



Diabetes and cardiovascular risk in severe mental illness: a missed opportunity and challenge for the future

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Introduction

Schizophrenia and bipolar disorder are major psychiatric disorders altering perception, thought, affect and behaviour and are characterised by intermittent loss of insight. The life-time prevalence of schizophrenia and bipolar illness is approximately 1–2%^{1–3} with a point prevalence for schizophrenia of 1 in 200–700 individuals.⁴ In this article the term severe mental illness (SMI) refers collectively to schizophrenia and bipolar disorder.

Individuals with SMI have a 3-fold increased risk of premature death and shortened life expectancy of approximately 10–20 years.^{5,6} Although suicide accounts for the highest relative risk of mortality, being up to 20-fold more common than in the general population,⁷ around three-quarters of deaths in people with SMI are caused by physical illness, and cardiovascular disease (CVD) is the most common cause of death.⁵

This review will examine the prevalence and aetiology of diabetes and CVD in people with SMI, and review the steps that can be taken to reduce the burden of physical disease in these individuals.

Methods

PubMed and other electronic databases were searched to identify articles that included the key words: diabetes, CVD, psychosis, schizophrenia, bipolar illness, antipsychotic, and each individual antipsychotic drug name.

ABSTRACT

Schizophrenia and bipolar illness are severe mental illnesses that affect around 1–2% of the population. They are associated with premature mortality with a reduced life-expectancy of 10–20 years. Although suicide and trauma contribute the highest relative risk of mortality, physical illness accounts for around three-quarters of all deaths, with cardiovascular disease being the most common cause of death. Traditional cardiovascular risk factors including diabetes, dyslipidaemia, obesity and smoking are all more common in people with severe mental illness (SMI).

Although there has been an increasing awareness of physical health issues in people with SMI, the level of screening for and management of cardiovascular risk factors has remained low. A number of national and international bodies have developed guidelines to address the challenge of physical morbidity in SMI. The principles of screening for and managing cardiovascular disease in people with SMI are similar to those in the general population, but there are additional challenges. Health care professionals within psychiatry, general practice and medical specialties need to work together to reduce the burden of physical health problems in people with SMI. Copyright © 2010 John Wiley & Sons.

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KEY WORDS

severe mental illness; dyslipidaemia; diabetes; obesity; smoking; cardiovascular disease; antipsychotics

Cardiovascular disease (CVD) in severe mental illness

Prevalence of CVD

The prevalence of CVD is increased approximately 2- to 3-fold in people with schizophrenia and bipolar illness, particularly in younger individuals.^{5,8–10} A retrospective cohort study of 46 136 people with SMI showed that the rates of CVD in those younger than 50 years old were 3.6-fold higher in those with schizophrenia and 2.1-fold higher in people with bipolar disorder compared with the general population.¹¹ The risk of stroke was 2.9- and 3.3-fold higher in people with schizophrenia and bipolar illness respectively.

Similarly, cardiovascular mortality is increased; in a systematic review that included nearly 23 000 deaths

in 37 studies undertaken in 25 countries, the all-cause standardised mortality rate (SMR) was 2.6-fold higher in people with schizophrenia than that in the general population.¹² Analysis by cause of death showed that the SMRs for natural, unnatural and cardiovascular causes were 2.4, 7.5 and 1.8 respectively. These SMRs have increased over the last 30 years, indicating widening health inequalities for people with SMI.¹² Increased SMRs ranging from 1.2–2.5 have also been found in large studies of people with bipolar disorder.¹³

Aetiology of CVD

Much of the excess CVD can be attributed to a higher prevalence of modifiable risk factors such as obesity, smoking, diabetes, and

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dyslipidaemia (Table 1).⁸ Sixty-eight percent of the 689 people with schizophrenia who participated in the US Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study were smokers compared to 35% of age-matched controls, 13% had diabetes *vs* 3% of controls and 27% *vs* 17% had hypertension.¹⁴ HDL cholesterol concentrations were significantly lower than those of the general population, while overall approximately one-third of subjects fulfilled the NCEP-ATPIII criteria for the metabolic syndrome at baseline.¹⁴ The mean baseline BMI in the CATIE study was 29.7 kg/m² with 36.6% of men and 73.4% of women having central obesity as defined by a waist circumference in excess of 102 cm and 88 cm respectively.¹⁴ The risk factors also appear at a younger age: in the CATIE study, over a quarter of male subjects aged 20–29 years and nearly a half of those aged 30–39 years had the metabolic syndrome at baseline (Figure 1).

In addition to the increased prevalence of known diabetes, the rates of undiagnosed diabetes are reported as being up to 70%, which may lead to prolonged periods of poor glycaemic control.^{15–19} The high rate of undiagnosed diabetes was first recognised in Singapore¹⁵ but this finding has been replicated in Europe and North America.

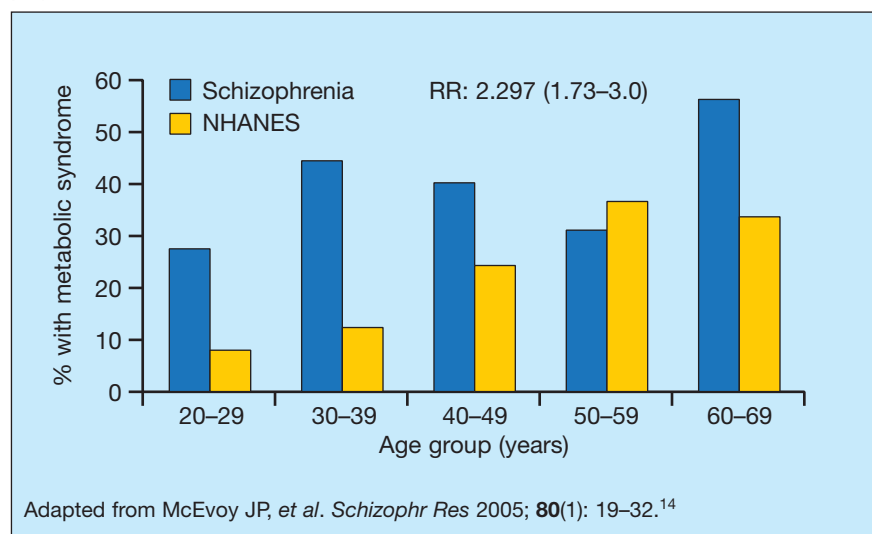
Some risk factors, however, are not markedly different in people with SMI. A meta-analysis of 12 papers on hypertension and 11 on dyslipidaemia found that hypertension was not significantly increased and neither was total cholesterol. However, most, but not all, studies report lower levels of HDL cholesterol and hypertriglyceridaemia.²⁰

Traditional risk factors do not appear to account for all of the excess risk, suggesting that there may be specific disease and/or treatment effects. Increased circulating concentrations of cortisol and catecholamines, and immunological alterations, such as altered cytokine expression, are often seen in psychotic illnesses and may provide a putative mechanism by which psychiatric disease itself contributes to the pathogenesis of CVD.^{21–23}

Table 1. Estimated prevalence of modifiable cardiovascular risk factors in people with schizophrenia and bipolar illness and relative risk compared with the general population

Modifiable risk factor	Schizophrenia		Bipolar illness	
	Prevalence	Relative risk	Prevalence	Relative risk
Smoking	50–80%	2–3	54–68%	2–3
Dyslipidaemia	25–69%	≤5	23–38%	≤3
Diabetes	10–15%	2–3	8–17%	1.5–3
Hypertension	19–58%	2–3	35–61%	2–3
Obesity	45–55%	1.5–2	21–49%	1–2
Metabolic syndrome	37–63%	2–3	30–49%	2–3

Figure 1. Prevalence of the metabolic syndrome by age in men with schizophrenia participating in the US Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study compared with the general population data from the NHANES database



Antipsychotic medication and CVD risk factors

There are concerns that antipsychotic medication may contribute to cardiovascular risk through weight gain. This is a well recognised side effect affecting between 15–72% of patients.²⁴ Antidepressants and mood stabilising drugs, such as lithium and valproate, may also induce weight gain albeit to a lesser extent.

There is a differential risk of weight gain between second generation (atypical) antipsychotics: clozapine and olanzapine have the highest risk, while quetiapine and risperidone have an intermediate risk, and aripiprazole, amisulpride

and ziprasidone have little effect on weight.²⁵ However, as the proportion of individuals experiencing more than 7% weight gain is greater with any second generation antipsychotic than placebo, no agent should be considered as truly weight neutral.²⁴ Some of the first generation antipsychotics – for example, chlorpromazine – are also associated with a comparably high risk of inducing weight gain. On an individual level, the change in weight in response to treatment with an antipsychotic is variable and largely unpredictable.

Prospective studies show that antipsychotic treatment is associated with an increase in LDL cholesterol



and triglycerides and a decrease in HDL cholesterol, the magnitude of which appears to reflect the propensity for weight gain of the individual antipsychotic drug. The effect on triglycerides is the most marked and there have been reports of elevations in triglycerides despite only modest weight gain, suggesting there may be a direct antipsychotic effect over and above that mediated by weight gain.²⁶

There is no consistent association between SMI and hypertension, possibly because weight gain and adrenergic blockade by the antipsychotics have opposing effects on blood pressure.²⁰

The use of antipsychotics is associated with an increased risk of diabetes, but the degree to which this reflects a drug effect remains controversial.²⁷ There are flaws in the methodology used to evaluate risk which make it difficult to draw firm conclusions. The association of diabetes and mental illness has been recognised for well over a century and abnormalities in insulin action were observed in the 1920s, well before the introduction of antipsychotic medication. This, coupled with observations of metabolic abnormalities in individuals with first-episode psychosis, suggests that individuals with SMI are at increased risk of diabetes independent of treatment.²¹ As many individuals change medication frequently during their illness, it is difficult to tease out a drug effect from the underlying risk associated with the illness.

Observational studies suggest that although there is an increased risk of diabetes in people receiving antipsychotics compared with the general population, this risk is small with little difference between drugs.²⁷ A meta-analysis of observational studies showed that there was a 1.3-fold increased risk of diabetes in people with schizophrenia taking second generation antipsychotics compared with those receiving first generation antipsychotics.²⁸ In a further systematic review of observational cohort studies, the attributable risk for individual second generation antipsychotics compared with first generation antipsychotics ranged from 5.3% more to 4.6%

fewer cases of diabetes with little observable difference between individual antipsychotics.²⁹ A systematic review of 22 prospective randomised controlled trials also found no significant differences in treatment-emergent glucose abnormalities in those taking second generation antipsychotics compared with any comparator antipsychotic or placebo.³⁰

Although these data are encouraging, some caveats are needed: there are individual cases of diabetes and diabetic ketoacidosis that have occurred following treatment with antipsychotic medication, including some that have recurred following re-challenge with the antipsychotic.³¹ Furthermore, in several randomised controlled trials, increases in blood glucose have suggested differences between drugs. In the CATIE study, for example, glycated haemoglobin (HbA_{1c}) increased to a greater extent with olanzapine (0.4%) compared with quetiapine (0.04%), risperidone (0.07%), perphenazine (0.09%) and ziprasidone (0.11%).³² If these small short-term changes persist with longer treatment, they may translate into clinically meaningful differences in the rates of diabetes between drugs. It is important to know about even small differences between drugs, since many patients will start treatment in early adulthood, and may remain on medication for much, if not most, of their adult lives. Furthermore, given our understanding of the relationship between obesity and diabetes, it is likely that where there is significant antipsychotic-induced weight gain leading to obesity over a prolonged period of treatment, this may contribute to the development of diabetes.

Effects of antipsychotics on mortality

Overall, it appears that antipsychotics have an adverse effect on several cardiovascular risk factors, but this needs to be placed in the context of their use. Antipsychotics have been the mainstay of the treatment of schizophrenia since their development in the 1950s and there is no credible debate amongst clinicians that people with SMI require pharmacotherapy as an integral

part of their treatment. Long-term treatment is needed to prevent relapse as individuals, who are well stabilised on medication, develop high rates of relapse when their antipsychotic therapy is discontinued³³ or switched to placebo.³⁴

It is also informative to examine the effects of antipsychotics on all-cause and CVD mortality. A naturalistic study of all 2230 patients diagnosed with schizophrenia in Finland showed that untreated individuals had a 12.3-fold higher risk of dying, a 37.4-fold increased risk of suicide, and a 23–59% higher risk of hospital re-admission compared with patients taking antipsychotics.³⁵ Using the same nationwide register in Finland, the effect of the atypical antipsychotics on mortality in 66 881 people with schizophrenia was subsequently compared with the total Finnish population of 5.2 million. Compared with perphenazine, a first generation antipsychotic, the adjusted hazard ratios for all-cause mortality ranged from 1.41 (95% CI 1.09–1.82) for quetiapine to 0.74 (0.60–0.91) for clozapine.³⁶ When long-term exposure was assessed, treatment with any antipsychotic was associated with lower mortality than no treatment. After adjustment for confounders, including the severity of psychiatric illness, clozapine and olanzapine were associated with the lowest mortality, despite these drugs being associated with the most weight gain. There was no difference in cardiovascular deaths between drugs.

A large UK study of 46 136 people with SMI and 300 426 healthy controls showed that people with SMI had an increased risk of coronary heart disease (CHD) and stroke. Those prescribed antipsychotics were at a higher risk, with the highest doses being associated with the highest risk of CVD death. Exposure to second generation antipsychotics, however, was not related to CHD mortality. Compared with the healthy control group, the fully adjusted hazard ratios for CHD death were 1.38 for those not prescribed any antipsychotics, 0.86 for those ever prescribed atypical antipsychotics, and 2.12 for those receiving conventional antipsychotics only (Figure 2).¹¹



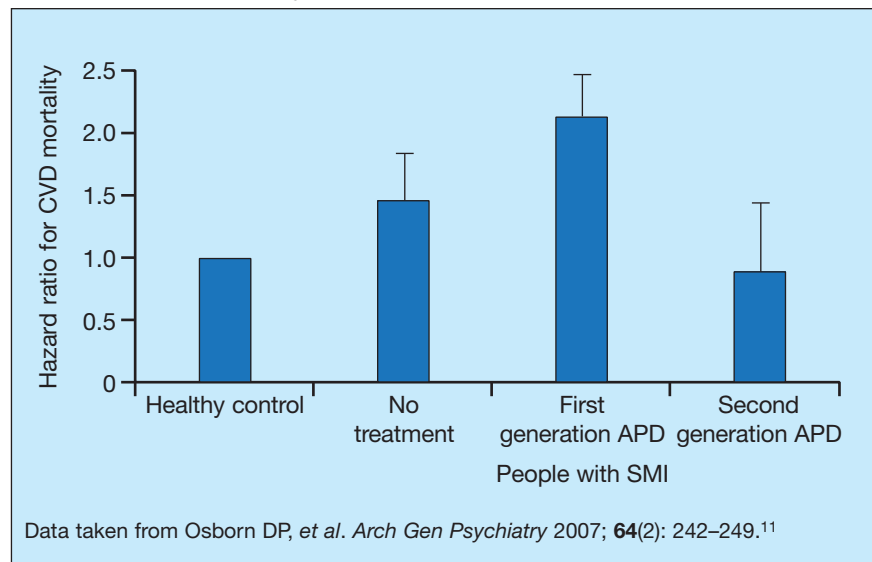
Screening and managing CVD risk factors: a missed opportunity

Over the last decade, there has been an increasing awareness of the issue of physical health in people with SMI, and both national and international groups have developed screening and monitoring guidelines.^{37–42} The National Institute for Health and Clinical Excellence (NICE) guidance places the primary responsibility for physical health screening with primary care (Box 1).^{37,38} Registers should be developed in primary care to facilitate the monitoring of the physical health of people with SMI. This should be assessed at least annually with a focus towards diabetes and CVD risk. Where individuals are at high risk, they should be actively managed in line with NICE guidance for the rest of the population. It is important that physical health care is well coordinated between primary and secondary care services. Any results undertaken in primary care should be communicated to psychiatry services. Furthermore, there is a responsibility for health care professionals in secondary care to ensure that people with schizophrenia receive physical health care from primary care, and this should form part of the clinical care plan.

This recommendation should ensure that all people with SMI receive the screening they need, but in reality this is not happening. There remains uncertainty about who within the clinical team should take responsibility for the screening,⁴³ and this confusion is compounded by poor access to basic equipment and lack of confidence about the interpretation of abnormal results within mental health settings. Although people with SMI report the same level of interest in their cardiovascular health,⁴⁴ they are less likely to take up opportunities for preventative medical care and screening.⁴⁵

Even where cardiovascular risk factors are detected, there is evidence of undertreatment. In the CATIE study, the number of patients with dyslipidaemia, hypertension and diabetes receiving no treatment for these problems was 88%,

Figure 2. Hazard ratios for cardiovascular disease in a large UK study of 46 136 people with SMI and 300 426 healthy controls. People with severe mental illness (SMI) who are receiving no medication or first generation antipsychotics (APD), but not second generation antipsychotics, had an increased risk of coronary heart disease and stroke



62% and 38% respectively.⁴⁶ In a European study of 2463 people with schizophrenia only 10.9% of patients were being treated for hypertension, 7.1% for a lipid disorder, and 3.5% for type 2 diabetes, despite biochemical evidence of hyperglycaemia and dyslipidaemia in 26% and 70% of patients respectively and clinical evidence of untreated hypertension in 39%.⁴⁷

In our own study of 71 people with SMI, 12% had a CVD risk score in excess of 20%, the threshold for primary preventative medication.¹⁹ None of the patients was receiving aspirin, only two had been prescribed lipid lowering medication, and one patient was receiving anti-hypertensive treatment.

Assessment of cardiovascular risk

The principle of cardiovascular risk assessment is similar to that of the general population and involves the application of age, sex, smoking status, systolic blood pressure and total cholesterol, or the ratio of total to HDL cholesterol, to locally relevant risk engines.⁴⁸ It should be acknowledged, however, that people with SMI are typically younger, have higher blood pressure and are more likely to be smokers than the populations used to derive CVD risk scoring

systems, such as Framingham and SCORE. Furthermore, as traditional risk factors do not wholly explain the excess CVD seen in people with SMI, traditional risk engines may ignore important but unmeasured factors and therefore underestimate the risk of CVD in people with SMI, and lack sensitivity to detect people with SMI at high risk of CVD. There is no reason, however, to suggest that they overestimate the risk and therefore, if a high-risk individual is identified, primary prevention should be instituted. Further research is needed to validate the current risk engines in people with SMI.

It is particularly important that clinicians assess CVD risk before the initiation of antipsychotic medication to monitor any subsequent metabolic effects. The suggested frequency of further testing varies slightly according to different guidelines but will depend on the patient's medical history and the prevalence of baseline risk factors. Most tests should be repeated about three months after the initiation of treatment, and at least annually thereafter. During the initial phase of treatment, it is important to measure weight weekly to identify those individuals who gain weight rapidly with antipsychotics.



Box 1. National Institute for Health and Clinical Excellence recommendations regarding management of physical illness in people with schizophrenia³⁷

11.4 Promoting recovery
11.4.1 Primary care
11.4.1.1 Develop and use practice case registers to monitor the physical and mental health of people with schizophrenia in primary care
11.4.1.2 GPs and other primary healthcare professionals should monitor the physical health of people with schizophrenia at least once a year. Focus on cardiovascular disease risk assessment as described in 'Lipid modification' (NICE clinical guideline 67) but bear in mind that people with schizophrenia are at higher risk of cardiovascular disease than the general population. A copy of the results should be sent to the care coordinator and/or psychiatrist, and put in the secondary care notes
11.4.1.3 People with schizophrenia at increased risk of developing cardiovascular disease and/or diabetes (for example, with elevated blood pressure, raised lipid levels, smokers, increased waist measurement) should be identified at the earliest opportunity. Their care should be managed using the appropriate NICE guidance for prevention of these conditions
11.4.1.4 Treat people with schizophrenia who have diabetes and/or cardiovascular disease in primary care according to the appropriate NICE guidance
11.4.1.5 Healthcare professionals in secondary care should ensure, as part of the Care Programme Approach, that people with schizophrenia receive physical healthcare from primary care as described in recommendations 11.4.1.1–11.4.1.4

Management of CVD risk factors

The management of diabetes and cardiovascular risk factors in people with SMI is also similar to that in the wider population, but there are additional challenges to ensure that the person with SMI understands the need for lifestyle modification and medication.

Smoking

Smokers should be encouraged to quit and individuals should be referred to appropriate health services to promote this. It is important to ensure that the person with SMI is aware of the risks of smoking because basic medical education is frequently missing in this patient group. Behavioural counselling as well as pharmacological approaches, such as nicotine replacement, can be used in people with SMI. In addition to individual approaches, it is important to change the culture of

smoking in psychiatric institutions, where tobacco has been used as an anxiolytic in the past. Health care professionals should set an example by refraining from smoking on psychiatric wards and at clinics.

Obesity

The management of obesity is difficult, but the previous nihilism surrounding treatment has been challenged by a number of observational studies and randomised controlled trials of lifestyle and pharmacological interventions.^{49–51} A meta-analysis of 10 randomised trials involving 482 patients demonstrated that non-pharmacological interventions for two to six months were associated with a reduction in mean body weight of around 2.5kg.⁴⁹ Although these results are encouraging, obesity management should be seen as 'a marathon rather than a sprint', and it is encouraging that longer observational studies

have demonstrated that further weight loss is achievable with ongoing support.⁵²

Given the frequent lack of basic medical education, even simple advice can lead to meaningful changes in behaviour. In the longest running weight management clinic for people with SMI, the only predictor of weight loss was continued attendance at the clinic, emphasising the need to engage the patients in the process and to design programmes without a defined end-point.⁵²

A range of unlicensed pharmacological treatments have been tried to treat or prevent antipsychotic-induced weight gain.⁵¹ Most treatments have only limited effectiveness while some may have adverse effects on mental state. There is preliminary evidence from short-term studies that metformin may attenuate weight gain in both adult and adolescent patients taking antipsychotics and, indeed, one recent controlled trial suggested that metformin is more effective than lifestyle interventions.^{53,54} A recent systematic review including 495 patients found that metformin led to reduction in weight or attenuation of weight gain in 10 out of 11 studies.⁵⁵ While longer more definitive trials are needed, metformin may be considered in patients with additional risk factors, such as a personal or family history of metabolic dysfunction.⁸

It is worth considering switching antipsychotics, particularly when the therapeutic response to the antipsychotic is limited. Several studies have shown that switching from olanzapine to either quetiapine or aripiprazole is associated with weight loss.^{56–58} This switch should be undertaken with care as it may also be associated with a worsening of the psychiatric illness and many patients will not tolerate the switch. Adding aripiprazole to existing treatment with olanzapine has also been tried,⁵⁹ although an expensive combination, this was associated with significant weight loss without worsening of the mental state.

Dyslipidaemia

Target levels of total cholesterol and LDL cholesterol are the same as those for the general population



(<5mmol/L and <3mmol/L respectively) but more rigorous goals of <4.0mmol/L and <2.0mmol/L are appropriate for individuals with established CVD or diabetes.

Diet modification to replace saturated fat with monounsaturated and polyunsaturated fats from vegetable and fish oils should be encouraged, not least because this may also have a beneficial effect on the psychosis of individuals with SMI. Where there is a high CVD risk, pharmacotherapy, most likely with a statin, will be required. Although no CVD outcome trials have been performed in people with SMI, several studies have demonstrated that statins are effective in the management of dyslipidaemia in patients with SMI.⁶⁰ Despite the former anxiety that lipid lowering medication may be associated with suicide or traumatic deaths, there is no evidence that this is a concern for people with SMI.

Diabetes

Most individuals with SMI have type 2 diabetes and the currently available treatment algorithms appear appropriate for people with SMI. Oral hypoglycaemic agents with less weight gain may have advantages because of the high prevalence of obesity in people with SMI.

Insulin treatment should be initiated and monitored by health care professionals with expertise in diabetes management. Special care, including the involvement of the patient's family and carers, should be taken to prevent hypoglycaemia in patients on insulin treatment.

Many health care professionals working in diabetes clinics lack the necessary skills to address the mental health needs of people with SMI. While this is important for all aspects of CVD prevention, it is particularly important for diabetes management where the philosophy is to empower the person with diabetes to self-manage their condition. Similarly, many psychiatry teams do not have the knowledge to manage diabetes and so close collaboration between mental and physical health services is needed.

In order to control the diabetes effectively, the patient needs to understand the condition and its

Key points

- Cardiovascular disease and diabetes occur more commonly and at an earlier age in people with severe mental illness compared with the general population
- Much of the excess CVD can be attributed to a higher prevalence of modifiable risk factors
- Antipsychotics form an essential component of the treatment of people with severe mental illness. Although antipsychotics may worsen CVD risk factors, overall they reduce mortality
- Screening and treatment of modifiable risk factors will reduce the burden of CVD in people with severe mental illness
- Close collaboration between mental and physical health services is essential to achieve this

management. Consequently, there is a need to treat the psychosis and sometimes the effect of an antipsychotic on weight needs to be carefully balanced with effective treatment of the mental illness.

Lifestyle intervention programmes involving dietary modification, weight loss and increased physical activity are effective in the prevention of type 2 diabetes.^{61,62} As the principles of these programmes are similar to those used in the lifestyle modification programmes in people with SMI to achieve weight loss, it is hoped that these may also lead to diabetes prevention in people with SMI although this has not been formally assessed.

Metformin is associated with a reduction in incident diabetes and a Consensus Development Panel recently recommended the use of metformin for very-high-risk individuals to prevent diabetes.⁶³ There is evidence from short-term studies that metformin improves insulin sensitivity, glucose and HbA_{1c} in people with SMI, but longer studies are needed.^{53,55}

Hypertension

The management of hypertension in SMI is the same as that in the general population, with target blood pressure levels of <140/90mmHg being recommended. Lifestyle modification to reduce smoking and salt intake are important first steps but some patients may require pharmacological therapy. European and UK guidelines stress the importance of choosing antihypertensive agents best suited to individual patient's needs as the achieved blood pressure is more important than the agent used to achieve this.

Conclusion

Rates of diabetes and CVD are increased in people with SMI. Although the mental illness and its treatment contribute to this excess risk, traditional CVD risk factors play a more important role. The screening for and management of traditional CVD risk factors have largely been ignored in people with SMI and this has created significant health inequalities.

The prevention of CVD in people with SMI is similar to that in the general population. It is not a question of complex interventions but the systematic introduction of screening and management of CVD risk factors. Doing the simple things well may be just what is needed to reduce CVD in SMI. This will necessitate closer working between psychiatrists, general practitioners and hospital diabetologists and cardiologists.

Conflict of interest statement

Professor Holt has undertaken lectures for Astra Zeneca, Eli Lilly, GlaxoSmithKline, and Novo Nordisk. He has served on advisory boards for Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, and Novo Nordisk. He has received funding to attend conferences from Astra Zeneca, Eli Lilly, GlaxoSmithKline, and Novo Nordisk. Professor Peveler has received fees for speaking from Eli Lilly and Astra Zeneca. He has served on advisory boards for Bristol-Myers Squibb. He has received support to attend conferences from Eli Lilly and Schering Plough.

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