**Effectiveness and cost-effectiveness of a cardiovascular risk prediction algorithm for people with severe mental illness (PRIMROSE).**

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Authors’ contributions: see Acknowledgements

Conflict of interest disclosures: None to disclose

Word Count: 4,620

**ABSTRACT**

**Objectives:** To determine the cost-effectiveness of two bespoke severe mental illness (SMI)-specific risk algorithms compared to standard risk algorithms for primary cardiovascular disease (CVD) prevention in those with SMI.

**Setting:** Primary care setting in the United Kingdom (UK). The analysis was from the National Health Service (NHS) perspective.

**Participants:** 1000 individuals with SMI from The Health Improvement Network Database, aged 30-74 years and without existing CVD populated the model.

**Interventions:** Four cardiovascular risk algorithms were assessed; (1) general population lipid, (2) general population BMI, (3) SMI-specific lipid and (4) SMI-specific BMI, compared against no algorithm. At baseline, each cardiovascular risk algorithm was applied and those considered high-risk (>10%) were assumed to be prescribed statin therapy whilst others received usual care.

**Primary and secondary outcome measures:** Quality adjusted life years (QALYs) and costs were accrued for each algorithm including no algorithm, and cost-effectiveness was calculated using the net monetary benefit (NMB) approach. Deterministic and probabilistic sensitivity analyses were performed to test assumptions made and uncertainty around parameter estimates.

**Results:** The SMI-specific BMI algorithm had the highest NMB resulting in 15 additional QALYs and a cost saving of approximately £53,000 per 1,000 patients with SMI over 10 years, followed by the general population lipid algorithm (13 additional QALYs and a cost saving of £46,000).

**Conclusions:** The general population lipid and SMI-specific BMI algorithms performed equally well. The ease and acceptability of use of an SMI-specific BMI algorithm (blood tests not required), makes it an attractive algorithm to implement in clinical settings.

**ARTICLE SUMMARY**

**Strengths and limitations of this study:**

* Health economic modelling employs mathematical modelling to extrapolate outcomes including both effects and costs beyond trial data, allowing the long-term effectiveness and cost-effectiveness of an intervention to be determined.
* To our knowledge, this is the first economic analysis to determine the effectiveness and cost-effectiveness of using CVD risk algorithms in SMI patients in primary care and subsequent treatment with statin therapy.
* A patient level simulation model using real patient primary care data was developed, allowing the accumulating history of each individual to predict their transitions, costs and health outcomes.
* Deterministic and probabilistic sensitivity analyses was undertaken to account for variability in data inputs.
* The most widely used CVD risk algorithm in general practice in England was not used due to lack of availability of coefficients for the algorithm.

1. **BACKGROUND**

People with Severe Mental Illness (SMI), defined as schizophrenia, bipolar disorder and other non-organic psychotic conditions, have an increased risk of cardiovascular disease (CVD) compared to the general population1,2. This is due to an increased prevalence of modifiable cardiovascular risk factors3,4,5, that some antipsychotic drugs may cause weight gain and abnormalities of lipid and glucose metabolism6,7, and that cardiovascular risk factors may be under-treated in people with SMI2. Up to 88% of people with schizophrenia have untreated dyslipidaemia and up to 66% have untreated hypertension3.

Cardiovascular risk algorithms are widely used in clinical practice to guide primary prevention CVD strategies8, in particular the initiation of lipid-modifying medication (statins). Guidelines for the initiation of statin therapy in clinical practice is country-specific, with ten year CVD risk thresholds of 7.5% being recommended in the USA9, 10% in Europe10 and 10% recently recommended by the National Institute for Health and Care Excellence (NICE) in the UK11. A number of CVD risk algorithms exist12,13,14, including QRISK2 which is endorsed by NICE for use in primary care in the UK. The current Quality Outcomes Framework (QOF) incentivises annual monitoring and assessment of CVD risk using QRISK2 in primary care15. It also incentivises annual monitoring of blood pressure, alcohol and smoking status for patients with SMI15. Previously, QOF indicators also included measurements of total to high density lipoprotein (HDL)-cholesterol ratio, glucose levels and weight in those with SMI16. Despite the presence of QOF indicators, monitoring of CVD risk remains low17,18. In addition, QRISK2 may incorrectly estimate CVD risk in some high risk populations19. As a result, population specific algorithms have been developed20,21,22. In 2015, an SMI-specific CVD risk algorithm, *PRIMROSE*, was developed and validated23 using data from primary care attendees in the UK. In addition to variables common to other CVD risk algorithms, it includes: psychiatric diagnosis, antipsychotic medication, harmful use of alcohol, use of antidepressants, and social deprivation. The PRIMROSE algorithm is available as both a lipid model (including measures of total cholesterol and HDL-cholesterol), and a body mass index (BMI) model (where lipid measures are replaced with measures of BMI). Both PRIMROSE models have been shown to perform better than the general population based Framingham algorithm at predicting new CVD events23. However, the effectiveness and cost-effectiveness of these models in clinical practice is unknown.

The aim of this study is to evaluate the 10 year costs and consequences of an SMI-specific risk algorithm (PRIMROSE) compared to using general population CVD risk algorithms, in the risk management and primary prevention of CVD in those with SMI. Our analysis was from a UK primary care population perspective using English health care costs.

1. **METHODOLOGY**

**2.1 Study design**

We developed a patient level simulation to hypothetically model the progress of people with SMI over 10 years, accumulating the history of each individual to predict their transitions, costs and health outcomes. Real primary care data were used to capture the heterogeneity of the primary care SMI population. The model was created in Microsoft Excel 2010 in line with methodological recommendations for evaluations of new health care technologies and interventions24,25.

**2.2 Population**

A cohort of 38,824 people with SMI was identified in The Health Improvement Network (THIN)26, an anonymised longitudinal primary care database. THIN includes electronic medical records for more than 11 million individuals, registered with over 500 general practices in the UK. Available patient information includes demographics, local area deprivation (Townsend quintile), diagnoses, prescriptions, referrals, hospitalisations, laboratory tests, immunisations and clinical measures (e.g. blood pressure, cholesterol). The demographics, prevalence of major conditions and mortality rates in THIN are similar to the UK general population27. Rates and demographics of people with SMI are also comparable to epidemiological estimates seen in previous studies of SMI28. Due to missing data, multiple imputation was used to generate 10 imputed data sets29 which were used to calculate transition probabilities of primary CVD events and all-cause mortality (see section 2.5). Individuals in the extracted cohort had a recorded diagnosis of schizophrenia or schizoaffective disorder, bipolar disorder, other long term psychotic illness (non-organic psychoses) and/or were listed on the SMI register28; were within the age limits of CVD risk assessment tools (30 to 74 years); and were free of CVD at their last point of contact (n = 33,206)23, where CVD was defined as a recorded diagnosis of coronary heart disease (CHD) including myocardial infarction (MI), angina, and major coronary surgery and revascularization, or cerebrovascular disease (CVA) including haemorrhagic stroke, ischaemic stroke and transient ischaemic attack (TIA).

Due to computational complexities of our economic model, the patient level simulation used a sample of 1,000 patients randomly selected from one of the imputed datasets using the random number generator in Microsoft Excel. Data from patients’ last known appointments (complete and imputed) were used as their baseline data in the model.

**2.3 CVD risk assessment tools**

We calculated a CVD risk score for each of the 1,000 patients using four different CVD risk algorithms in four separate analyses. The risk algorithms assessed are:

(1) a general population lipid algorithm,

(2) a general population BMI algorithm,

(3) an SMI-specific lipid algorithm and

(4) an SMI-specific BMI algorithm.

Algorithms (1) and (2) are based on an adaptation of the widely used Cox Framingham algorithm14, herein referred to as the general algorithm, which was created and validated using THIN data. Algorithms (3) and (4) are derived from UK SMI patients in THIN, aged 30 to 90 years (PRIMROSE)23 (eTable 1). Performance of these algorithms has been previously tested23. Results demonstrated both SMI-specific algorithms (PRIMROSE) had higher, and therefore better, discrimination and calibration statistics than the general population algorithms. Calibration plots indicated both SMI-specific algorithms predicted CVD risk more accurately than the general population algorithms.

A fifth analysis using no CVD risk algorithm was included to estimate the costs and consequences of no intervention.

**2.4 Model Structure**

The patient level economic model includes: (i) a decision tree to identify those at risk of CVD over 10 years and eligible for statin therapy (Figure 1a); and (ii) a Markov state transition model of 10 one-year cycles where patients can remain healthy, have a primary CVD event, have a secondary CVD event or die (Figure 1b and section 2.5).

At baseline all patients in the economic model enter the decision tree and one of the four CVD risk algorithms described above is applied to calculate their 10-year CVD risk score. Those scoring over the CVD risk threshold (e.g. 10%) are considered at high risk and receive statin therapy. Individuals classified as low risk are assumed not to receive statin therapy and remain in “usual care”. Patients already on statin therapy before baseline remain on statins, regardless of their risk characteristics. However, if a patient is already on statin therapy and their cholesterol levels for their last GP consultation are above target levels (defined as total cholesterol > 5 mmol/L or total cholesterol to HDL-cholesterol ratio > 4mmol/L)30,31, their statin therapy is altered according to the average weighted changes that occur in statin prescribing as calculated from the THIN database. We applied the CVD threshold of 10% recently recommended by NICE to each of the models to reflect future clinical practice11. The 20% threshold as per current Quality and Outcomes Framework (QOF) guidelines15 was also applied (see Supplementary Appendix). In the no algorithm scenario patients do not enter the decision tree.

After patients are classified as high risk and receive statin therapy, or low risk and receive usual care, all patients enter the economic model in a ‘healthy’, free of CVD, state and continue to cycle through the economic model for 10 one-year cycles or until they die. Patient level survival models32 are used for each annual cycle to determine if a patient (i) remains in their current health state, (ii) has a primary non-fatal CVD event, (iii) has a secondary non-fatal CVD event, (iv) has a fatal CVD event, or (v) dies from non-CVD related causes. All events occur at the beginning of a cycle.

This was repeated for each of the CVD risk algorithms in separate analyses.

**2.5 Transition probabilities**

In the model, events were assumed to have occurred when the patient specific probability of an event was more than a random number generated in Excel. For example, if a patient’s probability of a primary CVD event in a cycle was 16.3% and the random number (taking possible values between zero and one) generated was 0.155 (15.5%), the patient was assumed to have had a primary CVD event. If, however, the random number generated was 0.45 (45.0%), the event did not occur. Events for patients were carried over cycles so that only patients that had a primary CVD event could have a secondary CVD event.

The probability of having a primary CVD event each year after baseline was calculated from the 10 imputed datasets of the SMI cohort using a survival model (Weibull distribution to allow calculation of time-dependent hazard functions)32. Separate models were estimated for CHD and CVA. Development of these models was based on 38,824 people in THIN with SMI and aged over 18 years, with a maximum follow-up of 16 years. The covariates used included age, sex, systolic blood pressure (SBP), use of anti-hypertensive therapy, HDL-cholesterol, use of cholesterol lowering/altering therapy, height, weight, presence of diabetes, smoking status, history of heavy drinking, type of SMI, use of first generation anti-psychotic therapy, use of second generation antipsychotic therapy, and history of depression or use of anti-depressant therapy. The coefficient for each covariate was calculated from the 10 imputed datasets for each model and is reported in eTable 2.

Primary CVD included both non-fatal and fatal events. A non-fatal CVD event comprised CHD and its sub-states, and CVA and its sub-states. The sub-states of a primary CHD event included stable angina, unstable angina, MI, coronary artery surgery and unclassified CHD; whilst a primary CVA event included TIA, haemorrhagic stroke, ischaemic/unclassified stroke and unspecified cerebrovascular disease. Non-fatal primary events were separated into sub-states of CHD and CVA so that costs and consequences could be allocated to each sub-state. The proportion of patients in each non-fatal CVD sub-state and the proportion of patients dying from a primary CVD event was equal to the proportion of patients in each group of these diagnostic categories found in the original cohort of people with SMI used to develop and test the risk algorithms in THIN (eTable 3).

The probability of having a secondary CVD event was calculated from the model in the Reduction of Atherothrombosis for Continued Health (REACH) Registry33. The REACH algorithmis not SMI-specific; however, it is an international equation to predict recurrent CVD based on patient level characteristics over 20 months from a primary CVD event. Two equations are reported; one for secondary CVD and one for secondary fatal CVD. For each of the equations reported, the adjustment for country variable was omitted given that UK in the REACH algorithm is the comparator value and hence a coefficient for the UK is not reported. There was no information in our dataset regarding the number of vascular beds, presence of coronary heart failure (CHF), presence of atrial fibrillation (AF) and cardiovascular treatment with aspirin. For all patients in the model it was assumed that there was only one vascular bed affected, CHF and AF were absent and they were not receiving cardiovascular treatment with aspirin. The 20 month estimate was converted to a 12 month estimate using the formula *p = 1- exp {-rt}* where *p* is the probability*, r* is the rate and *t* is the time period of interest32.

Secondary CVD events comprised non-fatal and fatal events. Non-fatal secondary events were separated into sub-states of MI and stroke for cost and consequences purposes. The proportion of patients in each sub-state was based on percentages of people in each group in the REACH registry’s four year follow-up data34 (eTable 3). As the proportion of patients in each sub-state for fatal secondary events was unknown, we assumed an equal proportional distribution.

The probability of dying from causes other than CVD was calculated using a survival model (Weibull distribution) and the THIN SMI population described in section 2.2 (eTable 2).

**2.6 Effectiveness of CVD risk management strategy**

The benefits of statin therapy were modelled by applying the relative risk reduction of CVD from statin use from a Cochrane review (0.73 and 0.78 for CHD and stroke respectively)35 to the predicted risks of CVD for all patients newly prescribed statins. As prescription of statins at baseline is a variable in the primary CVD event survival models estimated from THIN (eTable 2) the risk of a primary CVD event for patients with a statin prescription at baseline was already modified.

**2.7 Costs**

Costs included in our model were the cost of the CVD risk algorithm, CVD risk management and CVD events (eTable 4). The cost of the risk algorithm comprised of the cost of the time taken for the GP to complete the CVD risk prediction algorithm, which was estimated to be an additional 5 minutes on top of a regular consultation36; as well as the cost of a blood test37 for the lipid algorithms. This was calculated as £20 for CVD risk algorithms requiring a blood test and £19 without. The cost of CVD risk management for those identified as high risk comprised of the cost of statin therapy (£21 per person per year). We assumed 20 mg of atorvastatin was prescribed, as per current Quality Outcomes Framework (QOF) CVD prevention guidelines15. This was applied for the duration of the model, assuming 100% adherence with statin therapy. For patients already on statin therapy but with high cholesterol, a weighted average change in prescription costs was applied. All prescription costs were taken from the British National Formulary (BNF)38.

The costs of fatal and non-fatal CVD events were extracted from an economic evaluation of statins for primary prevention of coronary events39. The cost of CHD surgery was calculated from the weighted mean of reference costs for CHD surgical operations37. The cost of unclassified CHD and unspecified CVA was calculated as the average of all CHD and CVA events respectively given there is no information on the cost of unclassified and unspecified events. All costs were inflated to 2012/2013 values using conversion rates in Curtis, 201336.

**2.8 Outcomes**

The mortality and morbidity impact was evaluated using quality adjusted life years (QALYs) as recommended by NICE in the UK40. QALYs are calculated by multiplying a utility score (preference based value of a health state of an individual) by the amount of time in that health state. A utility score of 1 represents perfect health and 0 death. All patients in the model were assumed to have the utility score of someone whose SMI symptoms are being managed (0.865)41. If a patient had a non-fatal CVD event, a utility decrement was applied (eTable 4). This was applied for the year of the event and every year thereafter, until the end of the model or the patient died. The utility decrements associated with non-fatal CVD events of angina, MI, TIA and stroke were taken from the same economic model as CVD costs mentioned in the section *2.7 Costs*. Where utility decrements were unknown, we assumed the utility decrement associated with coronary heart disease (CHD) surgery was the same as myocardial infarction (MI); the utility decrement associated with unclassified CHD was the weighted average of stable angina, unstable angina and MI; and the utility decrement associated with unspecified cerebrovascular disease (CVA) was the weighted average of stroke and transient ischaemic attack (TIA).

Cost-effectiveness was calculated using the net monetary benefit (NMB) approach32. The NMB is defined as the total discounted QALYs for 1,000 patients over 10 years, multiplied by a given willingness to pay, minus the total discounted cost for 1,000 patients over 10 years, where the willingness to pay is the maximum monetary value a decision maker is willing to pay for a QALY. The scenario with the highest NMB is the preferred option. We tested willingness to pay values of £20,000 and £30,000 per QALY from the results of the probabilistic sensitivity analysis40. Cost-effectiveness acceptability curves (CEACs) were constructed to calculate the probability that each algorithm had the highest NMB for a range of values of willingness to pay for a QALY.

All future benefits (QALYs) and costs were discounted at 3.5% per annum40.

**2.9 Sensitivity analyses**

Deterministic and probabilistic sensitivity analyses were performed to test assumptions made and uncertainty around parameter estimates. Variables in the probabilistic sensitivity analyses, confidence intervals and distributions are reported in eTable 4. For cost inputs, where confidence intervals were not reported, we assumed the standard deviation was equal to the mean, as recommended by Briggs et al.32.

One way sensitivity analyses included a base case deterministic analysis where all input parameters with variability were held at their mean value, and subsequent analyses varying a single input to test the assumptions made (whilst all other input parameters remained at their mean value). We tested the following assumptions using 5,000 iterations for each analysis:

* All costs, treatment costs associated with CVD risk management with statin therapy, intervention costs of using the CVD risk algorithms and cardiovascular event costs were doubled in separate analyses to explore the potential underestimation of costs in our model.
* The utility associated with SMI was reduced to represent relapse (0.479) and SMI with extra pyramidal symptoms (EPS), a drug induced movement disorder with acute and tardive symptoms (0.604) 41 in separate analyses.
* The treatment effect of statin therapy was reduced to the upper odds ratio of the 95% confidence interval (CI) published in the Cochrane review of the effect of statin therapy on CVD in the general population37 to explore potential differences that may be present with effectiveness of statin therapy in an SMI population compared to the general population. These values were 0.8 and 0.89 for CHD and stroke respectively.
* Adherence with statin therapy was reduced to 50% in line with rates of non-adherence with statin therapy42.

The probabilistic sensitivity analysis was conducted in line with Decision Support Unit guidance43 for patient level simulations with 100 inner loops for the patient level simulation and 1,000 outer loops for the probabilistic sensitivity analysis. The model values for each of the 1,000 outer loops were calculated from the mean of each inner loop.

1. **RESULTS**

**3.1 Patient characteristics**

Baseline characteristics of the 1,000 patients and the total eligible cohort are reported in Table 1.

**3.2 Classification of those at high risk**

Table 2 and eTable 5 summarise the proportion of patients classified as ‘high risk’ of CVD by the four algorithms at 10% and 20% thresholds respectively. The SMI-specific BMI algorithm classified the highest number of patients as ‘high risk’ of CVD (326 patients at 10% and 117 at 20%) and resulted in the greatest number of new statin prescriptions (255 patients at 10% and 81 at 20%). The general BMI algorithm classified the lowest number of patients as ‘high risk’ (222 patients at 10% and 65 at 20%) and generated the lowest number of new statin prescriptions (175 patients at 10% and 44 at 20%).

**3.3 Clinical and cost outcomes**

The number of CVD events, cost and QALYs per 1,000 patients with SMI over 10 years for each algorithm (including no algorithm) is reported in Table 3. At the 10% threshold in 1,000 patients over 10 years, a CVD risk algorithm plus statin treatment prevents a minimum of 9 (general BMI algorithm) and maximum of 13 (SMI-specific BMI algorithm) primary CVD events (1 fatal) and 3 to 4 secondary CVD events across all models. This is equivalent to a 4-6% reduction in primary CVD events and a 12-16% reduction in secondary CVD events. The 20% model prevents 3 to 5 primary events (0 to 1 fatal) and 1 to 2 secondary events (eTable 6).

The number of events stratified by risk and statin therapy at baseline is reported in eTable 7.

All four CVD risk algorithms result in more QALYs for less cost compared to when no algorithm and no additional statin therapy is given (Table 3). The SMI-specific BMI algorithm has a higher net monetary benefit (NMB) (£43,797 representing 0.03% of the total NMB) than the general lipid algorithm, and all other algorithms. The SMI-specific BMI algorithm has the highest NMB for 45% of iterations of the probabilistic sensitivity analysis at a willingness to pay value of £20,000 (Figure 2). The results for the 20% threshold are similar (eFigure 1).

Results of sub-analyses and deterministic analyses are reported in the Supplementary Appendix (eResults 1.1 – 1.2).

1. **DISCUSSION**

**4.1 Discussion**

This is the first study to model the long-term effectiveness and cost-effectiveness of a CVD risk algorithm plus risk management strategy in people with SMI. Prescribing statins to patients with SMI in primary care with a CVD risk score over 10% resulted in a 4-6% reduction in primary CVD events and a 12-16% reduction in secondary CVD events over 10 years. The provision of a relatively low cost identification tool (the risk algorithm) and relatively low cost intervention (statins) compared to the high cost of CVD events means that the intervention saves up to £53,000 per 1000 patients over 10 years or £53 per patient administered a CVD risk algorithm. Using a 10% threshold for identifying high risk patients resulted in fewer CVD events than the 20% threshold and hence greater cost savings.

The aim of our economic modelling strategy was to identify if there is any added value in using an SMI-specific risk algorithm, rather than standard general population risk scores, for CVD prevention in people with SMI. The best performing risk assessment tool was the SMI-specific BMI algorithm. This may have been a result of its classification of more individuals at high risk of CVD and eligible for statin therapy than other algorithms. Differences between this algorithm and the general population lipid algorithm were minimal, with the SMI-specific BMI algorithm resulting in an additional 2 QALYs compared to the general lipid algorithm, at an additional cost saving of approximately £6,000 per 1000 individuals over 10 years. Given there is little to no difference between the two tools economically, the decision regarding which algorithm to use in routine clinical practice becomes one of implementation, advocacy and ease of use. One could argue in favour of using a general population derived lipid model as these are already used in UK general practice and hence require no change. On the other hand, the SMI-specific BMI model, although potentially requiring additional training and implementation costs, could confer additional benefit by raising awareness of the need to improve CVD outcomes in people with SMI, and providing a model which requires no blood test to estimate risk, a limitation of other CVD risk algorithms as many people, with and without SMI, decline blood tests44. The ease of implementation and delivery of the SMI-specific BMI model means it could be used in any setting, including mental health care and non-clinical settings without blood results. This is particularly important as many people with SMI do not attend primary care and monitoring of CVD risk factors remains low in other settings45-49. The SMI-specific BMI model provides an opportunity to target more people with SMI, to increase identification of those at high risk of CVD and decrease the physical, social and financial burden associated with CVD.

Whilst current CVD prevention guidelines are based on CVD risk assessment using risk algorithms, there are other ways to target CVD prevention including identification of CVD risk factors for CVD risk management. We are currently evaluating methods of identifying CVD risk factors in those with SMI in primary care settings in England, and decreasing CVD risk via a nurse-led care intervention50.

**4.2 Strengths and limitations**

CVD events in primary prevention populations are rare requiring large sample sizes and long follow-up periods to be able to show statistically significant differences in CVD events between trial arms. Therefore, most primary prevention CVD trials use proxy outcomes, such as lipid levels, to determine effectiveness rather than the prevention of actual CVD events. This can limit the conclusions that can be drawn for economic evaluations of primary CVD prevention interventions using trial data only, given the cost, morbidity and mortality implications of CVD events. Our economic model/analysis has the strength of using real patient level primary care data for patients to model the long term costs and consequences of a CVD primary prevention intervention, making it a better representation of real life. Few economic evaluations using patient level simulations have attempted to use primary care data before and none have been performed within SMI populations, despite their high cardiovascular risk.

There were some weaknesses in our model/analysis. First, we assumed that adherence with statin therapy is the same as that seen in clinical trials. Overall, statins tend to have high rates of non-adherence42 and adherence is likely to be higher in trials51 where a gold standard of clinical care is provided, participants are monitored more closely and those recruited are generally pre-disposed to follow advice about medication. When we tested this in a deterministic analysis, assuming an adherence of 50%, the SMI-specific BMI and general lipid algorithms had the highest NMB at £20,000 per QALY. The effects of statin therapy were also taken from a systematic review and meta-analysis in a general population. This was tested in our deterministic analyses assuming a lower level of effectiveness. We also assumed the benefits of statin therapy were constant over 10 years, which may not be true.

Secondly, we were unable to obtain the coefficients for the algorithm used most widely in general practice in England, QRISK212. Instead we used the Framingham CVD risk prediction algorithm, but re-estimated to the UK general population. We cannot be sure this version is equivalent to QRISK2 in predicting risk although previous analyses showed the re-estimated Framingham performed well in the SMI population23. Further to this, previous studies have reported that it is unlikely that using a different general population CVD risk algorithm will have a significant impact on the results of a cost-effectiveness analysis52.

It was assumed that all people with SMI were in a “stable” mental state free of symptoms, which might not be realistic. This was done for simplicity and because the focus was reduced CVD events and not improved SMI treatment. Our deterministic models demonstrated that reducing the assumed utilities for SMI patients did not have a significant impact on the results.

Thirdly, we were unable to validate the economic model externally as there was no other data source on CVD events in primary care patients with SMI. An internal validation comparing the number of CVD events recorded in the THIN data and the number of CVD events predicted when no algorithm was employed, showed comparable results. Therefore, whilst our model population was considerably smaller than the larger cohort of 38,824 individuals, it was representative of the SMI population in THIN.

1. **CONCLUSIONS**

This is the first economic model/analysis to quantify the costs and consequences of assessing SMI patients in primary care with a CVD risk algorithm and prescribing statins to those classified as high risk. Our model suggests that there is a significant economic benefit associated with the improved management of modifiable CVD risk factors for patients with SMI, using statins. The SMI-specific BMI algorithm functioned better than the other CVD risk algorithms tested. The ease and acceptability of use for patients (due to lack of blood test) and potential to increase awareness of CVD risk in SMI patients, makes it an attractive algorithm to implement in a range of settings. Once implemented, re-evaluation and comparison of the SMI-specific BMI algorithm to current practice using real-life data is necessary, as this has the potential to influence continuity of care for people with SMI at risk of CVD the UK.

**ACKNOWLEDGEMENTS**

**Competing interests:** All authors declare: no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

**Financial support:** This paper summarises independent research supported by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference Number: RP-PG-0609-10156). The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Disclaimer:** The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health.

**DATA SHARING**

No additional data available.

**Author contributions:**

Dr Zomer and Ms Hunter had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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**Table 1:** Baseline characteristics for extracted SMI population who were free of CVD and aged 30-74 years and sample of 1000 patients, where continuous variables are reported as mean (standard deviation) and discrete variables are reported as n (%).

|  |  |  |
| --- | --- | --- |
| **Baseline characteristics** | **Total population** | **Sample of population** |
| n | 33,026 | 1,000 |
| Age, mean (SD), years | 50.3 (12.0) | 50.2 (12.0) |
| Female, No. (%) | 16,155 (48.7) | 513 (51.3) |
| Type of SMI, No. (%) |  |  |
| Schizophrenia | 11,495 (34.8) | 335 (33.5) |
| Bipolar disorder | 8,822 (26.7) | 256 (25.6) |
| Other non-organic psychotic disorders | 9,098 (27.6) | 313 (31.3) |
| On SMI registry but no diagnoses | 3,611 (10.9) | 96 (9.6) |
| SBP, mean (SD), mmHg | 128 (16) | 128 (16) |
| Anti-hypertensive therapy, No. (%) | 5,402 (16.4) | 164 (16.4) |
| Total cholesterol, mean (SD), mmol/L | 5.4 (1.1) | 5.3 (1.0) |
| HDL-cholesterol, mean (SD), mmol/L | 1.3 (0.4) | 1.4 (0.4) |
| Lipid lowering therapy, No. (%) | 3,545 (10.7) | 97 (9.7) |
| Weight, mean (SD), kg | 80.0 (18.9) | 79.5 (18.8) |
| Height, mean (SD), m | 1.7 (0.1) | 1.7 (0.1) |
| BMI, mean (SD), kg/m2 | 28.0 (6.1) | 27.9 (6.0) |
| Diabetes, No. (%) | 2,412 (7.3) | 74 (7.4) |
| Smoking status, No. (%) |  |  |
| Non-smoker | 11,474 (34.7) | 355 (35.5) |
| Ex-smoker | 3,726 (11.3) | 100 (10.0) |
| Current smoker | 17,826 (54.0) | 545 (54.5) |
| History of heavy drinking, No. (%) | 4,706 (14.3) | 139 (13.9) |
| Depression, No. (%) | 21,190 (64.2) | 633 (66.3) |
| Anti-depressant therapy, No. (%) | 13,055 (39.5) | 377 (37.7) |
| First generation antipsychotic therapy, No. (%) | 4,982 (15.1) | 133 (13.3) |
| Second generation antipsychotic therapy, No. (%) | 10,691 (32.4) | 311 (31.1) |
| Townsend score of deprivationa, No. (%) |  |  |
| 1 | 4,886 (14.8) | 143 (14.3) |
| 2 | 5,332 (16.2) | 158 (15.8) |
| 3 | 6,639 (20.1) | 183 (18.3) |
| 4 | 8,048 (24.4) | 269 (26.9) |
| 5 | 8,121 (24.6) | 247 (24.7) |
| Calendar yearb, mean (SD) | 2007.7 (3.5) | 2007.7 (3.5) |

a. Townsend score of deprivation is an index made up of unemployment, overcrowding, non car ownership and non home ownership, where 1 represents lower degree of deprivation and 5 represents higher degree of deprivation, b. Calendar year refers to the calendar year in which the baseline data was collected to account for any time trends.

**Table 2:** Number of people (out of 1000) classified as high and low risk by the various CVD risk algorithms at a CVD risk threshold of 10%; further stratified by use of statin therapy at baseline.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Algorithm** | | | |
| **General lipid algorithm** | **SMI-specific lipid algorithm** | **General BMI algorithm** | **SMI-specific BMI algorithm** |
|
| High risk (>10%) |  |  |  |  |
| Total | 268 | 241 | 222 | 326 |
| Currently prescribed statins | 58 | 59 | 47 | 71 |
| Not currently prescribed statins | 210 | 182 | 175 | 255 |
|  |  |  |  |  |
| Low risk (<10%) |  |  |  |  |
| Total | 732 | 759 | 778 | 674 |
| Currently prescribed statins | 39 | 38 | 50 | 26 |
| Not currently prescribed statins | 693 | 721 | 728 | 648 |

**Table 3:** Costs, QALYs, NMBs and number of events per 1000 individuals for each CVD algorithm (including no algorithm) when a CVD risk threshold of 10% was employed.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcomes** | **Algorithm** | | | | |
| **General lipid algorithm** | **SMI-specific lipid algorithm** | **General BMI algorithm** | **SMI-specific BMI algorithm** | **No algorithm** |
|
| Costs and QALYs, mean (95% CI) |  |  |  |  |  |
| Costs of administering algorithm | 20,006 | 20,006 | 19,010 | 19,010 | n/a |
| (19,906 - 20,106) | (19,906 - 20,106) | (18,935 - 19,085) | (18,935 - 19,085) |  |
| Costs of new statin prescriptions | 38,371  (37,849 - 38,892) | 33,465  (33,012 - 33,919) | 31,611  (31,183 - 32,040) | 47,152  (46,510 - 47,794) | n/a |
| Costs of CVD events | 1,871,508 | 1,882,462 | 1,891,266 | 1,855,697 | 1,985,044 |
| (1,698,400 - 2,044,617) | (1,708,721 - 2,056,202) | (1,717,495 - 2,065,038) | (1,683,643 - 2,027,751) | (1,807,487 - 2,162,602) |
| Total costs undiscounted | 1,929,885 | 1,935,933 | 1,941,887 | 1,921,859 | 1,985,044 |
| (1,756,824 - 2,102,946) | (1,762,235 - 2,109,631) | (1,768,154 - 2,115,621) | (1,749,857 - 2,093,861) | (1,807,487 - 2,162,602) |
| Total costs discounted | 1,666,228 | 1,671,497 | 1,676,569 | 1,659,340 | 1,712,136 |
| (1,515,958 - 1,816,499) | (1,520,650 - 1,822,345) | (1,525,676 - 1,827,462) | (1,509,988 - 1,808,692) | (1,557,767 - 1,866,506) |
| QALYs discounted | 6,828 (6,813 - 6,843) | 6,827 (6,812 - 6,842) | 6,826 (6,811 - 6,841) | 6,830 (6,815 - 6,845) | 6,815 (6,800 - 6,831) |
| Cost compared to no algorithm | -45,908 | -40,639 | -35,567 | -52,797 |  |
| QALYs compared to no algorithm | 13 | 12 | 11 | 15 |  |

**Table 3:** Costs, QALYs, NMBs and number of events per 1000 individuals for each CVD algorithm (including no algorithm) when a CVD risk threshold of 10% was employed (continued).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcomes** | **Algorithm** | | | | |
| **General lipid algorithm** | **SMI-specific lipid algorithm** | **General BMI algorithm** | **SMI-specific BMI algorithm** | **No algorithm** |
|
| Net monetary benefit,  mean (95% CI) |  |  |  |  |  |
| £20,000 WTP threshold | 134,898,309 | 134,872,660 | 134,841,184 | 134,942,106 | 134,593,353 |
| (134,467,161 - 135,329,457) | (134,439,483 - 135,305,838) | (134,407,261 - 135,275,106) | (134,513,538 - 135,370,673) | (134,147,224 - 135,039,482) |
| £30,000 WTP threshold | 203,180,577  (202,601,927 - 203,759,228) | 203,144,739  (202,563,347 - 203,682,603) | 203,100,060  (202,517,517 - 203,682,603) | 203,242,828  (202,667,604 - 203,818,053) | 202,746,098  (202,146,931 - 203,345,265) |
|  |  |  |  |  |
| Events,  mean (95% CI) |  |  |  |  |  |
| Primary non-fatal CHD | 81.87 (75.70 - 88.05) | 82.53 (76.33 - 88.74) | 82.98 (76.76 - 89.21) | 81.25 (75.14 - 87.37) | 87.57 (81.12 - 94.02) |
| Primary fatal CHD | 9.26 (8.56 - 9.95) | 9.33 (8.63 - 10.03) | 9.38 (8.68 - 10.09) | 9.18 (8.49 - 9.87) | 9.89 (9.16 - 10.62) |
| Primary non-fatal stroke | 104.18 (94.50 - 113.86) | 104.64 (94.93 - 114.35) | 104.92 (95.21 - 114.63) | 103.43 (93.80 - 113.06) | 108.77 (98.91 - 118.63) |
| Primary fatal stroke | 7.25 (6.56 - 7.93) | 7.27 (6.58 - 7.95) | 7.30 (6.62 - 7.99) | 7.18 (6.50 - 7.85) | 7.55 (6.86 - 8.24) |
| Secondary non-fatal CVD | 14.77 (13.73 - 15.81) | 14.97 (13.92 - 16.03) | 15.15 (14.09 - 16.21) | 14.48 (13.46 - 15.50) | 17.20 (16.03 - 18.38) |
| Secondary fatal CVD | 6.53 (6.10 - 6.96) | 6.64 (6.20 - 7.07) | 6.65 (6.22 - 7.09) | 6.41 (5.99 - 6.83) | 7.78 (7.28 - 8.27) |
| Death from other causes | 119.43 (118.63 - 120.24) | 119.40 (118.59 - 120.21) | 119.35 (118.55 - 120.16) | 119.40 (118.59 - 120.20) | 119.05 (118.25 - 119.85) |

QALYs are the quality adjusted life years, NMB is the net monetary benefit, WTP is the willingness to pay, and discounted costs and QALYs reflect time-preference for current benefits over future ones.