Clinical and cost-effectiveness of an intervention for reducing cholesterol and cardiovascular risk for people with severe mental illness in English primary care: a cluster randomised controlled trial

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Summary

Background People with severe mental illnesses, including psychosis, have an increased risk of cardiovascular disease. We aimed to evaluate the effects of a primary care intervention on decreasing total cholesterol concentrations and cardiovascular disease risk in people with severe mental illnesses.

Methods We did this cluster randomised trial in general practices across England, with general practices as the cluster unit. We randomly assigned general practices (1:1) with 40 or more patients with severe mental illnesses using a computer-generated random sequence with a block size of four. Researchers were masked to allocation, but patients and general practice staff were not. We included participants aged 30–75 years with severe mental illnesses (schizophrenia, bipolar disorder, or psychosis), who had raised cholesterol concentrations (5·0 mmol/L) or a total:HDL cholesterol ratio of 4·0 mmol/L or more and one or more modifiable cardiovascular disease risk factors. Eligible participants were recruited within each practice before randomisation. The Primrose intervention consisted of appointments (≤12) with a trained primary care professional involving manualised interventions for cardiovascular disease prevention (ie, adhering to statins, improving diet or physical activity levels, reducing alcohol, or quitting smoking). Treatment as usual involved feedback of screening results only. The primary outcome was total cholesterol at 12 months and the primary economic analysis outcome was health-care costs. We used intention-to-treat analysis. The trial is registered with Current Controlled Trials, number ISRCTN13762819.

Findings Between Dec 10, 2013, and Sept 30, 2015, we recruited general practices and between May 9, 2014, and Feb 10, 2016, we recruited participants and randomly assigned 76 general practices with 327 participants to the Primrose intervention (n=38 with 155 patients) or treatment as usual (n=38 with 172 patients). Total cholesterol concentration data were available at 12 months for 137 (88%) participants in the Primrose intervention group and 152 (88%) participants in the treatment-as-usual group. The mean total cholesterol concentration did not differ at 12 months between the two groups (5·4 mmol/L [SD 1·1] for Primrose *vs* 5·5 mmol/L [1·1] for treatment as usual; mean difference estimate 0·03, 95% CI –0·22 to 0·29; p=0·788). This result was unchanged by pre-agreed supportive analyses. Mean cholesterol decreased over 12 months (–0·22 mmol/L [1·1] for Primrose *vs* –0·36 mmol/L [1·1] for treatment as usual). Total health-care costs (£1286 [SE 178] in the Primrose intervention group *vs* £2182 [328] in the treatment-as-usual group; mean difference –£895, 95% CI –1631 to –160; p=0·012) and psychiatric inpatient costs (£157 [135] *vs* £956 [313]; –£799, –1480 to –117; p=0·018) were lower in the Primrose intervention group than the treatment-as-usual group. Six serious adverse events of hospital admission and one death occurred in the Primrose group (n=7) and 23, including three deaths, occurred in the treatment-as-usual group (n=18).

Interpretation Total cholesterol concentration at 12 months did not differ between the Primrose and treatment-as-usual groups, possibly because of the cluster design, good care in the treatment-as-usual group, short duration of the intervention, or suboptimal focus on statin prescribing. The association between the Primrose intervention and fewer psychiatric admissions, with potential cost-effectiveness, might be important.

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Introduction

An increased risk of cardiovascular disease morbidity and mortality in people with severe mental illnesses is well established, including schizophrenia, psychoses, and bipolar affective disorder.[1] This health inequality has been recognised for many years but the latest evidence suggests that the mortality gap continues to widen, partly because gains from primary prevention in the general

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Research in context

Evidence before this study

People with severe mental illnesses have an increased risk of morbidity and mortality from cardiovascular disease compared with the general population. We searched for randomised controlled trials of interventions to reduce cardiovascular disease risk in people with severe mental illnesses published in English. On May 19, 2014, we searched the Cochrane Library for existing systematic reviews and the Cochrane Depression, Anxiety and Neurosis, and Cochrane Schizophrenia Group Trial Registers for additional randomised controlled trials from January, 1966, using the search terms: (schizophrenia OR severe mental illness OR bipolar OR mania OR manic OR hypomani OR psychos OR psychotic OR postpsychotic OR post psychotic OR rapid cycling OR schizoaffective) AND (physical OR cardio OR metabolic OR weight OR tobacc OR smok OR medical OR alcohol OR nutrition OR diet OR health OR diabete OR blood pressure OR hypertension OR cholesterol OR statin). 11 026 papers were identified, of which 15 systematic reviews and 28 randomised controlled trials were relevant. Although some evidence existed for effectiveness for pharmacological and behavioural interventions targeting weight (metformin, topirimate, diet, and exercise) and smoking (bupropion, nicotine replacement therapy, and standardised stop smoking services), we found no evidence for interventions targeting cholesterol, hypertension, diabetes, or multiple cardiovascular disease risk factors. Most trials had small sample sizes, short length of follow-up, and were done in secondary care, which limited their generalisability to other settings.

Added value of this study

To our knowledge, this is the first pragmatic cluster randomised controlled trial of a behavioural change intervention targeting multiple cardiovascular disease risk factors in people with severe mental illnesses compared with treatment as usual in primary care in England. The primary outcome of total cholesterol at the 12-month follow-up did not differ between the intervention (Primrose) and treatment-as-usual groups; however, psychiatric inpatient and total health-care costs were lower in the Primrose group and total cholesterol concentrations decreased in both groups at 12 months.

Implications of all the available evidence

The decrease in admissions and costs with the Primrose intervention might be important. General practices should continue to optimise evidence-based treatments for cardiovascular disease prevention in people with severe mental illnesses with the same interventions used in the general population.

population have not been observed to the same degree in people with severe mental illnesses.[2,3] Less evidence exists regarding which interventions effectively decrease the cardiovascular risk in people with severe mental illnesses, and few studies have taken a pragmatic or multi-risk factor approach to decreasing the cardiovascular disease risk in real-life settings. Interventions focused on single risk factors have shown some promise, including smoking cessation[4] and weight reduction,[4,5] and statins have been shown to decrease cholesterol concentrations effectively in large studies[6] of people with severe mental illnesses. Based on economic modelling, screening for cardiovascular disease risk in people with severe mental illnesses (with risk algorithms) and prescribing statins for those individuals with a 10-year risk of more than 10%, might be cost-effective in UK primary care.[7]

We developed a pragmatic intervention aimed at reducing cardiovascular disease risk factors among people with severe mental illnesses in primary care in England, using published evidence and evidence from focus groups,[8] and incorporating scientific behaviour change theory.[9] Nurses and health-care assistants were trained to deliver the intervention and to target relevant cardiovascular disease risk factors in a collaborative way, with recommended risk reduction strategies for the participant risk profile. We selected the cluster trial design to minimise the risk of contamination of the intervention between the trial groups. Our aims were to compare the clinical effectiveness and cost-effectiveness of the intervention versus treatment as usual for people with severe mental illnesses.

Methods

Study design and participants

We did this cluster randomised trial with general practices from across England as the unit of cluster. We included people aged 30–75 years on the Quality and Outcomes Framework register for severe mental illnesses, including schizophrenia, bipolar affective disorder, or other non-organic psychosis, with a mean total cholesterol concentration of 5·0 mmol/L or a total:HDL cholesterol ratio of 4·0 mmol/L or more and one or more additional cardiovascular disease risk factors, including hypertension, diabetes, raised glycated haemoglobin (HbA_{1c}; 42–47 mmol/mol), raised body-mass index (BMI; >30 kg/m²), or current smoker.[10] We excluded people currently under the care of acute psychiatric services, with organic psychoses or personality disorder diagnoses, with less than 6 months life expectancy, pre-existing cardiovascular disease, or who were pregnant. General practices in England were eligible to participate in the study if they had an available nurse or health-care assistant who could deliver the intervention and at least 40 patients on their practice register with severe mental illness. Data from screening, baseline assessments, and follow-up were collected in the general practices from patient questionnaires and medical records by research nurses.

The trial was delivered according to the published protocol.[10] Ethics approval was obtained from the

City Road and Hampstead Research Ethics Committee (reference number 12/LO/1934; approval granted Jan 10, 2013). Local National Health Services approvals were obtained before the start of each recruitment wave from regional research and development departments.

Randomisation and masking

We randomly assigned general practices to the Primrose intervention or treatment as usual (1:1) using a computer-generated random sequence with an undisclosed fixed block size of four to facilitate blinding. The randomisation was done by a senior statistician from the local Clinical Trials Unit (PRIMENT) who was not involved in the Primrose trial. The allocation was communicated to the practices by the Primrose trial manager.

It was not possible to mask patients or general practice staff, including nurses and health-care assistants, to the treatment allocation. However, the researchers collecting the outcome data were masked to allocation, as were the statisticians and health economists doing the analysis (the randomisation variable was kept separate from the main dataset without a label).

Eligible participants were recruited within each practice before randomisation. This process was repeated in waves of between ten and 15 practices, and randomisation was revealed at the end of each recruitment wave. Eligible participants were introduced to the study by local research nurses and gave written consent at baseline interview before being randomly allocated to treatment groups.[10]

Procedures

The development of the Primrose intervention and its content have been described previously.[8,10] In summary, the intervention was developed from what we considered the best existing published evidence regarding cardiovascular disease risk management in severe mental illnesses, expert consensus (professionals and service users), focus groups,[8] and updated systematic reviews. The intervention was shaped by mapping all of this evidence onto the Behaviour Change Wheel[9] to identify eight key behaviour change strategies that health-care professionals could use to help decrease cardiovascular disease risk in people with severe mental illnesses. These included setting a behavioural goal, involving supportive others, creating an action plan, recording progress, providing positive feedback, reviewing progress, coping with setbacks, and forming habits. These strategies were incorporated into a 2-day training package and manual for general practice nurses.

The nurses or health-care assistants were trained on two occasions to use the behaviour change strategies to set goals that would reduce the most important risk factors for each participant, in a flexible collaborative manner. The intervention involved offering participants appointments on a weekly to fortnightly basis for up to 6 months. Within the appointments, the nurse or health-care assistant and participant focused on agreeing goals to lower cardiovascular disease risk such as adhering to statins, improving diet or physical activity levels, reducing alcohol, or quitting smoking. Tools included health-care plans with goals and actions, signposting to relevant services, and initiating and continuing clinically indicated cardiovascular disease-related prescriptions including statins. Adherence was monitored and encouraged, and patients were asked if they wanted to involve supportive others (carers or professionals) to help improve engagement with goals. British Heart Foundation leaflets on keeping your heart healthy[11] were given to intervention nurses or health-care assistants to distribute to participants at their first Primrose appointment.

Nurses or health-care assistants were each provided with an audio recorder and asked to record all Primrose intervention appointments with recruited patients. We used a random 20% sample of audio-taped appointments to determine the extent to which the intervention was delivered to protocol.

Nurses and health-care assistants from practices allocated to treatment as usual were not trained in the Primrose intervention. They were informed of their trial group allocation and received British Heart Foundation leaflets[11] to mail out to participants. The usual clinical pathways for cardiovascular disease risk factors were continued in this group.

Outcomes

The primary outcome was difference in mean total cholesterol concentration for participants between groups at the 12-month follow-up. Secondary outcomes were also collected at an interim 6-month timepoint to monitor for high attrition at 12 months (appendix). Secondary outcomes at 12-month follow-up were cardiovascular disease risk scores, including QRISK and the severe mental illnesses-specific PRIMROSE cardiovascular disease risk score,[12] blood pressure, lipid concentrations, HbA_{1c}, BMI, and waist circumference. Behavioural measures included validated physical activity,[13] diet[14] and alcohol[15] questionnaires, and questions on smoking status and number of cigarettes smoked. Other measures included quality of life,[16] wellbeing,[17] medication adherence (psychiatric and cardiovascular disease medications including statins),[18] uptake of statin medications, and satisfaction with services.[19] Data regarding health-care service use and medication prescriptions were collected by self-report and from medical records for the health economic analysis (appendix).[10]

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Statistical analysis

The sample size was based on a standardised mean difference of 0·4 for the primary outcome of total cholesterol concentration at 12 months, which indicated that 132 participants would be required per group with

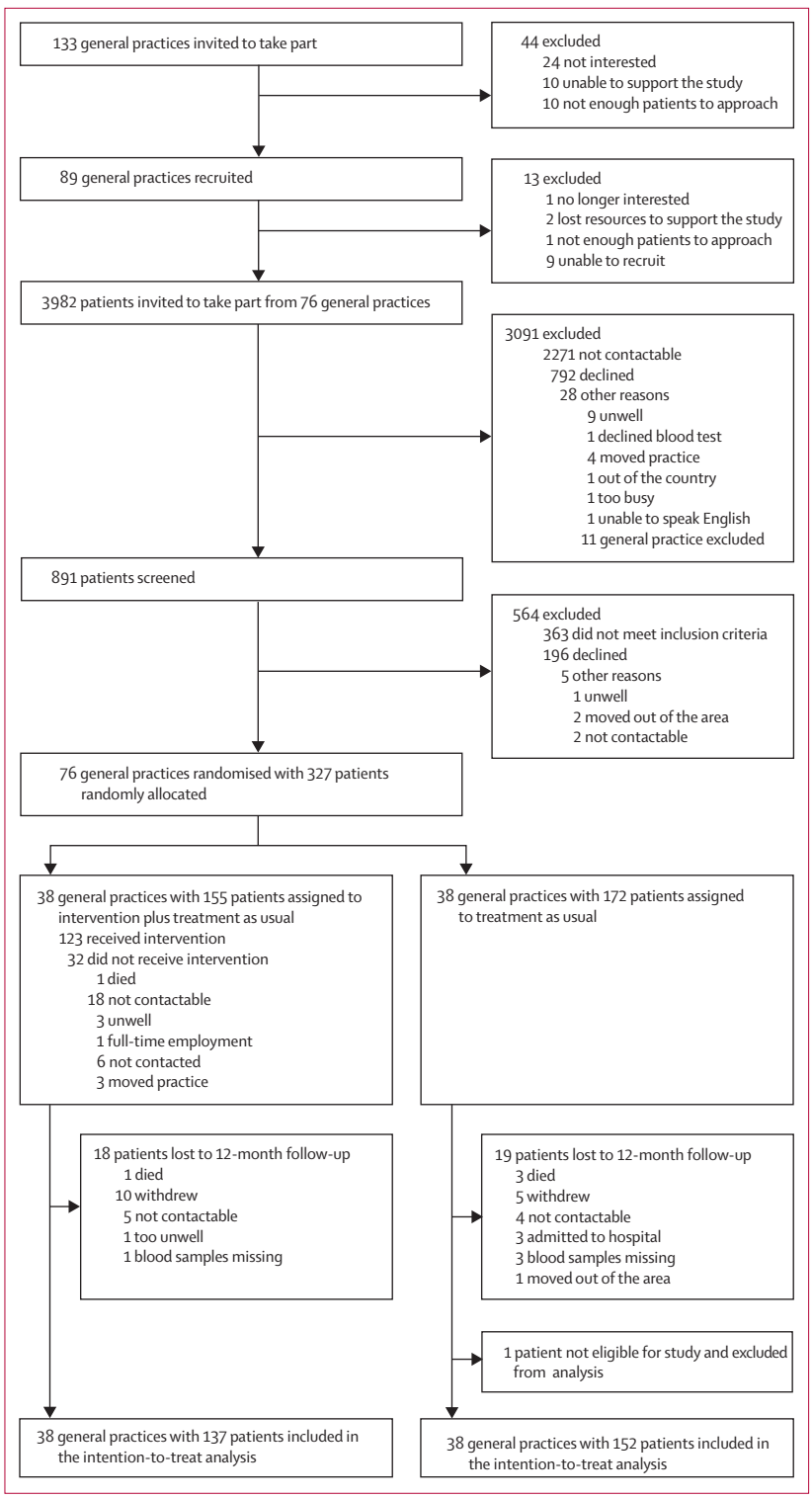

Figure: **Trial profile**

90% power and 5% level of significance. We inflated the sample size to account for the cluster design by assuming we would retain an average of four participants per practice and using an intraclass correlation coefficient (ICC) of 0·02, which has been reported as average for clustering in primary care trials.[20] This calculation indicated that we required 140 participants per group in the analysis. Finally, we increased the target sample size to allow for a 20% loss to follow-up, requiring 350 participants.

All analyses used intention-to-treat principles (ie, those participants with outcome data were analysed in the group they were randomised to). We analysed the primary outcome of total cholesterol concentration at 12 months using random effects linear modelling to account for clustering within general practice, controlling for baseline total cholesterol concentration. We used three supportive analyses for the primary outcome. (1) We adjusted for large imbalances in baseline characteristics between randomised groups. (2) We adjusted for baseline predictors of missing data for 12-month total cholesterol. We investigated these using random effects logistic regression; variables that were statistically significant ($p<0·05$) were included as predictors of missing data in the supportive analysis. (3) We adjusted for the number of Primrose appointments attended. This number was set to 0 for those participants in the treatment-as-usual group. All supportive analyses also controlled for baseline total cholesterol.

We analysed continuous secondary outcomes using random effects linear modelling and smoking status (current *vs* non-current) using random effects logistic regression. We adjusted all analyses for baseline values of the outcome. We did all analyses using Stata version 14.

The primary economic analysis was from the health-care cost perspective over the duration of the trial (12 months). We calculated the incremental cost per quality-adjusted life-year (QALY) gained and the probability of cost-effectiveness for a range of values of willingness to pay for a QALY gained (appendix).

We designed and applied fidelity checklists to appointment transcripts to assess fidelity to the intervention. We generated a percentage score for each appointment by dividing the total number of intervention components delivered by the maximum number of intervention components that should have been delivered.

We had an external Trial Steering Group, as agreed by the funding body. The trial is registered with Current Controlled Trials, number ISRCTN13762819.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We recruited general practices from Dec 10, 2013, to Sept 30, 2015; participant recruitment occurred between

May 9, 2014, and Feb 10, 2016, with 12 months' follow-up between May 6, 2015, and Feb 17, 2017. We randomly assigned 76 general practices from diverse regions across England to the Primrose intervention group (n=38 with 155 patients) or to the treatment-as-usual group (n=38 with 172 patients; figure). 41 professionals (22 health-care assistants, 18 nurses, and one general practitioner) were trained to deliver the Primrose intervention. In three of the 38 general practices, two members of staff were trained because the original staff member left the practice part way through the study.

Most baseline characteristics of participants were similar between the two groups (table 1). About half the participants had a record of bipolar disorder, roughly a third had a record of schizophrenia or schizoaffective disorder, and almost a fifth had other psychoses (table 1). About half the participants were current smokers and total cholesterol concentrations were raised (table 1). Mean BMI was above the threshold for obesity with high mean waist circumferences (table 1). Baseline characteristics of participants that appeared unbalanced between the two groups and were likely to be associated with the outcomes included having a mental health key worker, sex, living independently, being prescribed a statin or second-generation antipsychotic, and having a record of diabetes (table 1).

At the 12-month follow-up, all 76 general practices remained in the study and we analysed 137 (88%) of 155 patients in the Primrose intervention group and 152 (88%) of 172 patients in the treatment-as-usual group for the primary outcome (figure). The number of participants with 12-month follow-up data exceeded the requirements of the original sample size calculation. The primary outcome measure of total cholesterol in the two groups at 12 months did not differ at the 5% level (5·4 mmol/L [SD 1·1] in the Primrose intervention group *vs* 5·5 mmol/L [1·1] in the treatment-as-usual group; mean difference estimate 0·03, 95% CI –0·22 to 0·29; p=0·788; table 2). The mean total cholesterol decreased in both groups over the 12-month follow-up period by 0·22 mmol/L (SD 1·1) in the Primrose intervention group and by 0·36 mmol/L (1·1) in the treatment-as-usual group. The adjusted (for baseline total cholesterol and randomised group) ICC for the primary outcome at 12 months was 0·07 (95% CI 0·02–0·29).

The results from the supportive analyses were consistent with what was observed for the primary analysis when adjusting for the baseline differences in participants (mean difference estimate 0·09, 95% CI –0·16 to 0·34; p=0·47) or when adjusting for variables that predicted missing data on the primary outcome (0·06, –0·19 to 0·30; p=0·65) and adjusting for number of Primrose intervention appointments attended (0·02, –0·31 to 0·36; p=0·89). These predictors were being in full-time employment, having a mental health key worker, or being treated for hypertension.

Secondary clinical outcomes did not differ between the groups at 12 months (table 2). Coefficients were close to zero effect with 95% CIs spanning unity and zero (table 2). This outcome held true for the cardiovascular risk factors, including BMI, waist circumference, HDL cholesterol, total:HDL cholesterol, blood pressure, smoking, physical activity, and fibre-related or fat-related diet. Satisfaction

	Primrose intervention group (n=155)	Treatment-as-usual group (n=172)
Sex		
Male	67/155 (43%)	87/171 (51%)
Female	88/155 (57%)	84/171 (49%)
Age (years)	51 (10)	51 (10)
Ethnicity		
White	134/154 (87%)	155/171 (91%)
Black	11/154 (7%)	5/171 (3%)
Asian	5/154 (3%)	5/171 (3%)
Other	4/154 (3%)	6/171 (4%)
Townsend quintile		
1 (least deprived)	22/136 (16%)	17/119 (14%)
2	7/136 (5%)	11/119 (9%)
3	17/136 (13%)	11/119 (9%)
4	30/136 (22%)	28/119 (24%)
5 (most deprived)	60/136 (44%)	52/119 (44%)
Marital status		
Single	66/154 (43%)	68/170 (40%)
Married or cohabiting	59/154 (38%)	64/170 (38%)
Separated or divorced	25/154 (16%)	34/170 (20%)
Widowed	4/154 (3%)	5/170 (3%)
Lives independently	115/155 (74%)	109/170 (64%)
Employment		
Unemployed	71/155 (46%)	76/171 (44%)
Part-time paid employment	18/155 (12%)	26/171 (15%)
Full-time paid employment	13/155 (8%)	22/171 (13%)
Paid employment with paid support or employment training	1/155 (1%)	1/171 (1%)
Employed (paid to limit without affecting benefits)	4/155 (3%)	1/171 (1%)
Voluntary work	19/155 (12%)	22/171 (13%)
In education	8/155 (5%)	7/171 (4%)
Looking after home and family	13/155 (8%)	31/171 (18%)
Retired from paid work	27/155 (17%)	27/171 (16%)
Primary diagnosis		
Schizophrenia or schizoaffective disorder	54/155 (35%)	51/171 (30%)
Bipolar affective disorder	71/155 (46%)	88/171 (51%)
Other psychoses	30/155 (19%)	32/171 (19%)
Has mental health key worker	68/155 (44%)	53/171 (31%)
Has support worker	27/155 (17%)	25/171 (15%)
On Care Programme Approach	103/149 (69%)	101/154 (66%)
Cholesterol (mmol/L)		
Total cholesterol	5·7 (0·9)	5·9 (1·0)
HDL	1·3 (0·4)	1·3 (0·5)
LDL	3·5 (0·8)	3·5 (0·8)
Total:HDL	4·8 (1·4)	4·9 (2·1)

(Table 1 continues on next page)

	Primrose intervention group (n=155)	Treatment-as-usual group (n=172)
(Continued from previous page)		
Triglycerides (mmol/L)	2·3 (1·7)	2·3 (1·3)
HbA_{1c} (mmol/mol)	41 (11)	39 (8)
Glucose (mmol/L)		
Fasting	5·5 (1·4)	5·5 (0·8)
Non-fasting	6·1 (1·3)	5·4 (0·9)
Blood pressure (mm Hg)		
Systolic	127 (17)	129 (19)
Diastolic	82 (11)	82 (11)
BMI (kg/m²)	32 (6)	32 (6)
Waist circumference (cm)	107 (16)	108 (15)
AUDIT score	2 (0–7)	3 (0–7)
History of heavy drinking	35/155 (23%)	38/171 (22%)
Smoking status		
Non-smoker	40/155 (26%)	47/171 (27%)
Ex-smoker	35/155 (23%)	44/171 (26%)
Current smoker	80/155 (52%)	80/171 (47%)
Cigarettes smoked per day for current smokers	20 (10–20)	15 (10–20)
QRISK2-2016	7·0 (3·8–14·9)	8·1 (3·5–14·2)
Framingham		
Lipid	10·7 (6·4–17·3)	10·5 (6·0–18·9)
BMI	11·9 (6·9–20·6)	12·2 (6·2–21·2)
Primrose score		
Lipid	3·7 (2·4–7·0)	3·7 (2·1–6·9)
BMI	4·7 (2·8–8·0)	4·8 (2·5–7·5)
DINE score		
Fibre	29 (20–38)	32 (23–41)
Fat	29 (22–37)	31 (22–40)
Unsaturated fat	9 (8–10)	9 (9–11)
IPAQ activity total MET (min)	1386 (304–3564)	1200 (396–3111)
Type 1 diabetes	0	1/171 (1%)
Type 2 diabetes	22/155 (14%)	12/171 (7%)
Diagnosis of diabetes in past 5 years	19/155 (12%)	13/171 (8%)
Prescription		
Antihypertensive drug	45/155 (29%)	48/171 (28%)
Statin	36/155 (23%)	27/171 (16%)
Diabetes drug	20/155 (13%)	13/171 (8%)
Antidepressant	90/155 (58%)	92/171 (54%)
First-generation antipsychotic drug	21/155 (14%)	22/171 (13%)
Second-generation antipsychotic drug	83/155 (54%)	109/171 (64%)
QALYs (area under curve)		
EQ-5D-5L	0·734 (0·249)	0·775 (0·209)
WEMWBS score	42 (12)	43 (10)
MMS		
Psychiatric medication	6 (5–8)	7 (5–7)
Cardiovascular disease prevention medication	7 (6–8)	7 (6–8)

Data are n/N (%), mean (SD), or median (IQR). HbA_{1c}=glycated haemoglobin. BMI=body-mass index. AUDIT=Alcohol Use Disorders Identification Test. DINE=Dietary Instrument for Nutrition Education. IPAQ=International Physical Activity Questionnaire. MET=metabolic equivalent of task. QALY=quality-adjusted life-year. EQ-5D-5L=five-level EuroQol five-dimensional. WEMWBS=Warwick–Edinburgh Mental Well-being Scale. MMS=Morisky Scale of Adherence.

Table 1: **Participant characteristics at baseline**

with primary care services on the client satisfaction scale was high in both groups, with no differences between the groups in terms of wellbeing on the Warwick–Edinburgh Mental Well-being Scale at 12 months (table 2). Adherence to medications for physical and psychiatric conditions, as recorded on the Morisky scales, was also similar in both groups (table 2). Among the 155 participants in the Primrose intervention group, attendance at appointments was fair with 72 (46%) attending six or more appointments, 36 (23%) attending two to five appointments, 15 (10%) attending one appointment, and 32 (21%) people attending no appointments.

Most research nurses who collected data correctly guessed the treatment allocation despite being masked—of those participants who responded, the nurses correctly guessed the allocation of 108 (75%) of 144 in the Primrose group compared with 133 (82%) of 163 in the treatment-as-usual group.

30 serious adverse events were reported for 25 people (seven events for seven participants in the intervention group and 23 events for 18 participants in the control group). One death, three psychiatric hospital admissions, and three general hospital admissions were reported in the intervention group and three deaths, 11 psychiatric hospital admissions for nine people, seven general hospital admissions for six people, one admission to a crisis house, and one diagnosis of cancer were reported in the control group.

Total health-care costs were lower in the Primrose intervention group than the treatment-as-usual group (adjusted mean £1286 [SE 178] *vs* £2182 [328]; mean difference –£895, 95% CI –1631 to –160; p=0·012), and there was a significant reduction in the number and cost of mental health inpatient stays in the intervention group compared with the control at 12 months (£157 [135] *vs* £956 [313]; –£799, –1480 to –117; p=0·018; appendix). In the Primrose group, more eligible people with severe mental illnesses were accessing services for smoking, weight reduction, and diabetes at months 6 and 12 than in the treatment-as-usual group, but relevant health-care promotion activities occurred in both groups (appendix).

Adjusting for baseline differences, the intervention group had a mean of 0·769 QALYs (95% CI 0·751 to 0·787) compared with a mean of 0·780 for treatment as usual (0·764 to 0·796), with a difference in QALYs of –0·011 (–0·034 to 0·011; p=0·41; appendix). The mean 12-month health-care cost per patient for the Primrose intervention (including intervention costs but excluding those participants who did not attend and training) was £2580 (SE 249; 95% CI 1899 to 3261) with a total mean cost of £3404 (401; 2467 to 4340) for treatment as usual, with a cost difference of –£824 (95% CI –568 to 1079; p=0·11) in favour of the Primrose group. Because the intervention had a lower mean cost per patient, but slightly fewer QALYs, there is a greater probability that the intervention is cost-effective at lower values of willingness to pay for a QALY gain, with an

89% probability it is cost-effective at a £20 000 willingness to pay for a QALY gained and 98% at a £0 willingness to pay for a QALY gained (appendix).

A moderate level of adherence to the intervention manual (including use of behaviour change techniques) was achieved with 67·7% of all intervention components delivered to protocol. The mean percentage score for nurses (79·5% [SD 15·2]) was significantly higher than the mean percentage score for health-care assistants (64·3% [16·5]; t=2·23; p=0·037). Regarding statin prescriptions, few statins appeared to be initiated in either group by 12 months (table 2).

Discussion

In this cluster randomised trial of the practitioner-led Primrose intervention, the primary outcome of total cholesterol concentration at 12 months did not differ between intervention and control groups in general practices in England. The manualised Primrose intervention was developed from the best published evidence, with a wide range in expert input, including service users with severe mental illnesses and health-care professionals. It incorporated behavioural scientific theory, and fidelity to the intervention manual was acceptable. However, evidence that statin initiation or adherence was addressed in either group was scarce.

The intervention was associated with fewer admissions for mental health in terms of adverse events, and this result was substantiated by the cost-effectiveness analysis, which revealed significantly lower costs for admissions for mental health and between an 89% and 98% probability that the Primrose intervention is cost-effective. A strength of this analysis is that the outcomes were collected from medical records with rare missing data. The probability that the Primrose intervention is cost-effective at 12 months was heavily dependent on the willingness to pay for a QALY gain, with low values of willingness to pay for a QALY gained having a higher probability of being cost-effective. Thus, the intervention is cost saving, but for fewer QALYs. Most of the cost savings were a result of a reduction in the cost of inpatient mental health care in the Primrose group. Whether the EuroQol five-dimensional questionnaire and QALYs are the correct denominator for a health prevention intervention can be questioned, particularly given that most interventions were designed to have an impact on cardiovascular health outcomes in the distant future.

For this pragmatic trial, we designed an intervention that aimed to reflect real-life clinical settings in which participants with severe mental illnesses present with multiple cardiovascular risk factors which require modification simultaneously, and in a collaborative manner between health-care professionals and patients. Choosing a single outcome measure in such circumstances is difficult, but because all our participants had raised total cholesterol concentrations, we chose difference in total cholesterol as the main outcome measure. This outcome measure would not capture changes in smoking or blood pressure, but it might be affected by changes in diet, exercise, or weight, which were all goals in the intervention. However, no differences in cholesterol concentrations were seen between groups. Although we considered choosing a cardiovascular disease risk score as the main outcome (involving more component modifiable cardiovascular disease risk factors), these risk scores are not sensitive to change because they are affected so heavily by an individual's age and sex. There is no evidence that any other cardiovascular disease risk factors among our secondary outcomes differed between groups, so our choice of cholesterol as the primary outcome is unlikely to explain the absence of main effects in the Primrose intervention group.

Other limitations include the fact that only a few people with severe mental illnesses per practice participated, which could in part have been due to being invited to participate in a randomised controlled trial that involved having several blood tests, therefore uptake might be higher in clinical settings. The small number per practice

	Primrose intervention group (n=155)	Treatment-as-usual group (n=172)	Mean difference estimate (95% CI)*	p value
Cholesterol (mmol/L)				
Total	5·4 (1·1)	5·5 (1·1)	0·03 (–0·22 to 0·29)	0·788
HDL	1·3 (0·5)	1·3 (0·4)	–0·01 (–0·07 to 0·05)	0·64
LDL†	3·3 (1·0)	3·3 (0·9)	..	..
Total:HDL	4·5 (1·4)	4·4 (1·3)	0·13 (–0·16 to 0·42)	0·36
HbA_{1c} (mmol/mol)	41 (11)	40 (9)	0·14 (–1·36 to 1·65)	0·85
Blood pressure (mm Hg)				
Systolic	125 (16)	126 (17)	–0·97 (–4·34 to 2·40)	0·57
Diastolic	80 (10)	80 (10)	0·56 (–1·69 to 2·81)	0·63
BMI (kg/m²)	32 (7)	32 (7)	–0·44 (–1·18 to 0·30)	0·24
Waist circumference (cm)	106 (16)	107 (15)	–0·55 (–2·33 to 1·23)	0·55
AUDIT score	2 (0–5)	3 (0–7)	–0·51 (–1·45 to 0·42)	0·28
Smoking				
Current smoker	62/134 (46%)	68/155 (44%)	0·79 (0·36 to 1·70)*	0·54
QRISK2-2016	7·6 (3·7–14·5)	8·5 (3·6–12·9)	0·46 (–0·49 to 1·41)	0·35
Framingham				
Lipid	9·4 (5·9–16·8)	9·9 (5·4–16·7)	0·40 (–0·98 to 1·77)	0·57
BMI	9·9 (6·8–19·3)	12·5 (6·8–20·0)	–0·39 (–2·03 to 1·26)	0·65
Primrose score				
Lipid	3·5 (2·3–6·9)	3·8 (1·9–6·9)	–0·42 (–1·35 to 0·51)	0·38
BMI	4·3 (2·7–7·6)	4·5 (2·7–8·4)	–0·80 (–2·06 to 0·46)	0·21
DINE score				
Fibre	30 (22–37)	31 (23–40)	–0·32 (–2·79 to 2·14)	0·80
Fat	30 (23–35)	29 (22–37)	0·04 (–1·95 to 2·02)	0·97
Unsaturated fat	9 (8–11)	9 (8–11)	0·06 (–0·32 to 0·44)	0·75
IPAQ activity total MET (min)	1386 (462–4239)	1371 (438–4158)	–139·6 (–1323·9 to 1044·7)	0·82
Type 1 diabetes‡	0	1/163 (1%)	..	..
Type 2 diabetes‡	24/144 (17%)	14/163 (9%)	..	..

(Table 2 continues on next page)

	Primrose intervention group (n=155)	Treatment-as-usual group (n=172)	Mean difference estimate (95% CI)*	p value
(Continued from previous page)				
Prescription				
Antihypertensive drug‡	41/144 (28%)	44/163 (27%)	..	..
Statin	38/144 (26%)	31/163 (19%)	1·11 (0·50 to 2·49)*	0·80
Newly prescribed statin at 12 months	9/144 (6%)	10/163 (6%)	1·01 (0·38 to 2·71)*	0·99
Diabetes drug‡	22/144 (15%)	15/163 (9%)	..	..
Antidepressant‡	85/144 (59%)	83/163 (51%)	..	..
First-generation antipsychotic drug‡	29/144 (20%)	21/163 (13%)	..	..
Second-generation antipsychotic drug‡	77/144 (53%)	96/163 (59%)	..	..
QALYs (area under curve)				
EQ-5D-5L	0·775 (0·232)	0·782 (0·227)	–0·011 (–0·034 to 0·011)	0·41
WEMWBS score	43 (12)	45 (10)	–1·53 (–3·52 to 0·45)	0·13
MMS				
Psychiatric medication	7 (5–8)	7 (5–8)	0·14 (–0·23 to 0·52)	0·46
Cardiovascular disease medication	7 (5–8)	7 (6–8)	0·25 (–0·33 to 0·83)	0·40
CSQ-8	27 (24–31)	27 (24–31)	0·31 (–0·83 to 1·45)	0·59

Data are mean (SD), n/N (%), or median (IQR). All results were adjusted for baseline values apart from CSQ-8, which was only collected at the 12-month follow up. HbA_{1c}=glycated haemoglobin. BMI=body-mass index. AUDIT=Alcohol Use Disorders Identification Test. DINE=Dietary Instrument for Nutrition Education. IPAQ=International Physical Activity Questionnaire. MET=metabolic equivalent of task. QALY=quality-adjusted life-year. EQ-5D-5L=five-level EuroQol five-dimensional. WEMWBS=Warwick–Edinburgh Mental Well-being Scale. MMS=Morisky Scale of Adherence. CSQ-8=Client Satisfaction Questionnaire-8 items. *Odds ratio as indicated. †Analysis not done because of large amount of missing data (data available for 153 [47%] of 326 participants). ‡For descriptive analysis.

Table 2: **Outcomes at 12 months' follow-up**

could have implications for scalability; however, as the number was smaller, it was feasible for practice nurses or health-care assistants to integrate into their normal clinical workload, and arguably a higher number of patients might have made the delivery of the intervention less feasible. If the number of patients with severe mental illnesses within a practice were small, a service could be offered by a single nurse to a cluster of practices, making the delivery of training and case-load more cost-effective.

Another limitation was that the intervention did not target psychotropic medication management, which can have an effect on obesity and metabolic parameters for people with severe mental illnesses. The ICC for the primary outcome was high between practices, indicating that effects differed more than we expected between individual general practices (the clusters). This large practice effect might indicate that the intervention was delivered variably by different professionals in different settings, which is supported by the differences we observed in fidelity scores between nurses and health-care assistants.

The economic findings were particularly caused by a reduction in admissions for mental health at 12 months in the Primrose group. We cannot rule out the possibility that this reduction occurred by chance.

The participants and practices that agreed to take part in the Primrose trial might not be representative of the wider populations with severe mental illnesses and raised cardiovascular disease risk factors because they could have been more motivated to address their physical health. We compared our trial participants to a sample of 38 824 patients with severe mental illnesses from 430 general practices in England used in our previous work.[12] The characteristics were similar in terms of age (51 years in this trial *vs* 49·5 years in our previous study) and sex (male participants accounted for 47% in both samples), with a slightly higher mean BMI (32 kg/m² *vs* 28 kg/m²) and total cholesterol (5·8 mmol/L *vs* 5·5 mmol/L) in this trial. This outcome is probably due to our trial inclusion criteria targeting participants with raised cardiovascular disease risk factors. Both studies had the same HDL cholesterol concentration (1·3 mmol/L) and number of current smokers (49%). Our trial sample also had higher deprivation (participants living in the most deprived areas was 44% *vs* 23%), which could have been due to us targeting general practices with larger severe mental illnesses lists in urban areas. However, a strength of our study was the geographical spread of recruited general practices that included both rural and urban practices across the north and south of England.

Our inclusion criteria for people with severe mental illnesses included those individuals with schizophrenia, bipolar, and other psychoses; however, we did not include broader definitions of severe mental illnesses—eg, personality disorder.[21] Therefore, the findings of our study might not apply to people outside our definition of severe mental illnesses.

The practices randomised to the treatment-as-usual group could have provided much better health care to their severe mental illnesses participants than would have been observed in routine practices outside a trial environment, partly because they were practices with an interest in research and an interest in severe mental illnesses and cardiovascular disease, but also because they were aware that their patients with raised cardiovascular disease risk factors would not receive the Primrose intervention when they were allocated to treatment as usual. The economic analysis confirmed that relevant cardiovascular disease health promotion activities were accessed in both groups during the duration of the trial. The high levels of satisfaction in both groups (27/32 on the Client Satisfaction Questionnaire-8 items) might also reflect good health care being provided in both groups. The mean total cholesterol concentrations did decrease in both groups of the trial over the 12 months of follow-up.

Although the Primrose intervention seemed acceptable to participants and to general practices, we cannot recommend it over treatment as usual in England in terms of improving medical outcomes. However, it did result in cost savings and reduced admissions, a finding worthy of further exploration.

The mortality gap between people with and without severe mental illnesses continues to widen in UK general practices,[2] so it is essential that treatment as usual continues to incorporate all of the evidence-based interventions for cardiovascular disease prevention in an integrated way, which has the best chance of reducing the main excessive risk factors in people with severe mental illnesses. These risks include high rates of smoking, which can be amenable to targeted cessation support,[22] obesity, which can be managed with pharmacological and behavioural techniques,[23] and prescribing statins, which we have previously shown to reduce cholesterol concentrations in people with severe mental illnesses with effects comparable to the general population.[6]

All participants in both groups of the Primrose trial received screening for cardiovascular disease risk factors and feedback before being randomly assigned, which is not observed for everyone in routine general practice care.[24] It is important that cardiovascular disease screening is maintained as policy in routine primary care for people with severe mental illnesses, since the application of risk scores and then prescribing statins could well be cost-effective in the short term and long term in severe mental illnesses.[7] The findings from the Primrose trial mirror findings from an individualised randomised controlled trial[25] in the USA of tailored cardiovascular disease care delivered in a behavioural health home in an urban psychiatric centre, which compared 447 outpatients with severe mental illnesses and cardiovascular disease risk factors. Although health-care quality improved in the integrated behavioural health home, the results did not translate into improved medical outcomes for the people with severe mental illnesses, over and above usual care. An accompanying editorial[26] argued that these integrated care models contain crucial elements of physical health care, but that they might struggle to show benefits in trial settings for medical outcomes, given the heterogeneous nature of the target population, as well as their varied risk factor profiles. Additionally, the study authors note that, as in our trial, screening and feedback in their treatment-as-usual group could have been enough to improve outcomes in the usual care group. Large-scale observational studies, with routine data from both primary and secondary care settings, might be better suited than trials to evaluate whether evidence-based screening and interventions are being delivered to people with severe mental illnesses, and ultimately whether these interventions are decreasing the cardiovascular disease mortality gap in this group of people.

In summary, the more intense behavioural intervention of Primrose was not more effective than treatment as usual in primary care, in which treatment as usual involved active screening and feedback to people with raised cardiovascular risk factors. The intervention was well attended and costs seemed to be reduced and psychiatric hospital admissions were reduced in the Primrose group. The absence of effectiveness in our primary outcome might be explained by the infrequent prioritisation of statins in both trial groups.

Contributors

DO was the chief investigator, wrote the final manuscript, and designed the study with all authors contributing to study design and intervention development. KW was the deputy chief investigator. AB did the literature search, managed trial set up and the running of the trial, and produced the CONSORT diagram. RHu did the economic evaluation and wrote the supplementary health economics material. LM and RO analysed the data and produced the data tables. LA led the design of the literature review and fidelity assessment supervised by SMi. SH coordinated the trial and did the fidelity analysis. SMo supervised the design of the economic evaluation. RO designed the statistical analysis plan and co-authored it with LM and RHu. IN, KW, LM, MK, and RO through the PRIMENT Clinical Trials Unit were involved in the trial design, operational overview of the running of the trial, and the final analysis and interpretation of the findings. DO, KW, MK, RHo, SMi, IN, RP, TB, TC, and HG all provided clinical and trial expertise to the study design. LM, RO, RHu, SMo, RB, RM, and IP all provided statistical expertise to the study design. VP coordinated patient and public involvement into the design and delivery of the study. All authors reviewed and interpreted the results and edited the manuscript.

Declaration of interests

TB reports personal fees from Janssen, Sunovion, Newron Pharmaceuticals, and Otsuka/Lundbeck, outside the submitted work. RHo reports personal fees from Eli Lilly, Janssen, Lundbeck, Sunovion, Sanofi, Novo Nordisk, and Otsuka, as well as non-financial support from Boehringer Ingelheim and Novo Nordisk, outside the submitted work. All other authors declare no competing interests.

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