Are there modifiable risk factors which will reduce the excess mortality in schizophrenia?

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Abstract

The 2009 World Health Organization report on global health risks identifies hypertension, smoking, raised glucose, physical inactivity, obesity and dyslipidaemia, in that order, as being the top six modifiable global mortality risk factors. Patients with schizophrenia have high levels of all these risk factors. There are a small number of studies showing that interventions can improve these, but prospective long-term studies are not available to show their impact on mortality. A number of studies are now supporting the view that patients with schizophrenia may be dying prematurely as they are not gaining access to or receiving the same medical care as the general population. The literature now suggests that low cardiorespiratory fitness and muscle strength are among the strongest predictors of all-cause mortality in the general population. Smoking is still one of the largest risk factors for premature all-cause mortality. The literature supports the thesis that lifestyle intervention programmes addressing exercise, smoking cessation and compliance with medication are likely to have significant impact on mortality in schizophrenia. It will be important to ensure that all patients with schizophrenia have advocates to ensure appropriate treatment and avoid prejudice, and to establish fitness standards in schizophrenia.

Keywords

Cardiorespiratory fitness, modifiable risk factors, mortality, prejudice, schizophrenia, stigma, weight management

Introduction

In 1911 Bleuler described the group of schizophrenias. He describes the lives of sufferers as unbearable because of their symptoms, including their 'Suicidal Drive' (Bleuler, 1950). The introduction of neuroleptic drugs has been associated with reduced suicide rates in those taking them (Tiihonen et al., 2006), and most live out of institutions. Many are in sexual relationships and are employed, even in the professions, with great variation in different countries (Marwaha et al., 2007). However, schizophrenia sufferers lose approximately 25 years of life (Kilbourne et al., 2009). It now behoves the body of mental health professionals to recognize the factors leading to the excess mortality and find appropriate preventative measures.

It has long been known that patients with schizophrenia have a higher prevalence of diabetes mellitus than the general population (Osborn et al., 2008), but more recently evidence has emerged describing changes such as shortened telomere length, which are also found in the elderly population and smokers (Fernandez-Egea et al., 2009; Kirkpatrick et al., 2008). How many of these features are innate and how many are due to environmental factors such as smoking is as yet unclear.

Research in Finland suggests that the early death rate from suicide, accident, violence and neglect may be largely preventable (Tiihonen et al., 2006). Those patients taking neuroleptics after discharge from hospital have a very much reduced mortality from these factors compared with those taking no antipsychotic medication. However, at the other end of life, these patients are dying prematurely from the same conditions as the general population: vascular disease including coronary and cerebral infarction, cancers, respiratory, metabolic and kidney disease and more rare conditions (Saha et al., 2007).

The epidemic of premature deaths in the West from heart disease in the 1950s and 1960s focussed medical attention on heart disease. Heart disease now accounts for less than 20% of mortality (Flegal et al., 2007). Commentators are now calling for the general factors that reduce all-cause mortality in the general population to be emphasized, including aerobic fitness, low blood pressure and non-smoking, which are more important even than weight and cholesterol (Blair, 2009). It is noteworthy that these are all modifiable features of healthy living. We know that schizophrenia patients who have signs similar to premature ageing are more vulnerable to these diseases (Kelly et al., 2000). Without contrary evidence, we must assume that they are equally sensitive to healthy modification of their lifestyle and appropriate

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medical management. With the move to specialist first-episode units for schizophrenia, there is a unique opportunity to set up long-term prospective studies to quantify baseline factors related to physical status and the impact of improved lifestyle and assertive management of both psychiatric and medical morbidity.

This paper will review the schizophrenia literature to examine to what extent modifiable risk factors cause the excess mortality and can be managed.

Method

A search was carried out in Medline, Embase and PsycINFO using the terms: schizophrenia and mortality and modifiable (OR reduction OR intervention). The search strategy covered the period 1987 until January 2010. Papers were included from the literature search which examined the link between schizophrenia and mortality and modifiable risk factors. Papers included in this review were limited to systematic reviews and meta-analyses when available; otherwise high-quality studies were reported if possible. Papers were excluded from the literature which included drug abuse and violence. In addition, the literature was non-systematically reviewed to examine the importance of mortality risk factors in the general population and whether these can be reduced in patients with schizophrenia. The search was not carried out to the standards of the Moose checklist, as no contacts with authors were made, and no attempt was made to identify unpublished work or search non-English-language journals.

Results

The literature search identified 974 papers and findings from these papers plus hand searches are described under the following headings:

- Excess mortality in schizophrenia
- Modifiable mortality risk factors in the general population
- Modifiable mortality risk factors in schizophrenia

- Non-modifiable mortality risk factors in schizophrenia
- Review of studies in schizophrenia designed to reduce mortality
- Can one reduce the mortality risk factors in schizophrenia?

Excess mortality in schizophrenia?

Systematic reviews show that patients with schizophrenia are at higher risk of mortality than the general population but are dying of the same causes (Leucht et al., 2007; Saha et al., 2007). Saha et al. reported that the median standardized mortality rate (SMR) for all-cause mortality was 2.58, with suicide having the highest SMR of 12.86, and the SMRs for cardiovascular and cancer deaths were 1.79 and 1.37, respectively. Saha et al. highlighted a widening mortality gap for patients with schizophrenia than the general population, which was possibly related to people with schizophrenia having not fully benefited from the improvements in health treatments available to the general population. This view is supported by the finding from Saha et al. that over the three-decade period for this study, case fatality rates in schizophrenia have remained constant, whereas in the general population these have in general declined. However, Leucht et al. report that stigma may also play an important role, denying patients access to the best medical care (Leucht et al., 2007). An earlier review of the excess mortality of mental disorders (Harris and Barraclough, 1998) showed the SMRs in schizophrenia for all-cause mortality to be 1.57, and cardiovascular and cancer deaths accounted for the largest number of deaths with SMRs of 1.04 and 1.00, respectively. Differences in the SMRs between these two reviews and others may be related to the differences in the timeframe of the studies included. This view is supported by changing mortality patterns reported in the general population for cancer and heart disease over the period 1975 to 2004 (Capewell et al., 1999; Jemal et al., 2008). The widening gap in cardiovascular deaths reported by Saha et al. may partially be associated with different historic smoking patterns (Saha, et al., 2007). Table 1 collates SMRs for patients with schizophrenia and smokers in the general population, showing

Table 1. Standardized mortality ratios (SMR) by disease category in schizophrenia studies and in cigarette smokers in the general population

Causes of death by disease category	SMR (95% CI) Schizophrenia (Harris and Barraclough, 1998) Systematic Review	SMR (10–90% Quantile) Schizophrenia (Saha et al., 2007) Systematic review	SMR (95% CI) Schizophrenia (Tran et al., 2009) Prospective Cohort study $n = 3470$, 11 yrs	SMR (95% CI) Schizophrenia (Brown et al., 2010) Prospective linkage study $n = 370$, 25 yrs	SMR (95% CI) Male cigarette smokers in the general population (Harris and Barraclough, 1998) Population = >18,450 Approximately 40 yrs
All-cause mortality	1.57 (1.53–1.60)	2.58 (1.18–5.76)	3.6 (3.3–3.9) males 4.3 (3.7–5.1) females	2.89 (2.47–3.37)	1.97 (1.92–2.02)
Circulatory	1.04 (1.00–108)	1.79 (1.10–3.60)	NOT GIVEN	2.58 (1.95–3.34)	1.85 (1.79–1.91)
Neoplasms	1.00 (0.95–1.06)	1.37 (0.71–2.40)	1.5 (1.20–1.90)	1.49 (1.00–2.12)	2.21 (2.10–2.32)
Respiratory	2.30 (2.13–2.48)	3.19 (2.20–9.30)	NOT GIVEN	4.99 (3.26–7.31)	2.97 (2.72–3.22)
Digestive	1.86 (1.64–2.09)	2.38 (1.79–17.5)	NOT GIVEN	2.89 (1.16–5.96)	2.84 (2.24–3.57)

similar raised SMRs across all disease categories except for neoplasms, which are raised further in smokers. These observations add support to the argument that a high percentage of the excess mortality in schizophrenia is possibly smoking related. A significant limitation with most of the mortality reviews, including those of Saha et al. and Harris et al., is their retrospective nature (Harris and Barraclough, 1998; Saha et al., 2007).

One of the first modern prospective studies measuring mortality in schizophrenia comes from France (Tran et al., 2009). This was an 11-year prospective study which showed an SMR for all-cause deaths to be 3.6 (men) and 4.3 (women). Suicide (4.2%) accounted for the greatest number of deaths, followed by cancer (2.2%) and then cardiovascular disease (2.0%). Lung cancer was the main cancer killing males (SMR 2.2), with breast cancer being the main cancer killing females (SMR 2.8). The hazard ratio (HR) for all cancer deaths in smokers was HR = 2.59, which is similar to the findings in smokers in the general population, HR = 2.21 (Table 1). A UK 25-year prospective linkage study shows a similar mortality pattern, with an all-cause mortality SMR of 2.89, lung cancer SMR of 2.65, breast cancer SMR of 1.96, cardiovascular disease SMR of 2.25 and suicide with a very high SMR of 18.18 (Brown et al., 2010). This study also showed higher SMRs in smokers (SMR 3.79, 95% CI 3.31–4.59) than in non-smokers (SMR 1.94, 95% CI 1.25–2.86), and that mortality was twice as high in smokers than in non-smokers (Relative Risk (RR) 2.16, 95% CI 1.31–3.59). Smoking-related diseases accounted for 70% of the excess natural-cause mortality in this schizophrenia population. Some 73% of the schizophrenia cohort in Brown et al.'s study smoked, whereas only 53% of the cohort in Tran et al.'s study smoked, and this may partially explain the higher SMR for lung cancer in the study from Brown et al. (SMR 2.65 vs. 2.10, respectively). Over the 25-year period of Brown et al.'s study, smoking in the general population fell from 39% to 25%, whereas there was no change in the smoking pattern in the patients with schizophrenia. Brown et al. argue that the continued high rates of smoking in the patients with schizophrenia is likely to explain much of the excess cardiovascular mortality.

There are some differences in SMRs between the prospective studies of Brown et al. and Tran et al. which are not easily understood. For example, these two recent prospective studies show contrasting findings regarding cancer in women, with the Brown study showing an SMR of 1.02, whereas Tran et al. showed a figure of 1.9 (Brown et al., 2010; Tran et al., 2009). This difference may be a chance finding, as the Brown study was roughly ten times smaller than the Tran study.

There is consistency among most of the epidemiological mortality findings, with SMRs being raised for both natural and unnatural causes in schizophrenia. However, a number of studies have found that the increased cancer or heart disease mortality cannot always be explained by increased incidence, which suggests that the excess deaths are at least partially associated with poorer patient access to, and poorer quality of, health care (Kisely et al., 2007, 2008; Laursen et al., 2009; Lawrence et al., 2000).

Modifiable mortality risk factors in the general population

Modifiable mortality risk factors can be defined as risk factors for mortality for which the means to reduce them are known. The World Health Organization (WHO) (2009) report identified the chief global risks for mortality as high blood pressure (13% of deaths globally), tobacco (9%), high blood glucose (6%), physical inactivity (6%), overweight/obesity (5%) and high cholesterol (5%). Blair published a ranking of attributable risk factors for mortality (Blair, 2009), which was different to the WHO (2009) report. He ranked physical inactivity as the leading attributable cause of mortality (16% and 17% in men and women, respectively), and diabetes, obesity and lipids had lower attributions (<4%). The differences in the ranking may relate to the fact that the WHO (2009) report does not include research published after 2004, including the western population studied by Blair's research team. The meta-analysis of cardiorespiratory fitness (CRF) studies (Kodama et al., 2009) demonstrated the importance of CRF, which was not only related to cardiovascular mortality but also correlated with all-cause mortality. These six risk factors are discussed below.

Physical inactivity/physical fitness. The WHO (2009) report on global mortality risk factors does not define what is meant by physical inactivity. Physical fitness has been defined in terms of CRF in units of metabolic equivalents (METS); 1 MET is the amount of energy expended at rest, or 3.5 mL oxygen per kilogram per minute. Myers et al. showed that in both healthy subjects and those with cardiovascular disease, a low peak exercise capacity achieved was a stronger predictor of an increased risk of death than established risk factors such as hypertension, smoking, and diabetes (Myers et al., 2002). A study of 9777 men who maintained or improved adequate physical fitness found that they were less likely to die from all causes and from cardiovascular disease during follow-up than persistently unfit men (Blair et al., 1995). This study is important as it shows that fitness training does bring about a reduction in all-cause mortality. A systematic review (Fogelholm, 2010) and meta-analyses (Kodama et al., 2009) confirm the importance of CRF as an important risk factor for all-cause mortality. The meta-analysis (Kodama et al., 2009) showed in relation to the dose-response analyses, a 1 MET higher level of maximum aerobic capacity was associated with 13% and 15% decrements in risk of all-cause and coronary heart disease/cardiovascular disease mortality, respectively.

The research linking CRF to insulin resistance further highlights its clinical relevance and importance (Leite et al., 2009). Physical fitness is also being defined in terms of muscle strength, and a large prospective study showed that mortality, all-cause, cardiovascular and cancer deaths were strongly correlated with low muscle strength (Ruiz et al., 2008). This study supports the view that cancer mortality can be reduced through fitness, especially through muscle strength. The WHO (2009) report indicates that physical inactivity is estimated to cause around 21–25% of breast and colon cancer burden.

Hypertension. Hypertension is an important risk factor for stroke, heart disease, kidney failure and increase in other diseases, not only in people with hypertension but also in those with average, or even below-average, blood pressure. Lewington et al. reported a twofold increase in stroke death and a twofold increase in ischaemic heart disease and vascular death for every 20 mm Hg increase in systolic blood pressure >115 mm Hg (Lewington et al., 2002). A major difficulty with hypertension is that it is often silent, so it is important that all patients are screened.

Smoking. The WHO (2009) report shows that worldwide smoking causes 12% of male deaths and 6% of female deaths. The marked decline in heart disease death between 1975 (320 deaths/100,000) and 2004 (140 deaths/100,000) is largely ascribed to the reduction in smoking (Capewell et al., 1999; Jemal et al., 2008). The Massachusetts Tobacco Control Program, over the period 1993 to 2003, was associated with a 29% reduction in smoking prevalence and a 31% decline in coronary heart disease mortality rates (Kabir et al., 2008). Smoking bans have also been associated with significant reductions in admission for coronary care, with Khuder et al. reporting a 47% reduction at 3 years (Khuder et al., 2007). Smoking is now recognized to be a significant risk factor for type 2 diabetes (Willi et al., 2007). The finding that smoking is a greater health inequality than social class suggests that unless individuals stop smoking, attempts to improve their health will be very limited (Gruer et al., 2009). Doll's study of male doctors followed up for over 50 years shows that smokers have not shared the increased lifespan of their non-smoking colleagues (Doll et al., 2004).

Diabetes mellitus. The WHO (2009) report suggests that raised blood glucose is the third largest risk factor for premature mortality, and worldwide is associated with 5.8% of deaths. Moreover, it causes all diabetes deaths, 22% of ischaemic heart disease deaths and 16% of stroke deaths. The incidence of type 2 diabetes is growing rapidly worldwide and is associated with increasing levels of obesity and physical inactivity (Tuomilehto et al., 2001). Type 2 diabetes is associated with reduced life expectancy of approximately 8 years in both men and women (Roper et al., 2001). Mozaffarian reported an 82% reduction in incidence of type 2 diabetes in people who have the full range of healthy lifestyle factors (Mozaffarian et al., 2009). Mortality in men with diabetes mellitus has been linked to exercise capacity. In normal-weight men the relative risk of mortality was RR = 6.6, 95% CI (2.8–15.0); RR = 3.2, 95% CI (1.4–7.0); and RR = 2.2, 95% CI (1.1–4.6) for the first, second, and third quartiles of fitness, respectively, as compared with the fourth quartile (p for trend 0.0001) (Church et al., 2004).

Obesity. The WHO (2009) report places overweight and obesity as being the fifth most important risk factor for premature mortality. Clearly, morbid obesity is a very significant mortality risk factor; however, there are new data which are raising questions about the risk balance for the overweight category. A US study examining 2.3 million deaths supports the view of increased risk for diabetes and kidney disease mortality in the overweight and obese categories compared with ideal weight (Flegal et al., 2007). Cardiovascular disease mortality was increased in the obese categories but not in the overweight category, and there was significantly lower all-cause excess mortality in the overweight category compared with the obese or ideal weight categories (Flegal et al., 2007). A study of 13,104 middle-aged individuals for 14 years found that weight gain in middle-aged or elderly individuals, except in very obese persons, was relatively harmless (Myrskylä and Chang, 2009).

Karelis et al. challenge the simplistic model of health risks being associated with increased body weight and discuss the move towards risk being closely associated with body composition, with levels of visceral fat being discriminatory (Karelis et al., 2004). Visceral fat has been found to be an independent predictor of all-cause mortality (Kuk et al., 2006). There are now several studies showing that mortality is more closely linked to levels of fitness than fatness (Fogelholm, 2010). However, the use of offspring body mass index (BMI) as a predictor of own BMI, a technique that avoids problems of reverse causality, suggests that positive associations of BMI with all-cause and cardiovascular mortality may be underestimated in conventional observational studies.

Cholesterol. Raised cholesterol is highlighted by the WHO (2009) report as being the sixth most important attributable cause of mortality in the general population. In the general population, familial hypercholesterolaemia is a well-established risk factor for premature mortality. This can afflict as many as 1/67 in some populations (Seftel et al., 1989). Statins largely prevent the very early mortality of patients with this abnormality of the low-density lipoprotein (LDL) cholesterol receptor. Equally, statins reduce mortality when used in secondary prevention of patients who have already suffered cardiovascular events associated with atherosclerosis (Vrecer et al., 2003). The role of statins in the management of diabetes mellitus is well established, although recent research shows they also increase the incidence of diabetes (Sattar et al., 2010). However, primary prevention measures of cardiovascular disease in the general population with raised cholesterol are less clear (Vrecer et al., 2003). Further, a meta-analysis of 11 studies on 65,229 patients followed up for 244,000 person-years did not find evidence for the benefit of statin therapy on all-cause mortality in a high-risk primary prevention set-up (Ray et al., 2010). In people aged over 70 there seems to be no benefit to lower cholesterol levels (Krumholz et al., 1994; Nissinen et al., 1989; Schatz et al., 2001). No study has shown significant reduction of all-cause mortality for older women (Vos and Rose, 2005). High cholesterol in old age is associated with less dementia (Mielke et al., 2005). Clofibrate was taken off the market because of an increase in all-cause mortality including suicide, although it reduced cholesterol very well indeed (WHO, 1984). Low cholesterol has also been linked to suicide (Zureik et al., 1996). Further, a meta-analysis of studies confirmed a small statistical link between low cholesterol and suicide, but

cholesterol-lowering studies did not lead to a significant increase in suicide completers (Lester, 2002).

Diet and alcohol. Although we have reviewed the mortality risk factors separately, there is emerging evidence that one needs to look at the impact of combinations of risk factors. For example, four simple health behaviours – not smoking, physical activity, eating a balanced diet and having a small amount of alcohol – were associated with a 14-year increased life expectancy (Khaw et al., 2008). The Monica study (Tunstall-Pedoe et al., 1997) showed reduced mortality with both moderate alcohol consumption and high urinary potassium (a measure of fresh food intake). The WHO (2009) reported that alcohol, tobacco, high blood pressure, high BMI, high cholesterol, high blood glucose, low fruit and vegetable intake, and physical inactivity account for 61% of cardiovascular deaths.

Modifiable mortality risk factors in schizophrenia

The literature revealed 974 papers when searched using the terms schizophrenia and mortality. There were only 12 papers identified when using the terms schizophrenia and mortality and modifiable (Table 2). Only one paper was found which specifically examined the association between heart disease mortality and modifiable risk factors, both clinical and behavioural, in schizophrenia (Kilbourne et al., 2009). This US study of 22,817 patients with schizophrenia examined the association between modifiable clinical risk factors (diabetes, heart disease, hypertension, cerebrovascular disease and other medical co-morbidities) and behavioural risk factors (current smoker, hazardous drinking, illicit drug use disorder or physical activity of less than once a week) for cardiac death (Kilbourne et al, 2009). The HR for dying from heart disease associated with schizophrenia was 1.37, and including clinical and behavioural risk factors, this reduced the HR to 1.17. The leading behavioural risk factors were lack of physical activity (HR = 1.66) and current smoker (HR = 1.32). Among the clinical risk factors, hypertension and diabetes were significant risk factors (HR = 1.38 and 1.51) whereas hyperlipidaemia was protective (HR = 0.88).

There are several studies and reviews which have examined the associated risk factors for all-cause mortality or heart-disease mortality in patients with severe mental illness (SMI) (Hamer et al., 2008; Osborn et al., 2007,

Table 2. Twelve papers identified using the search terms, schizophrenia & mortality & modifiable, and whether these paper are included in review

Reference	Title of paper	Paper referenced in section of the paper* titled: Modifiable mortality risk factors in schizophrenia	Paper referenced in other* sections of the paper
Kilbourne et al. (2009)	Excess heart-disease-related mortality in a national study of patients with mental disorders: identifying modifiable risk factors	YES	YES
Saravane et al. (2009)	Drawing up guidelines for the attendance of physical health of patients with severe mental illness	NO	NO
De Hert et al. (2009a)	Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Associationfor the Study of Diabetes (EASD) and the European Society of Cardiology (ESC)	YES	YES
Haupt et al. (2009)	Prevalence and predictors of lipid and glucose monitoring in commercially insured patients treated with second-generation antipsychotic agents.	NO	NO
De Hert et al. (2009b)	Metabolic syndrome in people with schizophrenia: a review.	NO	NO
Newcomer (2009)	Comparing the safety and efficacy of atypical antipsychotics in psychiatric patients with comorbid medical illnesses.	NO	NO
Kelly et al. (2007)	Reaching for wellness in schizophrenia.	NO	NO
Bromet et al. (2005)	Long-term diagnostic stability and outcome in recent first-episode cohort studies of schizophrenia.	NO	NO
Goff et al. (2005)	Medical morbidity and mortality in schizophrenia: guidelines for psychiatrists.	NO	NO
Paton et al. (2004)	Obesity, dyslipidaemias and smoking in an inpatient population treated with antipsychotic drugs.	NO	NO
Davidson (2002)	Risk of cardiovascular disease and sudden death in schizophrenia.	NO	NO
Haupt and Newcomer (2001)	Hyperglycaemia and antipsychotic medications.	NO	NO

Ray et al., 2009). However, the significance of these findings in schizophrenia is a little uncertain, as the disease category SMI includes a range of mental illnesses and in some cases includes dementia. However, the USA study (Kilbourne et al., 2009) reported similar findings for the association of heart disease mortality across the same clinical and behavioural risk factors in bipolar disorder, depression and schizophrenia. Osborn et al. found that patients with SMI, including schizophrenia, were about three times more likely to die from heart disease (Osborn et al., 2007). The analysis controlled for smoking and antipsychotic use, but it did not control for co-morbid medical conditions (diabetes, obesity, etc.), which may have explained these associations (Osborn et al., 2007). The Scottish Health Survey of 597 patients with SMI compared with 19,898 people in the general population examined the risk factors for all-cause and cardiac mortality over an 8.5-year period (Hamer et al., 2008). The principal findings were that patients with a history of psychiatric episodes had a high risk of all-cause mortality (HR = 3.25, 95% CI 2.63–4.02). Further, patients were more likely to be smokers (odds ratio (OR) = 4.69), have low physical activity levels (OR = 2.24), come from a low socioeconomic group (OR = 2.17) and be separated or divorced (OR = 2.02). Smoking rates were roughly twice as high in the SMI population (62.5% vs. 32.5%), which was associated with underweight or morbid obesity, and was less likely to be overweight and obese.

A French 11-year prospective study of 3470 patients with schizophrenia showed that among smokers there was a twofold increase in total cancer deaths (Tran et al., 2009). This study identified that there were two important predictors of death from lung cancer: duration of smoking and age >38 years. Further, this study showed for all cancer deaths the HR for smokers versus non-smokers was significantly raised (HR = 2.59; 95% CI (1.56–4.32)). A US study of 10 years' observation in 1213 patients with schizophrenia (Kelly et al., 2009) confirmed that smoking is a major risk factor for all-cause mortality. The HR for smokers versus non-smokers (aged 35–54 years) was HR = 2.1. The 5 and 10-year mortality rates for smokers aged 35–54 years were 7.0% and 14.2%, compared with 3.3% and 10.0% for non-smokers, respectively. Moreover, cardiac causes were identified in 43% of deaths in smokers but in only 19% of deaths in non-smokers. For those aged 35–54 years, the odds of cardiac-related death were increased by 12-fold in smokers relative to non-smokers. The findings from the UK prospective linkage study in schizophrenia (Brown et al., 2010) also supported the view that much of the excess cardiovascular mortality could be explained by smoking. These studies demonstrate the significant impact of smoking on mortality in schizophrenia, which is consistent with findings in the general population. Moreover, the two recent studies in schizophrenia (Brown et al., 2010; Tran et al., 2009) show continuing high smoking rates of 73% and 53%, respectively.

There has been concern about whether some antipsychotics are associated with an excess cardiovascular mortality which may be associated with their metabolic profiles (Hennekens et al., 2005). However, De Hert reported that patients with schizophrenia not taking antipsychotics have a higher risk for mortality and suicide than patients on regular antipsychotics, which means that one needs to consider any metabolic risk within this context (De Hert et al., 2009a). One of the most recent systematic reviews of antipsychotics and mortality showed inconsistent findings, although it supported the case for increased long-term mortality associated with antipsychotics as a class (Weinmann et al., 2009). Only four of these studies, out of 12, covered the time period when most atypicals became widely used, and none showed increased mortality with atypicals versus typical antipsychotics. There have subsequently been a number of new studies published which have examined the risk for all-cause and cardiovascular mortality in schizophrenia. The 11-year Finnish study (Tiihonen et al., 2009) showed no increased risk for cardiovascular disease or all-cause mortality with antipsychotics. Moreover, long-term treatment with antipsychotics was associated with lower mortality compared with no antipsychotics (HR = 0.81, 95% CI 0.77–0.84). Their findings also showed that for both clozapine and olanzapine, the two antipsychotics associated with greatest weight gain, that there were no signs of increased risk of death from ischaemic heart disease after 7–11 years of cumulative exposure to these agents. This study has been criticized on methodological grounds (De Hert et al., 2010); however, its strength is its size and duration. A US retrospective cohort study examined the comparative cardiovascular disease mortality between clozapine (n = 1084) and risperidone (n = 602) over a 10-year period 1994–2004 (Kelly et al., 2010). The risk of CVD mortality in schizophrenia did not differ between clozapine and risperidone in adults. A US study in patients with schizophrenia (n = 1920) and controls (n = 9600) found an inverse association between intensity of antipsychotic use and risk of myocardial infarction, making a deleterious effect of antipsychotics unlikely (Enger et al., 2004). However, several studies have shown increased mortality with typical antipsychotics (Joukamaa et al., 2006; Osborn et al., 2007; Waddington et al., 1998). A study in patients with tardive dyskinesia found higher rates of mortality in older patients, particularly those on conventional antipsychotics (Dean and Thuras, 2009). A Cochrane review of olanzapine versus other atypicals in schizophrenia found no differential risk of death, although olanzapine was associated with greater weight gain (Komossa et al., 2010).

A small number of studies have found that patients with mental illness have increased mortality rates for cancer, which is not always explained by increased incidence (Lawrence et al., 2000). A study from Nova Scotia found that for melanoma, prostate, bladder, and colorectal cancers in males, incidence rate ratios were lower than might be expected given the mortality and first admission rate ratios, which were no higher than those of the general population (Kisely et al., 2008). The author proposed several explanations including delays in detection or first diagnosis leading to more advanced disease, and also access to medical care. A study from Denmark found similar findings in SMI patients presenting with heart disease (Laursen et al., 2009). Individuals with severe mental disorder were found to have only negligible excess rates of contact for heart disease, but the findings of excess mortality from heart disease and lower rates of invasive procedures after first contact supports the

view that quality of treatment for heart disease was inadequate. Undertreatment may explain part of their excess cardiac mortality. A systematic review (Mitchell and Lord, 2010) supports this view of poor quality of care for patients with schizophrenia and heart disease.

Non-modifiable mortality risk factors in schizophrenia

There is growing recognition that schizophrenia itself has innate risk factors for premature mortality. A US study showed that the illness schizophrenia was associated with an increased risk of cardiac death, independent of clinical and behavioural risk factors (Kilbourne et al., 2009). Complete health visitor records from Hertfordshire in the UK have allowed follow-up of babies in relation to their weight. Low birth weight in this population was associated with increased rates of diabetes and other metabolic disorders (Phillips et al., 1994). In schizophrenia around 10% of patients have low birth weight, but to date there are no studies quantifying physical health outcomes in these patients. A number of studies are now reporting increased levels of abnormal glucose in drug-naïve first-episode patients (Spelman et al., 2007), although there are some reports of negative findings. Platelet abnormalities related to schizophrenia have been identified which potentially will increase the risk of stroke and heart disease (Dietrich-Muszalska and Olas, 2007; Dietrich-Muszalska et al., 2008) The findings that telomere length is reduced in schizophrenia may mean it is a disease of accelerated ageing (Fernandez-Egea et al., 2009). The finding of raised pulse pressure supports the view of increased risk of diabetes and dementia (Fernandez-Egea et al., 2009).The findings of increased levels of homocysteine in young male patients with schizophrenia is likely to be associated with increased risk for cardiovascular disease and cognitive impairment (Levine et al., 2002). Some studies in first-episode schizophrenia suggest that patients have raised visceral fat levels, putting them at increased risk for diabetes, hypertension and cardiovascular disease (Thakore et al., 2002).

Review of studies in schizophrenia designed to reduce mortality

We were unable to identify any published prospective studies in schizophrenia which had been designed to impact on mortality outcomes in schizophrenia. We examined over 974 papers in the systematic literature search.

Can one reduce the mortality risk factors in schizophrenia?

We must assume that patients with schizophrenia are as sensitive to health-improving measures as the general public. This section of the paper reviews the literature to examine the evidence that the top six WHO global mortality risk factors can be reduced in schizophrenia (WHO, 2009). While there are established targets for BMI, glucose, lipids and blood pressure in the general population, it will be important

to establish optimum standards in schizophrenia, as it cannot be just assumed that the values for the general population automatically apply in schizophrenia. It will also be important to establish whether managing these risks affects long-term outcomes in schizophrenia, either directly or indirectly through issues of compliance.

Physical fitness and strength. Those individuals who developed psychosis are more likely to be physically inactive (OR = 3.3, 95% CI (1.4–7.9)) and to have poor cardiorespiratory fitness (OR = 2.2, 95% CI (0.6–7.8)) compared with those who did not develop psychosis (Koivukangas et al., 2010). Muscular strength and CRF have been correlated with improvements in all-cause and cardiovascular mortality in the general population (Kodama et al., 2009; Ruiz et al., 2008). Most modern guidelines on managing the physical health risks associated with schizophrenia include a recommendation about the importance of physical activity levels and fitness. However, to date there are few data published on the assessment of physical fitness or desired levels to achieve a lower risk for cardiovascular or all-cause mortality in schizophrenia. The challenge to improve physical activity levels will be to determine the optimum programmes (Jerome et al., 2009), and currently there is a minimal evidence base. A review of the Cochrane Schizophrenia Group Trial register identified three randomized controlled trials of physical activity or exercise in schizophrenia (Gorczynski and Faulkner, 2010). Its conclusions were that current studies in schizophrenia were small, and that regular exercise programmes are possible, but larger randomized studies are required before any definitive conclusions can be drawn.

Assessment of physical activity in schizophrenia has been described (Lindamer et al., 2008) using the Yale Physical Activity Scale, stage of motivational readiness scale and an accelerometer. Using these tools, it was found that persons with schizophrenia spent less than half their time in physical activity and expended less than half the kilocalories than the controls. The Eurofit protocol for adults assesses four dimensions of fitness: aerobic fitness, muscular skeletal fitness, motor fitness and body composition (Oja and Tuxworth, 1995). This assessment tool looks promising, but to date there is little literature in schizophrenia. A study in Florida (Beebe et al., 2005) found in 10 patients with schizophrenia that a 16-week exercise programme which included a 6-min walking distance was associated with reductions in body fat ($p = 0.03$), greater aerobic fitness and lower BMI. A pilot study in Australia in six patients with schizophrenia showed, at 3 months, increased fitness level, exercise tolerance, reduced blood pressure and upper body and hand grip strength (Fogarty et al., 2004). Of 31 subjects, 20 completed a 12-month weight reduction programme which include an exercise component (Menza et al., 2004). The results of this simple study were impressive, showing improvements in weight ($p < 0.02$), BMI ($p < 0.02$), haemoglobin A(1c) levels ($p < 0.001$), diastolic ($p < 0.001$) and systolic ($p < 0.05$) blood pressure, exercise level ($p < 0.003$), nutrition knowledge ($p < 0.0001$), and stage of change (exercise ($p < 0.0001$) and weight ($p < 0.008$)). Vancampfort et al. examined systematically the impact of simple physical activity

on cardiometabolic parameters in schizophrenia (Vancampfort et al., 2009). They identified 13 studies which showed that physical activity, with and without diet counselling, resulted in modest weight loss, reductions in systolic and diastolic blood pressure and decreases in fasting plasma concentrations of glucose and insulin. They concluded by stating that there is a need to develop optimum interventional strategies for prevention and management of cardiometabolic risks in schizophrenia.

Hypertension. The prevalence of hypertension in schizophrenia is likely to be large, as demonstrated by two recent studies (Daumit et al., 2008; Smith et al., 2007) which reported high levels of untreated hypertension (34% and 50%, respectively). However, a systematic review and meta-analysis only found weak evidence to support excess hypertension in patients with SMI (Osborn et al., 2008). This raises an important question as to whether one can extrapolate findings from an SMI population to schizophrenia populations. Most guidelines for hypertension in schizophrenia appear to be extrapolated from the general population. It will be important to confirm whether these standards are appropriate in schizophrenia and which are the best treatments. Moreover, some antihypertensive drugs and antipsychotics are associated with sexual side effects, so it will be important to assess possible interactions.

Piette et al. report a study in 1686 veterans with schizophrenia and comorbid diabetes and hypertension, which examined the issue of medication compliance (Piette et al., 2007). This study showed that the adjusted odds of poor adherence were significantly higher for hypoglycaemic and antihypertensive medications than for antipsychotic medication (both adjusted ORs were 1.5, $p < 0.001$).

Smoking. Most studies in schizophrenia show smoking rates to be considerably higher than in the general population (Catts et al., 2008; Daumit et al., 2008; Williams and Foulds, 2007). However, the evidence base that it is easily modifiable in schizophrenia is small (Campion et al., 2008). Rates of smoking cessation in schizophrenia are roughly half those of the general population (Williams and Foulds, 2007). As nicotine can interfere with drug metabolism (cytochrome P450 and CYP1A2) which affects the metabolism of many antipsychotics including clozapine and olanzapine as well as haloperidol, smoking cessation needs to be carried out carefully, and likewise caution needs to be exercised regarding dosing in smokers. The evidence base relating smoking as an important risk factor for mortality in schizophrenia is very strong (Brown et al., 2010; Catts et al., 2008; Kelly et al., 2009; Tran et al., 2009). However, there is now strong evidence in the general population that avoiding passive smoking has major health benefits (Khuder et al., 2007). Hence, it will be important to establish smoke-free zones in clinical and residential areas for patients with schizophrenia.

Glucose. A UK systematic review and meta-analysis examined the relative risk of diabetes, dyslipidaemia, hypertension

and metabolic syndrome in people with SMI including schizophrenia (Osborn et al., 2008). This review examined 14,000 papers and the principal findings were that the data quality was poor, mainly cross-sectional, and often patients were not adequately screened. This systematic review highlighted a major gap in our understanding of the prevalence of risks in SMI and confirmed high rates of diabetes compared with a control group (RR = 1.87), but weaker evidence for dyslipidaemia and hypertension being in excess. However, two studies ($n = 966$ and $n = 1125$), one randomized controlled trial and one observational (Daumit et al., 2008; Smith et al., 2007, respectively) report very high levels of hypertension (34% and 50%, respectively) in schizophrenia.

A number of the current guidelines on the management of comorbid diabetes in association with schizophrenia support the view that it is important to manage psychotic symptoms to be able to manage the diabetes (Holt and Peveler, 2010). A retrospective chart review ($n = 72$) demonstrated that using aggressive anti-diabetic therapy, glycaemic control was achieved in a group of patients with schizophrenia and comorbid diabetes mellitus who were treated with atypical antipsychotics (Krosnick and Wilson, 2005). This study showed that pre-existing hepatitis was associated with a worsening of diabetes control. Another important question regarding diabetes is how its management affects schizophrenia outcomes. This question has been addressed by 3-year, prospective, naturalistic study ($n = 594$) which showed that the course of schizophrenia did not differ significantly between participants with and without diabetes (Ascher-Svanum et al., 2007). A community study in the USA examined how treatment of diabetes in patients with schizophrenia ($n = 101$) compared with that in diabetic patients with no mental illness ($n = 99$) (Dixon et al., 2004). This study found that HbA(1c) levels in the patients with schizophrenia were significantly lower than in patients who did not have SMI. This study concluded that patients with schizophrenia who are receiving regular mental heath care may have unrecognized benefits for diabetes management. A systematic review and meta-analysis found that atypical antipsychotics were associated with a higher risk of diabetes than typical antipsychotics in schizophrenia (Smith et al., 2008). However, a systematic review of prospective studies found no differences in the risk of developing glucose abnormality (Bushe and Leonard, 2007). A comprehensive review of the risk factors and management of diabetes in SMI has been published by the European Psychiatric Association (De Hert et al., 2009a).

Overweight and obesity. There are many studies now showing that patients with schizophrenia are able to lose some of their excess weight through weight reduction programmes, although the weight-loss figures are modest and relatively short term. A review of the Cochrane Schizophrenia Groups trials register identified 23 randomized controlled trials, which showed that both behavioural and pharmacological trials showed modest weight loss results (Faulkner et al., 2007). The majority of these studies were short-term studies and not in first-episode patients. A systematic review found that metformin (eight randomized controlled trials) showed promising weight loss results, but

again most of the studies were short term (Bushe et al., 2009). Further, a UK study reported an 8-year experience of a behavioural treatment programme in 112 patients with SMI of which 64 completed 1 year, and 35 patients 2 years with a mean weight loss 7.2 kg (Holt et al., 2010). A systematic review and meta-analysis of 10 non-pharmacological weight-management programmes in schizophrenia found that this approach was particular helpful in prevention of early weight gain associated with antipsychotic usage (Alvarez-Jiménez et al., 2008). They recommended switching antipsychotics in case of significant weight gain, especially where a poor response had been seen. We were unable to find studies which showed the impact of intentional weight loss in schizophrenia either on body composition or on long-term mortality.

Dyslipidaemia. It is well recognized that some patients with schizophrenia, even prior to treatment, have abnormal levels of LDL lipids and triglycerides (Kahn et al., 2008; McEvoy et al., 2007). In the general population there are now many studies evaluating the impact of lipid lowering in primary and secondary prevention of coronary heart disease and stroke; however, there are some concerns about its value in primary prevention, especially in vulnerable populations (Vrecer, et al., 2003). Hence, it is a priority to establish studies to evaluate the risk-benefits of lipid lowering in schizophrenia. However, until those studies are complete, physicians should use the relevant NICE guidelines or those specifically designed for patients with schizophrenia (De Hert et al., 2009a; Holt and Peveler, 2010).

A 3-month study demonstrated that statins prescribed to patients with schizophrenia and severe dyslipidaemia whilst taking antipsychotic medication led to a significant improvement in lipid profiles (Hanssens et al., 2007). Similarly, an earlier study with rosuvastatin proved effective in managing dyslipidaemia in patients with schizophrenia on antipsychotics (De Hert et al., 2006). This later study showed improvement in lipid profiles but no benefits in terms of high-density lipoprotein, waist measurement, BMI or glucose homeostasis. This study supports the view that statins can be safely used in the short term to control abnormal lipids levels in schizophrenia. However, there are no long-term data on its impact on either relapse or all-cause mortality, and again this is a priority for research. The preferred initial management is still very much a lifestyle modification approach including exercise and diet.

Discussion

This paper has utilized a systematic search strategy to identify the impact of modifiable mortality risk factors on all-cause mortality in schizophrenia, and to identify to what extent there is a literature which shows prospectively that these risks can be managed. However, this paper was not planned as a systematic review, as this topic area is too wide to be covered in one review paper.

The findings from this paper are that the six top global risk factors (modifiable risk factors) for premature mortality – hypertension, raised glucose, physical inactivity, overweight and obesity, and lipids (WHO, 2009) – have either been shown in research to be, or should in clinical practice be, amenable to being lowered in patients with schizophrenia. Moreover, the levels of these risk factors appear to be significantly raised in schizophrenia compared with the general population (De Hert et al., 2009a; Leucht et al., 2007; Saha et al., 2007). There are now many well-documented guidelines for physical health and wellbeing in schizophrenia (De Hert et al., 2009a; Lehman et al., 2004; NICE, 2002a; NICE, 2002b). Adopting these guidelines will be an important aid to minimizing a broad range of physical health risks, including both cardiovascular disease and diabetes. However, there is a dearth of prospective studies about managing these health risks, which have been shown to work in schizophrenia, hence the need to set up appropriate studies is urgently required (Citrome and Yeomans, 2005).

The WHO report on global health risks (WHO, 2009) quantifies the percentage of deaths globally attributed to each of the global mortality risk factors. Although these risk factors are raised in schizophrenia, there are few data showing their contribution to total mortality in schizophrenia. The WHO (2009) report states that understanding the role of these risk factors is pivotal to developing a clear and effective strategy for improving global health, hence it will be important to understand better the contribution of these factors to total mortality in schizophrenia. The study by Kilbourne et al. is one of the first studies in schizophrenia to identify the increased HR for cardiac mortality associated with both behavioural (illicit drug disorder, low physical activity, smoking and hazardous drinking) and clinical risk factors (diabetes, hypertension, heart disease, lipids) (Kilbourne et al., 2009). Paradoxically, this study showed that high cholesterol was protective for cardiac death. This finding will need to be verified; however, it raises a suspicion that one cannot assume that the mortality risk factors operate equally across schizophrenia and the general population.

A number of studies report on modifiable mortality risk factors in patients with SMI and although these findings are of interest, there is some uncertainly as to how they relate to schizophrenia (Hamer et al., 2008; Osborn et al., 2007; Ray et al., 2009). The findings from the Scottish Health Survey further support the view that low physical activity and smoking are major behavioural risk factors for all-cause mortality (Hamer et al., 2008). Although there are many reviews on mortality in schizophrenia, including the most recent by Saha et al. there is little information reported on the issue of quantification of modifiable clinical or behavioural risk factors which could explain the increased mortality risk in schizophrenia (Saha et al., 2007). This is an important subject for further research.

The schizophrenia literature has largely failed to address the issue of fitness, either CRF or muscle strength. This is possibly understandable, as an editorial pointed out that although this was now the largest public health challenge, its importance has not yet been grasped in primary care (Blair, 2009). Bearing in mind that CRF and muscle strength are strong indicators of both cardiovascular and all-cause mortality, it will be important to set up studies to assess these factors as well as developing programmes to improve patients function. However, a systematic review on the

benefits of simple exercise activities on cardiometabolic parameters was encouraging (Vancampfort et al., 2009). The challenge is to develop optimum physical activity programmes which can be implemented easily into clinical practice (Jerome et al., 2009).

There is very strong evidence that smoking in schizophrenia is a very important modifiable mortality risk factor. Smoking increases the risk of cardiovascular disease in patients aged 35–54 with schizophrenia by 12-fold (Kelly et al., 2009). The French study (Tran et al., 2009) showed that smoking was associated with a twofold increased risk for all cancer deaths in schizophrenia. The study of Kelly et al. showed that older patients with schizophrenia who smoked had a lower mortality rate than older non-smokers. The authors thought this to be a chance finding, as the cohort size for older patients was small. The French study was in a relatively young population, and also showed a high cardiac mortality. These findings raises the question: are patients with schizophrenia who are young at increased risk of cardiovascular disease and cancer mortality than older patients? In the general population, passive smoking is now recognized as a significant health risk and it will be important to introduce smoking bans in psychiatric units and community facilities. Clinical trials assessing cardiovascular risk in schizophrenia have largely ignored the impact of passive smoking, which makes interpretation of the findings more complex. The findings that the SMRs for coronary heart disease are significantly increased in schizophrenia raised concerns about the widening mortality gap with the general population (Saha et al., 2007). Brown argues that continued high rates of smoking in patients with schizophrenia against a background of falling smoking rates in the general population can explain much of the excess cardiovascular and other mortality in schizophrenia (Brown et al., 2010; Capewell et al., 1999). The observation of excess mortality associated with smoking in schizophrenia has also been shown in relation to lung cancer deaths (Catts et al., 2008).

With the introduction of atypical antipsychotics, which are associated with increased metabolic risk factors, there has been a major focus on the metabolic syndrome, cardiovascular disease and diabetes, which is very proper. With the recognition that cardiovascular disease mortality is only partially the explanation of excess deaths in schizophrenia, a focus needs to move to all-cause mortality (Table 1). This is exemplified by the debate on managing the risk factor overweight/obese. Intentional weight loss may reduce cardiovascular disease mortality (Adams, 2009) through reduction in fat, but weight loss may also lead to increased mortality through loss of bone and lean mass (muscle and organ). Our knowledge about weight change and mortality is still very much lacking (Adams, 2009). An alternative approach has been suggested (Ross and Bradshaw, 2009) utilizing lifestyle modification programmes characterized by increased physical activity and balanced diet which can reduce the risk of obesity and risk of related conditions with minimal change in weight. The benefits of this approach are reductions in abdominal obesity, visceral fat and cardiometabolic parameters and improvements in muscle mass and CRF (Ross and Bradshaw, 2009). There are some reports of this approach in schizophrenia (Smith et al., 2007), but it has attracted little interest as

judged by the number of publications in the literature. However, support for this approach comes from the UK (Khaw et al., 2008). This study showed that in the general population, four health behaviours were associated with 14 years of additional life.

Schizophrenia, the illness itself, appears to be linked to an increased risk of cardiovascular mortality, HR = 1.17 (Kilbourne et al., 2009). This finding may be related to genetic factors or even to low birth weight, but further research is required to answer this question. There has been a debate regarding whether antipsychotics themselves are a significant modifiable risk factor for excess mortality in schizophrenia. This debate appeared to start with the introduction of atypical antipsychotics, which are associated with a greater risk of weight gain than typical antipsychotics. The finding that weight gain in middle-aged and older patients has only a very small impact on increased mortality risk (Myrskylä and Chang, 2009) raises a doubt about the initial thinking. Further, our understanding about cardiovascular risk and mortality is being challenged, as it has now been shown that the Framingham risk assessment tool is poor at predicting cardiovascular mortality even in patients identified to be at high risk (Beary and Wildgust, 2009; Jackson et al., 2009). There are also some large epidemiological studies in the general population showing that a higher BMI is associated with a lower risk of suicide (Gravseth, et al., 2010; Magnusson, et al., 2006). There is also emerging evidence that stopping antipsychotics is a significant mortality risk factor (Tiihonen et al., 2006). High switching rates between antipsychotics and a failure to control for smoking, including passive smoking, may also be important confounders and may possibly explain some of the inconsistencies in the literature. These findings illustrate the complexity in our understanding of the mortality risk-balance equation in schizophrenia. However, this review has identified several studies showing higher mortality risk associated with typical antipsychotics but no mortality advantage for typicals over atypicals, except for perphenazine (Tiihonen et al., 2009). These findings support the view that if there is a differential mortality risk across antipsychotics, it is likely to be small. Large prospective studies are required to answer this question.

Stress is another potentially modifiable mortality risk factor in schizophrenia, which operates through raised cortisol and the hypothalamic–pituitary–adrenal axis. It may be linked with excess cardiovascular mortality as well as increased risk of cancer. This is an important topic which has now been systematically reviewed (Bradley and Dinan, 2010). Research links chronics stress to accelerated telomere shortening, which is associated with accelerated ageing (Epel et al., 2004), and in turn may be associated with earlier onset of cardiovascular and cancer diseases. Cognitive behavioural treatment has been shown to be effective in reducing stress, including reduction of raised cortisol. This topic is another important area for further research.

The literature on modifiable mortality risk factors in schizophrenia confirms that hypertension, smoking, low physical activity, raised glucose, obesity and cholesterol all play a role in the mortality risk equation. However, to date there are few data on how these risk factors combine, or how they vary by age, and gender, or interact with non-modifiable

risk factors. The finding that smoking overrides the mortality risks relating to social class illustrates the complexities in understanding how risk factors combine (Gruer et al., 2009). However, the WHO (2009) report suggests that in the general population, the net impact of combining attributable mortality risk factors is greater than their summation. It will be important to tease out how these risk factors interplay and their effect size in schizophrenia.

Conclusions

There is a very large evidence base supporting increased mortality in schizophrenia for the majority of diseases which cause death in the general population. In schizophrenia, rates of smoking, diabetes, hypertension, obesity and abnormal lipids are all high and are all potentially modifiable. A continued high level of smoking, including passive smoking, is a major mortality risk factor which may partially explain the excess cardiovascular mortality in schizophrenia. Low fitness, namely skeletal muscle mass and CRF are two new important targets established to minimize risk in the general population. We must assume schizophrenia sufferers will benefit equally from increased fitness, although there is limited evidence suggesting this conclusion. The positive benefits of lifestyle modification, based on findings in the general population, should encourage psychiatry to adopt these and monitor outcomes. Psychiatry in combination with general practice needs to monitor and manage carefully the usual physical health risks. The findings that the incidence for a number of medical conditions in schizophrenia is not raised, yet the corresponding SMRs are increased, support the view that patients with schizophrenia may not be accessing the care or are receiving inferior care. Mental health workers need to be advocates to challenge any prejudice involved.

Our understanding of the quantitative contributions of modifiable mortality risk factors to total mortality in schizophrenia is incomplete. It is important to set up long-term prospective studies to investigate the importance of these risk factors and their management to reduce the years lost to a population enjoying the improved quality of life brought by modern psychiatric treatments.

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