Primary care management of cardiovascular risk for people with severe mental illnesses: the Primrose research programme including cluster RCT

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Scientific summary

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Scientific summary

Background

People with severe mental illnesses (SMI), including schizophrenia, bipolar disorder and psychosis, die up to 20 years earlier than the general population from cardiovascular disease (CVD). They have increased risk factors including abnormal lipids, diabetes mellitus, smoking and obesity. They are less likely to be screened for risk factors or receive interventions for reducing CVD risk. We do not know the most effective ways to reduce this excess morbidity and mortality.

This programme of research aimed to develop and test better methods to predict and reduce excess CVD in people with SMI. We developed and validated new CVD risk scores for predicting incident CVD in SMI and assessed their economic impact if used to decide who should receive a statin prescription.

We also developed and tested the clinical and cost-effectiveness of a new intervention in primary care to lower levels of cholesterol and reduce CVD risk in SMI, and assessed if the intervention was delivered as intended.

The programme was developed and delivered collaboratively with patient and public involvement throughout including the research design, intervention development and delivery and interpretation of results with a Lived Experience Advisory Panel (LEAP).

Objectives

Work package 1

1. To develop and validate a CVD risk prediction score for people with SMI.
2. To determine its cost-effectiveness compared with standard risk scores used for the general population.

Work package 2

1. To identify barriers to, and facilitators of, CVD risk prevention in SMI from the health professional, patient and carer perspective through focus groups.
2. To evaluate evidence regarding CVD reduction in SMI by updating systematic reviews.
3. To investigate UK statin prescribing and effectiveness among people with SMI.
4. To develop an intervention in which primary care nurses/health-care assistants lower levels of cholesterol and reduce cardiovascular risk in SMI.

Work package 3

1. To determine the clinical effectiveness of the intervention in a cluster randomised controlled trial (RCT) in general practice.
2. To determine the cost and cost-effectiveness of the intervention compared with treatment as usual (TAU).
3. To assess fidelity to intervention delivery.
Work package 1: development and validation of a cardiovascular disease risk model

A predictive CVD risk assessment tool was developed and validated for people with SMI using data from The Health Improvement Network (THIN) UK primary care database on 38,824 people with SMI over a 15-year period. The work was peer reviewed and published in 2015 [Osborn DP, Hardoon S, Omar RZ, Holt RI, King M, Larsen J, 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;72:143–51].

Two new risk score models were built, one with serum lipids and another with body mass index (BMI) and no blood results. The new models used existing risk factors included in CVD risk scores and additional SMI-specific variables, such as diagnosis and psychotropic medications. Performance of the Primrose lipid and BMI CVD risk score models were compared in terms of predicting new-onset CVD, using discrimination statistics and calibration plots. They were then compared with published models from the USA and also with models we derived from the UK general population. Finally, these different SMI and general population models were compared in a cost-effectiveness modelling exercise, to see which performed better when used to determine who should receive statins in terms of net monetary benefit and quality-adjusted life-years (QALYs).

The results showed that the new Primrose SMI-specific CVD models performed better in terms of predicting future CVD in people with SMI. Compared with published US CVD prediction models (Cox Framingham models), D and c-statistics were higher for the Primrose lipid and BMI models for men and women. The SMI-specific models were also superior in performance than CVD models derived from a UK general population in primary care.

The health economics modelling showed that the Primrose BMI models had the highest cost savings, compared with general population-derived CVD risk score models if they were used to guide prescribing of statins at a high risk score threshold (> 10% 10-year CVD risk). The Primrose BMI model gave 15 extra QALYs and a saving of £53,000. The corresponding figures for the next best algorithm, a general population-derived lipid model, were 13 QALYs and £46,000 saved. This work was peer reviewed and published in 2017 [Zomer E, Osborn D, Nazareth I, Blackburn R, Burton A, Hardon S, et al. Effectiveness and cost-effectiveness of a cardiovascular risk prediction algorithm for people with severe mental illness (PRIMROSE). BMJ Open 2017;7:e018181].

Work package 2: developing the intervention

Focus groups and an update of a systematic review were used to inform the design of the Primrose intervention and training programme. The focus group study was peer reviewed and published in 2015 (Burton A, Osborn D, Atkins L, Michie S, Gray B, Stevenson F, Gilbert H, Walters K. Lowering Cardiovascular disease risk for people with severe mental illnesses in primary care: a focus group study. PLOS ONE 2015;10:e0136603).

Focus groups

A total of 14 focus groups with 75 participants identified barriers to and enablers of health professionals in primary care to deliver CVD risk-lowering interventions to people with SMI. Carers, community mental health staff, general practitioners (GPs), practice nurses and patients in primary care or community mental health settings were recruited. They were asked about the training, resources and systems required to lower CVD risk in SMI, while access to services, motivation and capability to lower CVD risk were explored with people with SMI. Discussions were audio-recorded. A framework analysis approach was used to identify themes for the design and delivery of the intervention and training.
Six themes were identified that needed to be addressed to manage CVD risk in people with SMI: (1) a shift to focusing on physical health rather than mental health problems in consultations, (2) the view among some professionals that smoking and weight interventions are not effective for people with SMI, (3) lack of confidence of nurses working with people with SMI, (4) consideration of the negative side effects of psychiatric medications, (5) patient motivation to improve physical health and (6) lack of patient engagement with CVD prevention and primary care services.

Five themes to increase the success of an intervention to manage CVD risk in SMI were identified: (1) practical suggestions for increasing attendance and service engagement, (2) involving significant others (family, friends or support workers), (3) seeing the same person at every appointment to ensure continuity, (4) providing healthy lifestyle advice and (5) working on realistic goals.

**Systematic review**

We updated existing systematic reviews regarding evidence on pharmacological and behavioural interventions to lower CVD risk in people with SMI.

A search for published systematic reviews and RCTs on interventions to manage levels of cholesterol, diabetes mellitus, hypertension, weight, smoking and alcohol was conducted in The Cochrane Library, the Cochrane schizophrenia and Cochrane depression, anxiety and neurosis group registers. A total of 15 relevant systematic reviews and 28 additional RCTs were identified from 11,028 references.

Pharmacological and behavioural approaches were effective for managing smoking and weight in SMI. There was limited evidence on reducing alcohol use and no evidence on management of cholesterol levels, diabetes mellitus, hypertension or multiple CVD risk factors.

**Intervention development**

The focus group findings were used in the training programme and manualised as strategies to improve patient engagement and motivation. Findings from the systematic review were used to train health professionals about effective interventions for weight loss and stopping smoking in people with SMI, and to direct them to use treatments that are effective in the general population for levels of cholesterol, blood pressure, hypertension, diabetes mellitus and alcohol misuse.

The intervention was developed collaboratively with a lived experience advisory panel and a lived experience advisor co-delivered the training. The final intervention involved 2 days of training, and 8–12 appointments with a nurse/health-care assistant (HCA) incorporating a hierarchical approach to effectively managing CVD risk factors including behavioural theory techniques.

**Investigating patterns of statin prescribing**

Differences in the prescription of statins were investigated for people with SMI in primary care using data from 25,246 people with SMI and 125,825 people without SMI between 2005–15 in the UK THIN database. Results from Poisson regression demonstrated that statin initiation was significantly more frequent in 30- to 59-year-olds with SMI than in those without SMI; however, rates were similar between 60- to 74-year-olds and significantly lower for those aged ≥ 75 years with schizophrenia [incident rate ratio (IRR) 0.69, 95% confidence interval (CI) 0.60 to 0.81]. The majority of the study data pre-dated a policy change recommending prescription of statins above the 10% CVD risk threshold, so we do not know what has happened to statin prescriptions in SMI since that change.

**Estimating the effectiveness of statins**

The evidence on the effectiveness of statins for the primary prevention of CVD in SMI was systematically reviewed. No studies assessing CVD events or associated mortality as outcomes were found. This gap was addressed with a study assessing the effectiveness of statins in 16,854 people with SMI in the THIN primary care database. It was found that when statins are prescribed to people with SMI they experience, a significant reduction in the level of total cholesterol for up to 2 years (of 1.2 mmol/l; p < 0.001). The rate
of combined myocardial infarction and stroke (IRR 0.89, 95% CI 0.68 to 1.15) and all-cause mortality (IRR 0.89, 95% CI 0.78 to 1.02) was reduced, but this was not statistically significant. The findings suggest that statin adherence is sufficient for the effective modification of lipids in people with SMI in UK primary care. Both statin studies were peer reviewed and published in 2017 (Blackburn R, Osborn D, Walters K, Nazareth I, Petersen I. Statin prescribing for prevention of cardiovascular disease amongst people with severe mental illness: Cohort study in UK primary care. *Schizophren Res* 2018;192:219–225; and Blackburn R, Osborn D, Walters K, Falcaro M, Nazareth I, Petersen I. Statin prescribing for people with severe mental illnesses: a staggered cohort study of ‘real-world’ impacts. *BMJ Open* 2017;77:e013154).

**Work package 3: cluster randomised controlled trial**

We delivered a cluster randomised, clinical effectiveness and cost-effectiveness trial, comparing a practitioner-led intervention (Primrose) with TAU in 76 general practices across England. Intervention arm nurses/HCAs were trained to work with 30- to 75-year-olds with SMI, who had raised levels of cholesterol and one or more other CVD risk factors, including diabetes mellitus, raised blood pressure, obesity and smoking. The intervention involved nurses/HCAs setting a goal with each patient to target behaviours that reduce levels of cholesterol and other CVD risk factors (e.g. adhering to statins, improving diet, increasing physical activity, stopping or reducing smoking or reducing alcohol intake). Nurses/HCAs were trained to use eight behaviour change techniques (BCTs) across 8–12 appointments over a 6-month period to help patients achieve their goal. BCTs included goal-setting, involving supportive others, action planning, recording and reviewing progress, positive feedback, forming habits and coping with setbacks. British Heart Foundation leaflets were given to the patient at their first appointment. The intervention was compared against routine GP practice with British Heart Foundation leaflets.

**Clinical effectiveness**

The main analysis assessed the primary outcome of total cholesterol level at 12 months, with data available for 137 out of 155 people with SMI in the intervention arm and 152 out of 172 people with SMI in the TAU arm. All practices remained in the study at the end. The number with data available exceeded the original sample size calculation. There were no differences in levels of total cholesterol between the two arms at 12 months (5.4 mmol/l Primrose vs. 5.5 mmol/l TAU; coefficient 0.03, 95% CI −0.22 to 0.29), even after controlling for baseline cholesterol level, number of appointments attended in the Primrose intervention or predictors of missing data on the primary outcome. There were also no significant differences in secondary outcomes including weight, CVD risk scores, blood pressure, body mass index, diet, exercise, well-being and medication adherence.

A total of 46% of patients in the Primrose intervention arm attended six or more appointments and 23% attended between two and five appointments. A total of 21% of people did not attend any appointments. Satisfaction with health care was high in both arms of the trial over the 12 months, and mean cholesterol levels decreased in both arms (−0.22 mmol/l Primrose vs. −0.39 mmol/l TAU).

There was no difference in the primary outcome measure over and above TAU. This may reflect better than standard general practice care in the TAU arm, where patients were screened for CVD risk and received feedback; as well as the difficulty of changing biomedical outcomes in an intervention targeting multiple risk factors in a heterogeneous sample of people with SMI.

**Cost-effectiveness**

The economic evaluation assessed whether or not the Primrose intervention was cost-effective compared with TAU from a health-care cost perspective, over 12 months.
The total health-care cost for the Primrose intervention group was £1286, with a total cost of £2182 for TAU (mean difference –£895, 95% CI –£1631 to –£160; p = 0.012). These lower health costs were mostly a result of fewer inpatient mental health costs (£157 in the Primrose intervention vs. £956 in TAU; –£799, 95% CI –£1480 to –£117; p = 0.018). There was no difference in QALYs (Primrose 0.769, 95% CI 0.751 to 0.787; TAU 0.780, 95% CI 0.764 to 0.796).

**Fidelity assessment**
The extent to which the intervention was delivered to protocol was examined through an assessment of a random 20% sample of transcribed audio-recordings of intervention appointments. The aims were to assess whether or not (1) the intervention was delivered as intended, (2) a clinically appropriate behaviour goal was set, (3) any intervention components were delivered more than others and (4) fidelity differed between nurses and HCAs.

A total of 67.7% of the intervention components were delivered, suggesting moderate adherence to the manual and training. None of the sample set a goal addressing statin adherence or initiation. Nurses had significantly higher fidelity (79.5%) than HCAs (64.3%) [t(20) = 2.23; p = 0.037].

**Overall conclusions**
- The SMI-specific risk scores are more effective for determining CVD risk and prescribing statins than general population risk scores.
- Statins are effective in people with SMI with effects on levels of total cholesterol that may translate into a reduction in CVD events.
- A manualised nurse-led intervention with 8–12 appointments in primary care to reduce levels of cholesterol showed no superiority in terms of level of total cholesterol or secondary outcomes over TAU.
- The intervention was attended by participants, and fewer inpatient psychiatric admissions were seen in the intervention arm.
- Manualised behavioural techniques can be delivered by HCAs/nurses following 2 days of training.
- Many health promotion activities occurred in both trial arms but there was limited evidence of statin initiation or monitoring.

**Implications for practice**
- General population risk scores can underestimate CVD risk in SMI and a model that does not require lipid blood results is most beneficial for deciding when to prescribe statins and prevent CVD in SMI.
- Statins are effective for lipid modification in UK people with SMI.
- The intervention was not superior for level of total cholesterol, nor for any of the secondary outcomes; however, we demonstrated that primary care nurses and HCAs can deliver CVD risk-reducing interventions to people with SMI despite some initial hesitance. Furthermore, the intervention was well attended with reduced costs in the intervention arm, and fewer inpatient admissions.

**Recommendations for research**
- The Primrose risk scores should be validated externally in a separate data set.
- The Primrose risk scores should be updated and compared with newer risk scores.
- Database studies should assess national statin prescribing to people with SMI over time, especially older age groups who were undertreated in UK practice, and to assess the impact of policy change to prescribe above 10% CVD risk for people with SMI. Statin initiation was infrequent in both arms of the RCT and this needs further exploration.
Future study designs may require larger sample sizes to determine the impact of statins on mortality and excess CVD in people with SMI. Discussions around statins and prescribing did not emerge either as a barrier or as a facilitator for reducing CVD risk in people with SMI in our focus group work. This requires further research to establish why it did not happen, despite the intervention programme training nurses/HCAs to explore statin prescription and adherence, and the potential concerns that patients with SMI might have around taking statins.

Naturalistic observations in real-life settings should examine organisational, behavioural and pharmacological CVD risk-reducing interventions and their impact on outcomes for people with SMI.

The potential effect of increased contact with a primary care health professional on hospital admissions warrants further investigation.

Further analysis of the RCT fidelity work should explore the content and communication aspects of the intervention appointments to help shed light on the lack of difference in results between intervention and control groups.

Future work could explore whether or not conversations about statins are happening between professionals and patients, and the reasons why statins might not be initiated for those who would benefit. This work could also explore why there may have been a focus on diet, physical activity and smoking within the consultations.

Research into future interventions could include mechanisms to ensure that evidence-based CVD risk reduction strategies are being offered and explained to people with SMI, including reviewing risk scores and explaining the role of statins.

**Trial registration**

This trial is registered as ISRCTN13762819.

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