter proteins. Eur Psychiatry. 2009; 24:164–170.

170. Krohze WK, Huf蛋en SJ, Popadak BA et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacology 2003; 28:519–526.

171. Zamor E, Oshorn D, Nazareth I et al. Effectiveness and cost-effectiveness of a cardiovascular risk prediction algorithm for people with severe mental illness (PRIME-ROSE). BMJ Open. 2017; 7:e018181.

172. Damen PB et al. The effectiveness of the Keeping the Body in Mind Xtend pilot lifestyle program on dietary intake in first-episode psychosis: Two-year outcomes. Obes Res Clin Pract. 2019; 13:214–216.

173. Curtis J, Watkins A, Rosenbaum S et al. Evaluating an individualized lifestyle and life skills intervention to prevent antipsychotic-induced weight gain in first-episode psychosis. Early Interv Psychiatry. 2016; 10:267–276.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow-diagram of included participants at risk of psychosis at age 18 or 24 years.
Perry et al.

**Figure S2.** Flow-diagram of included participants in sensitivity analysis of all participants at age 18 years.

**Figure S3.** Relative weighting of age vs other predictors in PRIMROSE(6).

**Figure S4.** Calibration plots of algorithms tested in ALSPAC at age 18 years and at mean age of original study (whole sample).

**Table S1.** Predictors included in QDiabetes, QRISK3 and PRIMROSE.

**Table S2.** Risk of bias assessment using PROBAST.

**Table S3.** Participant characteristics of studies included in systematic review.

**Table S4.** Algorithm characteristics of studies included in systematic review.

**Table S5.** Algorithm performance of studies included in systematic review.

**Table S6.** Characteristics of ALSPAC participants included in exploratory analysis (whole sample).

**Table S7.** Odds ratio and 95% CI for the association between predictors included in algorithms measured at 18 years and metabolic syndrome at 24 years in the ALSPAC Cohort.

**Table S8.** Discrimination statistics for algorithms tested on whole sample at age 18 years and mean age of original study.