Title: Reducing excess mortality due to chronic disease in people with severe mental illness: A meta-review of health interventions

Authors:
Amanda J. Baxter  
Meredith G. Harris  
Yasmin Khatib  
Traolach S. Brugha  
Heidrun Bien  
Kamaldeep Bhui

Affiliations:
1 The University of Queensland, School of Public Health, Herston AUSTRALIA 4002
2 Policy and Epidemiology Group, Queensland Centre for Mental Health, Wacol AUSTRALIA 4074
3 Wolfson Institute of Preventive Medicine, Barts & The London School of Medicine and Dentistry, Queen Mary University of London, UK
4 Department of Health Sciences, University of Leicester, Leicester General Hospital, UK

Corresponding author: Amanda Baxter, Queensland Centre for Mental Health Research, Locked Bag 500, Sumner Park BC, Qld 4074 AUSTRALIA. (E) amanda_baxter@qcmhr.uq.edu.au (Ph) +61 7 32718676
Abstract

Background: People with severe mental illness (SMI) have high rates of chronic disease and premature death.

Aim: To explore the strength of evidence for interventions to reduce risk of mortality in people with SMI.

Method: Meta-review of 16 systematic reviews of controlled studies. Mortality was the primary outcome (8 reviews). Physiological health measures (body mass index, weight, glucose levels, lipid profiles and blood pressure) were secondary outcomes (14 reviews).

Results: Antipsychotic and antidepressant medications had some protective effect on mortality, subject to treatment adherence. Integrative community care programs may reduce physical morbidity and excess deaths, but the effective ingredients are unknown. Interventions to improve unhealthy lifestyles and risky behaviours can improve risk factor profiles, but longer follow-up is needed. Preventative interventions and improved medical care for co-morbid chronic disease may reduce excess mortality, but data are lacking.

Conclusions: Improved adherence to pharmacological and physical health management guidelines is indicated.

Declaration of interest:

All authors have completed the ICMJE uniform disclosure form at [http://www.icmje.org/coi_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: AJB and KB received part and modest funding by NHS England in order to inform policy; authors report 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.
Introduction

People with severe mental illness (SMI), including schizophrenia, schizophrenia-like disorders, bipolar and severe affective disorders, on average die at a younger age compared with the general population.(1-4) In the United Kingdom (UK) men with SMI die 8 to 15 years and women 7 to 18 years earlier than those without mental disorders.(1) This life expectancy gap is increasing.(2)

Although suicide is an important cause of death in those with SMI, the majority of preventable deaths are due to chronic diseases, primarily cardiovascular, cerebrovascular, and respiratory disease.(2, 5) In England and Wales, people with schizophrenia have a three-fold greater risk of premature mortality compared with the general population.(5) Brown and colleagues(5) found that risk of unnatural deaths (violent deaths and suicide) declined significantly between 1982 and 2006, while the risk of premature death due to cardiovascular disease (CVD) more than doubled in comparison to the general population.

A complex web of factors contributes to this life expectancy gap. The side effects of psychotropic medications, particularly weight gain and impaired glucose tolerance, increase the risk of excess mortality in people with SMI directly through obesity and diabetes.(6) Unhealthy lifestyles include inactivity and diets that are high in fat and low in fruit and vegetables; these lifestyle factors may be consequences of negative symptoms of mental illness as well as poor emotional regulation.(7)

In addition, there is a growing body of evidence that unequal healthcare provision contributes to the life expectancy gap.(8) Mental disorders are associated with poorer clinical management of disease. People with SMI are less likely to receive timely and precise diagnosis because of ‘diagnostic overshadowing’, that is, physical complaints are overlooked and partially or totally attributed to psychological and psychiatric factors.(9) Differential access to effective care leads to poorer outcomes including preventable deaths(10) and incurs high costs in health care provision.(11)

Although evidence-based interventions for improving chronic disease outcomes are available, there is little evidence of committed implementation for people with SMI. This may be driven by a lack of awareness of gaps in health-care by the service providers, and poor knowledge about the strength of the evidence for specific interventions.(9)

Despite the extensive body of literature showing reduced life expectancy for people with severe mental illness, a comprehensive synthesis of existing evidence on interventions that might reduce mortality has not been attempted. This is necessary to guide practitioners and commissioners.

This meta-review aims to assess the evidence for the impact of health interventions in reducing excess mortality in people with SMI. Reviews were sought that examined trials that reported
mortality, or physical health outcomes in people with SMI compared to those receiving ‘usual care’. As the major causes of excess deaths in people with SMI are chronic diseases, we focus on interventions that may impact on physiological health indicators for these conditions.

**Methods**

**Search strategy**

The review was conducted in 2014 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We focussed on existing syntheses of the literature in which authors had looked at the effect(s) of health interventions in people with SMI, generally defined in the mental/physical health literature as psychotic disorders (schizophrenia, schizoaffective and schizophrenia like illnesses), bipolar disorder and severe major depression, and where mortality or physiological health parameters were reported as a primary outcome.

We used a broad search string (e.g., ['mental disorders' OR schizo* OR depress* OR bipolar*] AND [interventions OR treatment] AND [mortality OR survival]) to search: the Cochrane database of systematic reviews; the Database of abstracts of reviews of effects (DARE); the Campbell database of systematic reviews; and the Database of promoting health effectiveness reviews (DoPHER). We conducted additional searches of citation lists from research papers and reports to identify additional reviews. Specific databases searched and the search strings used are reported in the Appendix.

**Inclusion/exclusion criteria**

Systematic reviews were accepted if they included studies that compared an intervention versus control group conditions for people with SMI. Because reviews that included mortality or survival outcomes were scarce, secondary physiological outcomes associated with chronic diseases were also included: metabolic factors such as glycaemic control, dyslipidemia, and weight gain. We accepted any review that reported results of randomised controlled trials (RCTs), quasi-experimental studies and observational studies. Only reviews that employed a systematic search methodology and that reported effect sizes were included. No limitations were placed on language, date of publication, publication status. Reviews that only considered studies of individuals with pre-existing physical conditions, for instance cardiac patients, were excluded. Although this is an important area of research, causal direction is distinct in these patients compared with populations with SMI developing chronic diseases.

**Synthesis methods**

Titles and abstracts of all reviews were screened; relevant reviews were subjected to full text examination and were evaluated against the study criteria. Where multiple iterations of a review
were found (e.g., a 2014 update was found for a 2013 Cochrane review (14, 15)), only the most up-to-date review was included. All reviews entering the study were downloaded into an EndNote database and duplicates were removed. Information describing study design, sample and comparison groups, interventions and outcome data were extracted from the full text. Two researchers (AJB and YK) independently extracted the data and where discrepancies were found, a third reviewer (MH) adjudicated differences. Types of interventions were identified and grouped into broad categories. Given that meta-analyses were not possible due to heterogeneity in study design and focus, study findings were synthesised narratively to explore the impact of different types of interventions.

Quality assessment method

Review quality was assessed using AMSTAR,(16) a measurement tool developed specifically to assess the quality of systematic reviews with reference to the methodological and systematic rigour and synthesis of the evidence. The AMSTAR(16) enables the quality of a systematic review to be scored on the following 11 items (scoring as yes=1; no, can’t answer or not applicable=0):

1. Was an a priori design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of the studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest stated?

The authors of the AMSTAR (16) provide guidance notes as to how each item is scored. This guidance was followed, with the exception of item 11, where clear acknowledgement of potential sources of support in the systematic review, rather than ‘the review and the included studies’ sufficed to be scored as ‘yes’. The validity and reliability of AMSTAR have been established.(16, 17)

Results

Systematic search findings

The database and citation searches yielded a total of 134 unique reviews. In total, 16 systematic reviews met the study criteria and entered the review (see Figure 1).

<Figure 1 about here>
The reviews showed substantial heterogeneity in terms of target groups, implementation strategy, and outcomes measures for the different categories of intervention. Of the 16 reviews included, eight identified mortality as an outcome of interest, including four that looked at both mortality and physiological health parameters, and another eight identified only physiological health parameters as outcomes.

The quality of the 16 review studies varied. Out of a total score of 11 on the AMSTAR, six reviews achieved scores of 9 or above, six achieved scores between 6 and 8, and four achieved scores of 5 or lower. As there is no recommended cut-off for the AMSTAR, we will refer to the reviews scoring 9 or above as ‘high quality’, to those scoring between 6-8 as ‘medium quality’, and to papers scoring 5 or lower as ‘low quality’.

Overview of interventions

To facilitate comparisons of findings between reviews, we grouped similar intervention types into four broad categories:

i) mental health interventions;
ii) integrative community care;
iii) interventions for lifestyle factors; and
iv) screening and monitoring of health parameters.

Mental health interventions include psychiatric medications and psychological interventions including psycho-educational and behavioural therapies (e.g., cognitive-behavioural therapy (CBT)). Psychotherapies such as CBT are becoming increasingly available for people with SMI. These treatments can help link the person’s distress and problem behaviours to underlying patterns of thinking with the aim of enhancing coping strategies and general problem-solving skills.(18) We defined integrative community care as multi-professional team-based approaches to patient care, which aim to improve mental and physical health outcomes in people with SMI. Components of care include scheduled patient follow-ups and inter-professional communication between team members. Interventions aimed at improving lifestyle-related risk factors in people with SMI can take a variety of forms. We broadly categorised these reviews as having a primary outcome of reducing risky lifestyle factors. Intervention modalities included pharmaceutical treatments and/or psycho-educational or behavioural approaches. These latter incorporate techniques such as problem solving, goal-setting and self-monitoring, sometimes with a practical component in terms of an exercise regime or dietary counselling. These are generally informed and adapted from existing lifestyle programs developed for use in the general population.
Findings of the reviews are summarised below by intervention category. Table 1 provides a summary of the study characteristics, findings and AMSTAR quality ratings for each of the reviews included.

**Mental health interventions**

We found two systematic reviews that focussed on mortality-related outcomes associated with use of psychiatric medications, specifically antipsychotics (19) and antidepressants (20). Our search found one additional review that reported health outcomes of groups receiving psychological therapies (21).

The studies included in the two reviews looking at excess mortality and use of psychiatric medications varied enormously in terms of study design (including RCTs, data linkage studies, observational secondary analyses and cohort studies), follow-up periods, control groups and consideration for comorbidities and other risk factors (19, 20). In a medium quality review, Weinmann and colleagues (19) examined outcomes from 12 studies that looked at the risk of excess death in patients with schizophrenia prescribed antipsychotic medication. The majority of the studies included in their review showed that patients using antipsychotics were more likely to die prematurely compared with the general population. In comparing patients using antipsychotics to those not using antipsychotics, however, there was increased mortality only where multiple antipsychotics were prescribed (polypharmacy) with deaths increasing in relation to number of medications (relative risk [RR]=2.97, 95%CI 3.21 and 6.83 for 2, 3 or more drugs, respectively) or where patients had discontinued medication ((22, 23) cited in (19)). Two retrospective cohort studies reported a protective effect of antipsychotic use and these found a 2- to 10-fold reduction in mortality for patients who used antipsychotics compared to those who did not ((23, 24) cited in (19)) however observational studies may not adequately control for confounding variables such as disease severity and preferential prescribing (19).

A lower-quality review by Von Ruden and colleagues (20) identified three studies that looked at the association between selective serotonin re-uptake inhibitors (SSRIs) and mortality, all of which defined SSRI use as ‘exposure’ without providing information on period since treatment, mental health status or presence of other risk factors. Findings were heterogeneous with the first study reporting a positive association between SSRI exposure and hospitalisation or death (hazard ratio [HR]=1.47, 95%CI 1.26-1.70), the second reporting an inverse association with CVD mortality (RR 0.37, 95%CI 0.17-0.78) and the last finding no relationship with subsequent cardiac mortality or morbidity. ((25-27) cited in (20))

A third high-quality review to look at mental health interventions and their effect on mortality reduction, examined the long-term effects of CBT in people with schizophrenia. The authors identified two trials reporting mortality as an outcome, neither of which found a significant association between CBT and risk of excess mortality (21). We were unable to find any reviews that
looked at the effect of psychotherapies (aimed at improving symptoms of mental disorders) on physiological health outcomes in people with depression or bipolar disorder.

<Table 1 about here>

**Integrative community care**

Two Cochrane reviews evaluated health outcomes in people with SMI allocated to integrative community care management(28) and intensive case management.(29) In total the reviews identified twenty non-overlapping RCTs where all-cause and/or suicide deaths were reported as primary outcomes. In a high quality review, Dietrich and colleagues(29) pooled results from 14 RCTs comparing all-cause death for intensive case management versus standard care, and results from seven RCTs that evaluated mortality in intensive case-management groups versus non-intensive management, and found no significant difference in risk of death.(29) Malone and colleagues(28) found three RCTs that compared collaborative community health interventions versus standard care, producing a pooled RR of 0.47 (95%CI 0.17-1.34) for all-cause mortality. Although no results in either review were statistically significant, the authors report a general trend across the studies suggesting fewer deaths due to suicide/suspicious circumstances and few deaths overall in treatment groups. Neither study reported physical health makers as outcomes of interest.

**Interventions for lifestyle factors**

We found 10 systematic reviews that measured health outcomes associated with lifestyle and behavioural interventions in people with SMI. Three reviews reported mortality as an outcome of interest, all of which scored highly on the AMSTAR scale.(30-32) A Cochrane review by Tosh and colleagues (30) looked at interventions providing general health advice for people with SMI, reporting a broad range of outcomes including: social and psychological health; physical health, awareness and behaviours; and adverse events such as deaths. Of the seven studies identified in the review, two measured all-cause mortality((33, 34) cited in (30)) and found no significant difference for reduced mortality in those receiving the intervention compared with treatment as usual (RR 0.98, 95%CI 0.27-3.56).(30) A third study looking at fatal cardiovascular disease as an outcome found no significant reduction in cardiac fatalities.((35) cited in (30))

Hunt and colleagues (32) identified 32 studies in a systematic review and meta-analysis of RCTs that looked at psychosocial interventions for treatment of substance use, seven of which considered mortality. Analyses found no change in mortality risk associated with either intensive case management, integrated models of care or motivational interviewing alone.(32) However follow-up periods were short (the longest being 3 years) and there were low numbers of deaths in both case and control groups.(32)
A third review by Gierisch and colleagues (31) found 32 RCTs that evaluated the effect of behavioural and/or pharmaceutical interventions aimed at reducing CVD risk, including metabolic factors (weight, glycaemic control, or dyslipidemia). This review also intended to examine mortality but there were no deaths reported in the included studies.

Weight loss or obesity management were the most commonly measured health indicators (9 studies)(30, 31, 36-42), followed by metabolic risk factors such as glucose levels, lipid profiles and/or blood pressure (5 studies)(30, 31, 36, 39, 40) and harmful substance use (2 studies).(32, 39, 43) Studies identified in these reviews varied in terms of intervention types and outcome measures, and this hampered the ability to synthesise results; overall only four of the eleven reviews were able to report pooled effect sizes.(30-32, 36)

Overall, the reviews were consistent that interventions aimed at improving lifestyle factors can achieve modest but significant improvements in physical activity and eating habits.(38, 39). They showed that interventions could effectively reduce antipsychotic-induced weight gain(31, 41, 42) and achieve weight loss/BMI reduction in those already overweight(31, 36-42). Where reviews looked both pharmacological treatment and behavioural interventions, both approaches were associated with a similar magnitude of improvement in weight and/or BMI control.(31, 41, 42)

Few studies evaluated interventions specifically designed to address outcomes such as metabolic syndrome, glycaemic control, dyslipidemia, blood pressure or other physiological markers of disease; these were considered as secondary measures to other outcomes and so analyses were often underpowered. The review by Tosh and Colleagues found one study that specifically evaluated a lifestyle program and its effect on physical health((35) reported in(30)). While there was no effect found for mediation of metabolic syndrome in people with SMI, there was a trend for fewer metabolic risks, from 13 to 10, after one year of follow-up.(30)

A review by Gierisch and colleagues(31) found two out of the seven studies with glycaemic control as an outcome showed a significant improvement in the invention group over control group, in both cases metformin was prescribed as treatment.(31) More positively, of the 15 trials that measured blood lipid levels, 6 found significant improvement in treatment groups (in each case treatment was pharmacological).(31)

Caemmerer and colleagues(36) conducted a meta-analysis, focussing on effects of non-pharmaceutical interventions. This medium quality study showed treatment was associated with a significant improvement in insulin levels (3 RCTs, WMD= -4.93 uIU/mL, p<0.001) and fasting glucose levels (6 RCTs, WMD= -5.79 mg/dL, p<0.001).(36) Interventions were also significantly associated with improved profiles for total cholesterol, LDL cholesterol and triglycerides, but the same was not found for HDL cholesterol or systolic blood pressure.(36) A brief mid-quality review by Cabassa(40) found 13
studies reporting metabolic risk measures, of which seven found statistically significant improvements in at least one physiological measure.

**Screening and monitoring of health parameters**

We identified only one review meeting our criteria that looked at screening and/or monitoring of physical health parameters in people with SMI. Tosh and colleagues (15) found no trials reporting the effects of health care monitoring (either self-monitoring or by a healthcare professional). The low AMSTAR score for this review reflects the lack of data available on the impact on health outcomes of physical health screening in people with SMI.

**Discussion**

We sought to synthesise the current scientific evidence on interventions that may reduce excess mortality or improve physical health indicators of chronic disease in people with SMI. We evaluated the evidence relating to four broad intervention categories: mental health interventions; collaborative care interventions; interventions for risky lifestyle factors; and screening and monitoring of physical health parameters. Reviews suggest that psychiatric medications (antipsychotics and antidepressants) have some protective effect against excess mortality, but this is dependent on treatment adherence. Integrative community care programs may reduce physical morbidity and excess mortality associated with SMI, but the effective ingredients of the interventions need to be identified. Interventions to improve risky lifestyle behaviours can reduce the profile of risk factors, but studies with long-term outcomes are lacking. Screening and preventative interventions and improved care in those with comorbid chronic disease are expected to reduce excess mortality, however, there are currently no data available to support this. These findings highlight areas for policy, practice and research development. Below we explore the implications of our meta-review within the context of other research findings for each intervention category, taking into account a small number of studies post-dating the included systematic reviews.

**Mental health interventions**

We found the evidence on the effects of medication on mortality was equivocal. However a number of trials published subsequent to these reviews suggest that antipsychotics and antidepressants may be effective in reducing excess mortality but this is mediated by treatment adherence (44-46). In Finland, Tiihonen and colleagues (2009) (45) found that long-term use (7–11 years) of any antipsychotic treatment was associated with lower mortality compared to no drug use (adjusted hazard ratio [HR] 0.81, 0.77–0.84). It has been noted, however, that methodological aspects of this study such as the exclusion of deaths occurring during hospitalisation and the possibility of survivor bias, mean these findings should be interpreted with caution. (47)
In apparent support of the findings from Finland, a recent study from North America, Cullen and colleagues (2003) (44) showed that those with most consistent adherence to antipsychotic medications had a 25% lower risk of excess mortality compared to those with the poorest adherence, after controlling for medical comorbidities. A study of antidepressant use found that depressed patients receiving 12 or more weeks of antidepressant treatment had decreased risk of all-cause mortality across all drug classes compared with taking antidepressants for 0-11 weeks.(46) Effect sizes ranged from HR=0.51 (0.48-0.54) for SNRIs to HR=0.66 (0.62-0.71) for tricyclics.(46)

There are multiple impact pathways by which psychiatric medications may reduce risk of chronic disease and excess mortality. Medications can impact directly on physical health through biochemical mechanisms and indirectly by reducing duration and severity of symptoms with subsequent improvements in physical health. While there are known cardio-toxic effects associated with some older antidepressants (e.g., tricyclics), there is evidence that newer classes of antidepressants, specifically SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs), may normalise platelet activity,(48) improve cardiac risk markers(49, 50) and reduce risk of cardiac events.(46, 51-53)

Antidepressant medication may have a direct positive impact on biological factors shared by depression and cardiovascular disease including over-expression of pro-inflammatory cytokines, platelet activation and vasoconstriction.(54)

For both antipsychotic and antidepressant medications, mitigation of psychiatric symptoms may be important as reduced severity of mental disorders leads to better health behaviours, such as reduced smoking and alcohol intake(55) and more proactive physical health care seeking.(44) Comparison of long term health outcomes, at this stage however, is obscured by heterogeneity in the drug class(20) and underlying comorbidities and risk factors for chronic disease.(56)

**Integrative community care**

Existing summaries of the literature on integrative community care programs were unable to show significant impact on excess mortality in treatment groups, although a general trend for reduced deaths was noted across studies. Study authors report there few deaths in either treatment or sample groups in the short periods of follow-up (median=18 months). The recently published Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT) provides support for the efficacy of integrative care management strategies when longer intervention and follow-up periods apply.(57) During nine years of follow-up, people with major depression, when allocated a mental-health specialist case manager to work with their regular GP, were 24% less likely to have died, particularly due to chronic diseases, compared to those receiving usual care.(57)
The use of integrative care models to improve physical health in people with SMI is burgeoning in countries such as Canada and the US and this has become even more important in light of the Affordable Care Act. Whilst preventing excess mortality has been used as a key rationale for these models, there is little information as yet on survival as an outcome. However trials published subsequent to these reviews have demonstrated a range of other positive, short-term outcomes including improved cardio-vascular risk profiles. A number of RCTs are currently underway to address physical comorbidity outcomes in SMI, including the serious mental illness Health Improvement Profile (HIP) Study, the IMPACT Therapy trial and the Health Outcomes Management and Evaluation (HOME) Study.

Taking into account our findings, together with other research, we recommend further work is needed to identify the specific aspects of this approach that positively influence physical health. Researchers hypothesise that benefits of care management are likely multi-factorial: clinicians may become more sensitive to changes in physical health outside the filter of the mental disorder diagnosis and patients may be more aware of health issues, have more frequent contact with health services, and be primed to seek treatment, however evidence is lacking. Furthermore, as short-term research funding tends to prelude robust investigation of mortality as an outcome, researchers and funding bodies need to invest in longer periods of intervention and follow-up of health outcomes.

Interventions for lifestyle factors

Overall, our meta-review shows that interventions to improve risky lifestyle behaviours can reduce individual’s health risk profiles. One major limitation of studies in this intervention category was the short follow-up periods. This is important for two reasons. Firstly, this prevented us from drawing firm conclusions on the effectiveness of such programs in reducing mortality. Secondly, studies have shown that the positive effects of lifestyle interventions tend to deteriorate over time for people with SMI and the general population. Given the motivational difficulties associated with medication effects and psychopathology, the SMI group faces additional challenges in instituting lifestyle changes. Papers identified in these reviews suggest that more tailored approaches to treatment with continued proactive follow-up by usual mental health clinicians will likely contribute to more prolonged long-term changes in healthy behaviours.

The 2011 British mental health outcomes strategy ‘No Health without Mental Health’ sets out 6 objectives shared at all levels of community and government. It states one of its primary objectives as ensuring that “more people with mental health problems will have good physical health”. However the commitments made to achieve this reflect a ‘passive’ approach, for instance improving nutritional standards in catering services, improving access to fitness facilities and
developing alcohol and tobacco control plans. Given that the literature on lifestyle factors and collaborative care models suggests that proactive approaches tend to be more successful, these policies could be improved by integrating a component that ensures active follow-up by community service providers.

Screening and monitoring of health parameters

Screening, preventative interventions and improved physical health care for people with SMI and comorbid chronic disease are expected to reduce excess mortality, however there are currently no data available to support this. Nonetheless, available studies suggest there are inequities in terms of diagnostic timeliness, use of monitoring, and provision of physical health care interventions; each is considered below along with possible explanations.

Despite their increased exposure to chronic disease risk factors, many patients with SMI have limited access to general healthcare with less opportunity for metabolic risk factor screening and prevention(63) and lower rates of medical interventions than their counterparts in the general population.(64-67) Crump and colleagues(63) found that, despite their increased risk of mortality due to IHD and cancer, people with schizophrenia were less likely to receive diagnoses of IHD, hypertension, abnormal lipid levels, cancer or liver disease compared to those without schizophrenia. After restricting the analysis to those previously diagnosed with chronic disease, schizophrenia was only modestly associated with IHD mortality and was no longer associated with cancer mortality.(63) This, in turn suggests that reducing the life expectancy gap for people with SMI also requires improvements in the coverage, timeliness, and quality of physical health care for this group.

Whilst there is still insufficient information to determine a causal link, indirect evidence supports the hypothesis that mortality in people with SMI may be averted, to some degree, through ensuring better monitoring of physical health by mental health clinicians for chronic disease risk factors. Due to the known relationship between atypical antipsychotics and metabolic disturbances, guidelines to screen and monitor patients receiving these drugs have emerged over recent years, particularly in the case of clozapine.(68-70) However, uptake and compliance with these guidelines remains poor.(71, 72) There are no similar guidelines for monitoring of metabolic risk factors in patients not currently medicated, or on other medications. The Service Framework for Mental Health and Wellbeing(73) states that people with SMI should have an annual physical health check, preferably in primary care. However, adherence to guidelines on screening and treatment of chronic disease is poor(74) and there is little information on why these barriers exist. Furthermore, the thresholds at which risk factor intervention is considered to be warranted are often determined by structured tools such as the QRISK2 (75) which underpins the NHS Health Checks Programme and the Framingham Coronary Heart Disease Risk Score used in the USA (76). There is growing evidence, however, that these tools
can under-estimate chronic disease risk in those with SMI. (77) Trials are urgently required to identify why guidelines are not routinely applied in the case of persons with SMI, and the extent to which adherence to guidelines can impact on health indices and outcomes, and how appropriate general population screening tools and guidelines are for patients with SMI.

Patients with SMI are also less likely to receive standard surgical procedures (64-66) and medication (65, 67) for chronic diseases compared to patients without mental disorders, and this in turn supports a link between deficits in usual care and higher rates of mortality. (67) It is difficult to tell the degree to which this is explained by patient or doctor behaviour, or both. Given the apparent efficacy of case management programs in reducing CHD mortality, as reported earlier in this paper, it is likely that patient behaviours such as follow-up with health care professionals can improve treatment access and increases the likelihood of success of such interventions. However it is also possible that doctors are reluctant to offer surgical intervention because of concerns about patient capacity or co-operation, comorbid conditions or risk of developing complications post-operatively. This is a valid concern with higher documented rates of bleeding and septicaemia, and 30-day mortality in patients with schizophrenia following surgery. (10)

Why might these patterns occur? Chronic diseases are underdiagnosed in SMI patients and environmental factors such as lower socioeconomic status alone cannot account for this. (63) Therefore an element of the mental disorder itself (i.e., behaviour of the patient) or barriers to provision of care are responsible for the under-diagnosis and treatment of physical disorders. Although mental health clinicians reported that primary care services should take responsibility for risk factor screening and management, people with SMI favour physical health screening by their mental health care providers. (78) Diffusion of responsibility for mental and physical health care is a major barrier to ensuring adequate care for people with SMI and this has implications for the collaborative management and delivery of health care services. Additional training of physical health care providers to reduce stigma and improve understanding of mental disorders, and that of mental health clinicians on the importance of and delivery of care for physical health care conditions, and the communication and collaboration of all health care providers should be an important goal.

The excessive specialisation of health care providers and lack of consensus over who should take responsibility for the general healthcare needs of patients with mental illness has resulted in a continuing failure to provide appropriate services. (79, 80) In 2008 the World Health Organisation pointed out that, despite the potential of primary prevention and health promotion to prevent as much as 70% of disease burden, resources continued to be targeted to the treatment of physical illnesses once they have already developed. Given that individuals with SMI are more likely to develop chronic disease and experience poorer outcomes, this highly vulnerable group would reap substantial benefit from preventative actions such as screening, monitoring and prompt treatment
for chronic disease risk factors. A first step in implementing this approach would be improving adherence to guidelines for monitoring physical health factors in those prescribed antipsychotic medications.

Strengths and weaknesses

Some limitations should be acknowledged when considering these findings. This is a synthesis of reviews, based on systematic reviews published between 2007 and 2014. It therefore did not include some published trials conducted since these reviews were published, however we considered these when interpreting our findings and they did not alter our conclusions. A degree of judgement was required to classify some interventions into categories. This was because some reviews focussed on an intervention strategy (e.g., general medical advice), even though it formed part of a broader program while others brought together studies where care was delivered via specific platform (e.g., collaborative community care).

The quality of the included reviews varied substantially. Apart from the screening and monitoring of health parameters, however, all categories contained at least two reviews of good to high quality (scores of 8 or higher out of a maximum of 11) and scored on average between 7 and 9. Because of the variability of intervention strategies, outcome parameters, follow-up periods and statistical analyses it was not feasible to conduct statistical analyses necessary for meta-analysis.

A number of reviews were unable to be included because studies reported behavioural change outcomes but not physiological outcomes, for instance those looking at screening programs(81) and smoking cessation programs(43, 82-84). It may be that physiological outcomes are not measured in many cases due to the length of time it would take for any meaningful change in physical health to become apparent (for instance, in the case of smoking-related disease). However, to develop an evidence-base around programs that lead to improved health outcomes, physiological markers of change are required to enable us to draw more direct link between interventions and reduced premature mortality. This gap in our evidence synthesis highlights the importance of longitudinal follow-up of intervention outcomes to permit collection of physiological outcome measures.

Conclusion

The findings of this meta-review are important for practitioners, but also for commissioners and policy makers who set priorities and allocate resources. The health and financial implications of not intervening to reduce important causes of preventable deaths in people with SMI need recognition and remedy. The excess mortality rate is an important marker of general health among persons with SMI. The growing inequity in life expectancy, particularly due to heart disease mortality, underlines
the need for better physical health care programs for this group. Two areas that warrant immediate action are: (1) improving adherence to psychiatric pharmacological guidelines; and (2) improving adherence to guidelines for monitoring metabolic health in those with SMI. There is an urgent need to improve the inequitable screening, monitoring and treatment of chronic disease in people with SMI. Research efforts should focus on filling major evidence gaps regarding the barriers to provision of physical health monitoring in persons with SMI and elucidating the aspects of integrative community care programs that have a positive impact on long-term health outcomes.
Declaration of competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: AJB and KB received part and modest funding by NHS England in order to inform policy; authors report 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.

Contributors

AJB developed the paper concept and the study design, conducted the systematic review, extracted study data, interpreted study findings and drafted and revised the paper. She is the guarantor. MH adjudicated the double-extraction of study findings, helped define intervention categories, interpreted study findings and drafted and revised the paper. YK was the second data extractor, conducted the AMSTAR quality assessment of studies, and drafted and revised the paper. TSB helped develop the study concept, interpreted study findings and drafted and revised the paper. HB conducted the AMSTAR quality assessment of studies, and drafted and revised the paper. KB proposed and jointly developed the paper concept, interpreted study findings and drafted and revised the paper.

Transparency declaration

The lead author (AJB) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.
References


28. Malone D, Marriott S, Newton-Howes G, Simmonds S, Tyrer P. Community mental health teams (CMHTs) for people with severe mental illnesses and disordered personality. Cochrane Database of Systematic Reviews. 2007; (3).


77. Osborn DPJ, Hardoon S, Omar RZ, Holt RIG. 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(2): 143-51.
Database searches
Cochrane library (n=16)
DARE (n=31)
Campbell database (n=0)
DoPHER (n=8)
CINAHL and Medline (n=90)

Manual searches
Citations search (n=4)

All potential articles with duplicates removed. Titles and abstracts examined (n=134)

Reviews excluded because:
Intervention sample not people with SMI* or health outcomes not reported (n=103)

Full text articles examined (n=31)

Reviews excluded because:
Primary outcomes not physiological measures or effect sizes not reported (n=15)

Reviews meeting inclusion criteria (n=16)

* SMI: severe mental illness

Figure 1 Flowchart showing results from systematic search of the literature
Table 1: Summary of review papers that report the effect of interventions on physical health in people with severe mental illness

<table>
<thead>
<tr>
<th>Study group</th>
<th>Intervention(s)</th>
<th>Outcomes*</th>
<th>Review type</th>
<th># studies</th>
<th>Study types</th>
<th>Findings relevant to physical health outcomes</th>
<th>AMST AR score (out of 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental health interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Jones et al (2012) (21)</strong></td>
<td>People with current diagnosis of schizophrenia</td>
<td>CBT</td>
<td>Adverse effect/events including mortality, relapses and hospitalisation</td>
<td>Systematic review &amp; meta-analysis</td>
<td>20 RCTs</td>
<td>Death (2 RCTs) RR=0.57 (95%CI 0.12-2.60)</td>
<td>10</td>
</tr>
<tr>
<td><strong>Von Ruden et al (2008) (20)</strong></td>
<td>People prescribed or taking anti-depressants <em>(not necessarily with SMI)</em></td>
<td>Antidepressants</td>
<td>Cardiovascular events (including mortality)</td>
<td>Systematic review</td>
<td>13 Controlled clinical trials, cohort or case-control studies</td>
<td>Study heterogeneity prevented pooling of summary measures. <em>Includes at least 2 studies where patients had pre-existing CVD (ie depression was subsequent to cardiac disease), 6-7 where no diagnosis SMI was required</em></td>
<td>3</td>
</tr>
<tr>
<td><strong>Weinmann, Read &amp; Aderhold (2009) (19)</strong></td>
<td>Adults with schizophrenia, schizoaffective disorder or other severe mental illness such as bipolar disorder prescribed antipsychotics</td>
<td>Antipsychotic medications</td>
<td>All cause and cause-specific mortality</td>
<td>Systematic review</td>
<td>12 Controlled clinical trials, cohort or case-control studies</td>
<td>Study heterogeneity prevented pooling of summary measures. Antipsychotic dosage and mortality: 3 out of 5 reported a dose effect. Antipsychotic polypharmacy and mortality: 2 out of 4 found an increased risk. No evidence was found for increased mortality in relation to 1st versus 2nd generation antipsychotics.</td>
<td>8</td>
</tr>
<tr>
<td>Integrative community care</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dieterich et al (2010) (29)</strong></td>
<td>Adults with SMI (defined as schizophrenia, schizophrenia-like)</td>
<td>Intensive case management described as a package of care based</td>
<td>Mortality</td>
<td>Systematic review &amp; meta-analysis</td>
<td>38 RCTs</td>
<td>With standard care as the comparator: Any death (9 RCTs) RR=0.84 (95%CI 0.48-1.47); Death</td>
<td>8</td>
</tr>
</tbody>
</table>
disorders, bipolar disorder, depression with psychotic features or/and personality disorder; and not acutely ill)

on: a) the Assertive Community treatment model; b) Assertive outreach model (i.e. multidisciplinary team-based approach); or c) Case management model; with a caseload up to and including 20 people.

Malone et al (2007) (28) People presenting to, or being referred to, adult psychiatric services with SMI
Community mental health team (CMHT) treatment, defined as management of care from a multi-disciplinary, community-based team
Mortality
Systematic review & meta-analysis
3
RCTs
Any death (3 RCTs) RR=0.47 (95%CI 0.2-1.3); Death by suicide/suspicious circumstances (2 RCTs) RR=0.49 (95%CI 0.1-2.2); Death due to physical health (3 RCTs) RR=0.51 (95%CI 0.1-2.0)

Interventions for lifestyle factors

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Diagnosis</th>
<th>Description</th>
<th>Outcome</th>
<th>Method</th>
<th>Studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez-Jimenez (2008) (41)</td>
<td>Patients with schizophrenia taking antipsychotics</td>
<td>Non-pharmacological interventions</td>
<td>Mean change in body weight gain and BMI</td>
<td>Systematic review</td>
<td>10</td>
<td>WMD = -2.56KG (95%CI -3.20 to -1.92kg, p&lt;0.001)</td>
</tr>
<tr>
<td>Cabassa et al (2010) (40)</td>
<td>SMI</td>
<td>Behavioral techniques to improve dietary habits and increase physical activity</td>
<td>Weight loss, systolic blood pressure, diastolic blood pressure, HbA1C levels, triglycerides and central adiposity levels</td>
<td>Systematic review</td>
<td>23</td>
<td>Amongst single-group studies, mean weight loss of 4.3±5.6 pounds. Amongst the quasi-experimental studies, mean weight loss of 5.9±6 pounds. Among the RCTs mean weight loss of 3.7±2.3</td>
</tr>
<tr>
<td>Caemmerer, Correll &amp; Maayan (2012) (36)</td>
<td>Patients using antipsychotic medication</td>
<td>Non-pharmacological interventions</td>
<td>Weight loss or maintenance, insulin and glucose levels, blood lipids and systolic blood pressure</td>
<td>Systematic review &amp; meta-analysis</td>
<td>17</td>
<td>Non-pharmacological interventions resulted in a significant weight change of -3.12kg (95%CI -4.03 to -2.21; 14 studies) and a significant change of BMI of -0.94kg/m² (95%CI -1.45 to -0.43; 16 studies) compared to control. There was significant improvement in insulin levels (3 RCTs) (WMD= -4.93 uIU/mL, p&lt;0.001) and fasting</td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Interventions</td>
<td>Outcomes</td>
<td>Study Type</td>
<td>No. of RCTs</td>
<td>Findings</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
<td>---------------</td>
<td>----------</td>
<td>------------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>Faulkner et al (2007) (42)</td>
<td>Schizophrenia or schizophrenia-like illnesses</td>
<td>Pharmacological and behavioural strategies for reducing weight gain</td>
<td>Weight gain</td>
<td>Systematic review</td>
<td>23 RCTs</td>
<td>No summary measures reported.</td>
</tr>
<tr>
<td>Galletly &amp; Murray (2009) (37)</td>
<td>SMI</td>
<td>Lifestyle interventions targeting weight loss</td>
<td>Weight loss/obesity management</td>
<td>Systematic review</td>
<td>16 Not reported</td>
<td>Significant (p&lt;0.05) within-subject results were reported in 6 of the 11 weight loss studies</td>
</tr>
<tr>
<td>Gierisch et al (2013) (31)</td>
<td>Adults with SMI (schizophrenia or schizoaffective disorder, bipolar, or major depression with psychotic features)</td>
<td>Pharmacological, patient focused behavioural strategies for health behaviours and peer and family support interventions</td>
<td>All-cause mortality, CVD risk factors (glucose level, lipid level), weight control</td>
<td>Systematic review &amp; meta-analysis</td>
<td>35 RCTs</td>
<td>Mean weight loss associated with behavioural interventions was about -3.1 kg (95%CI -4.2-2.1); with anticonvulsants about -5.1kg (95%CI -9.5-0.7); and metformin about -4.1 (95%CI 6.8 to -1.7). In 2 studies metformin was also associated with small improvements in HbA1c. Six of 15 trials evaluating blood lipid levels found significant improvement with treatment (in each case pharmacological).</td>
</tr>
<tr>
<td>Hunt et al (2013) (32)</td>
<td>People with SMI (for example, schizophrenia, bipolar disorder and psychosis) and concurrent problem of substance misuse.</td>
<td>Psychosocial interventions for substance misuse categorised into a) Integrated models of care, b) individual approaches (CBT; Motivational interviewing; Contingency management) and c) Group approaches (skills training).</td>
<td>All-cause mortality</td>
<td>Systematic review &amp; meta-analysis</td>
<td>32 RCTs</td>
<td>Long-term integrated care was not associated with change in risk of death at 3 years (2 RCTs) RR=1.18 (95%CI 0.39-3.57). Motivational interviewing + CBT compared to usual treatment showed no benefit for reducing deaths after an average of 12 months (3 RCTs) RR=0.72 (95%CI 0.22-2.41).</td>
</tr>
</tbody>
</table>

glucose levels (6 RCTs) (WMD= -5.79 mg/dL, p<0.001).
<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Study Details</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Study Type</th>
<th>Studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tosh et al (2014) (30)</td>
<td>Adults with SMI (defined as schizophrenia, schizophrenia-like disorders, bipolar disorder, or serious affective disorders)</td>
<td>General health advice (defined as preventative information or counsel where it is left to the recipient to make the final decision)</td>
<td>Health measures (metabolic criteria and syndrome, heart score and physical work capacity) and adverse events (eg. weight gain, cardiac event, mortality)</td>
<td>Systematic review &amp; meta-analysis</td>
<td>7 RCTs</td>
<td>Death (2 RCTs) RR=0.98 (95%CI 0.27-3.56); Presence of metabolic syndrome (1 RCT) RR=1.25 (95%CI 0.35-4.49)</td>
</tr>
<tr>
<td>van Hessalt et al (2013) (39)</td>
<td>Adults with SMI (included were schizophrenia and psychosis, PTSD or mood disorders, and DSM-IV diagnosis, anxiety disorder or a combination of these)</td>
<td>Behavioural therapies including CBT, structured educational and skill-development programs, peer-led support groups, and improved access to facilities.</td>
<td>Weight, CVD risk factors (cholesterol, Framingham risk score), exercise, smoking, general health scores, diet</td>
<td>Systematic review</td>
<td>22 RCTs</td>
<td>No summary measures reported.</td>
</tr>
<tr>
<td>Verhaeghe et al (2011) (38)</td>
<td>SMI (not defined)</td>
<td>Lifestyle interventions targeting physical activity and eating habits</td>
<td>BMI; change in body weight; general health</td>
<td>Systematic review</td>
<td>14 Not reported</td>
<td>Weighted average weight change based on sample size in the intervention groups was -1.96 ± 1.84 kg (-1.74%) versus +1.77 ± 2.12 kg (+2.28%) in the control groups. Weighted average BMI change based on sample size in the intervention groups was -0.87 ± 0.69 kg/m2 versus +0.64 ± 0.96 kg/m2 in the control groups.</td>
</tr>
</tbody>
</table>

**Screening and monitoring of health parameters**

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Study Details</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Study Type</th>
<th>Studies</th>
<th>Results</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tosh et al (2014) (15)</td>
<td>SMI</td>
<td>Physical health care monitoring</td>
<td>Physical health, adverse effects of treatment</td>
<td>Systematic review</td>
<td>0 RCTs</td>
<td>No summary measures reported.</td>
<td></td>
</tr>
</tbody>
</table>

*Only physiological outcomes are reported here. Reviews may have captured and summarised other outcomes (eg quality of life, psychiatric symptoms, health services use) in addition to those pertinent to this meta-review.*

SMI: severe mental illness; CVD: cardiovascular disease; CBT: cognitive behavioural therapy; RCTs: randomised controlled trials; SSRIs: selective serotonin reuptake inhibitors; BMI: Body mass index.