The paradox of premature mortality in schizophrenia: new research questions

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Abstract

The life expectancy of patients with schizophrenia is reduced by between 15 and 25 years. Those patients dying of natural causes die of the same diseases as in the general population. In 2009 the World Health Organization (WHO) identified underlying global risk factors for mortality in the general population. However, there is little evidence in the literature assessing their validity in those with schizophrenia. The WHO report on global health risks (2009) identifies hypertension, smoking, raised glucose, physical inactivity, overweight and obesity, and high cholesterol as the six leading global mortality risk factors. Currently, there are minimal data on the contribution to mortality that these risk factors make in schizophrenia, and their optimum management. Both short and long-term studies are needed to address these gaps. New research has raised important questions about risk balance with regards to ideal body mass, with some studies showing that being overweight is associated with lower all-cause mortality and lower suicide rates. Cardiorespiratory fitness is being recognized as a more powerful predictor of mortality than smoking, hypertension or diabetes in men. However, there are virtually no published data on assessment of fitness levels in schizophrenia. New studies have raised concerns about the quality of physical care for patients with schizophrenia, which is another important avenue of future research. A greater biological understanding of the relationship between these disorders and schizophrenia would inform clinical practice. Low birth weight has been associated with increased risk for schizophrenia, and it will be important to explore this risk factor for both physical and mental health outcomes.

Keywords

Cardiorespiratory fitness, diabetes, hypertension, lipids, mortality, obesity, schizophrenia, smoking

Introduction

The World Health Organization (WHO) report on global health risks identified 24 mortality risk factors (WHO, 2009). The six leading risks were, in order of priority, high blood pressure, tobacco use, high blood glucose, physical inactivity, overweight and obese, and high cholesterol. Together, these six risk factors are responsible for raising the risk of chronic disease and account for 42.1% of global mortality. The relative importance of these risk factors varies across countries and by income group. Understanding the role of these risk factors is pivotal to developing a clear and effective strategy for improving global health.

In economically developed countries, people with schizophrenia die 20–25 years prematurely (Kilbourne et al., 2009). Much of this loss of life span is due to the same natural causes (cancer, respiratory disease, heart disease, digestive disease, etc.) as seen in the general population (Brown et al., 2000). Although in the general population the relative contribution of these risk factors to all-cause mortality and disease-specific mortality is now well described (WHO, 2009), the relative importance of these risk factors in schizophrenia is much less well understood. There is some evidence to support the view that schizophrenia may be a disease mimicking accelerated ageing (Fernandez-Egea et al., 2009; Kirkpatrick et al., 2008), which would suggest a need for reappraisal of guidelines both for risk assessment and for optimum medication doses. A systematic review and two recent studies in schizophrenia (Table 1) show the standardized mortality ratios (SMRs) are raised for all-cause mortality and also across disease categories of cancer, circulatory disease, respiratory disease and digestive diseases. These findings support the view that the relative contribution of risk factors to all-cause mortality and by disease in schizophrenia is likely to be different to that in the general population. Guidelines for physical health in schizophrenia are based on extrapolations from the general population; however, the attributable risks in schizophrenia for all-cause mortality and disease-specific mortality have been minimally evaluated.

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Table 1. Standardized mortality ratios (SMRs) by disease category in schizophrenia

Causes of death by disease category	SMR (Saha et al., 2007) (Systematic review)	SMR (% deaths) (Tran et al., 2009) (Prospective cohort study) $n = 3470$, 11 years	SMR (% deaths) (Brown et al., 2010) (Prospective linkage study) $n = 370$, 25 years
All-cause mortality	2.58	3.6 male/4.3 females (13.9%)	2.89 (44%)
Circulatory	1.79	SMR not reported (2.0%)	2.58 (15%)
Neoplasms	1.37	1.5 (2.25%)	1.49 (8%)
Respiratory	3.19	Not given	4.99 (7%)
Digestive	2.38	Not given	2.89 (2%)

Mortality trends in schizophrenia show a pattern of high rate of suicide in patients aged less than 40 years (SMR = 8.38), followed by increased rates of cardiovascular disease (CVD) (SMR = 1.10), respiratory disease (SMR = 2.80), digestive disease (SMR = 1.85) and genito-urinary diseases (SMR = 1.61) in older patients (Brown, 1997). To understand the mortality pattern in schizophrenia, it will be important to examine the mortality risk of patients by age group. For example, in the general population leukaemia is the most common cancer in people aged less than 40 years, whereas lung and breast cancer become the leading killers in older patients (Jemal et al., 2008).

Our understanding of the genetics of schizophrenia is incomplete, and more research is required to understand metabolism of drugs and toxic chemicals such as carcinogens in tobacco smoke in this patient population. There are likely to be differences between the sexes and between ethnic groups.

Recent studies in the general population suggest a re-valuation of accepted beliefs. Intentional weight loss seems to be associated with increased mortality (Sørensen et al., 2005). Low lipids are associated with frailty and increased mortality (Okamura et al., 2008). Overweight has been shown to be associated with the lowest risk of all-cause mortality (Flegal et al., 2007; Tunstall-Pedoe et al., 1997) as well as lower suicide rates (Gravseth et al., 2010; Magnusson et al., 2006). This paper will explore some of these paradoxes and propose new targets for future research.

Objective

The theme of this paper will be to explore whether the risk factors for premature mortality in the general population are directly relevant to people with schizophrenia. This will lead to the identification of new research targets in schizophrenia which may help address the paradox of excess premature all-cause mortality.

Method

A search was carried out in Medline, Embase and PsycINFO using the following terms: schizophrenia and mortality and modifiable (OR reduction OR intervention). The search was conducted for the time period 1987 to January 2010. Papers were included which examined the link between schizophrenia and mortality, with reference to smoking, hypertension, diabetes, physical inactivity, overweight/obesity and lipids. Papers which failed to separate out patients with schizophrenia from other mental disorders were excluded. Papers included in this review were limited to systematic reviews and meta-analyses when available; otherwise high-quality studies were reported. In addition, the literature was non-systematically reviewed to identify the leading mortality risk factors in the general population and whether these risk factors can be reduced in patients with schizophrenia.

Results

The systematic literature search identified 974 papers. Together with hand searches, 60 papers have been included in this paper and the results are presented under the headings mortality risk factors and antipsychotic medication.

Mortality risk factors

Hypertension. The WHO report on global health risks highlights hypertension as the leading global risk factor for mortality, accounting for 12.8% of deaths (WHO, 2009). A US study, in just over 22,000 patients with schizophrenia, showed that hypertension was an important risk factor for cardiac mortality (Kilbourne et al., 2009). There are excellent studies in the general population showing the benefits and the effectiveness of treatments to lower blood pressure. There is little in the literature examining the efficacy of antihypertensives in patients being treated with antipsychotics, some of which target similar receptors. However, 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 odds ratios were 1.5, $p < 0.001$). Antihypertensive therapy may be associated with sexual dysfunction (Ferrario and Levy, 2002), which is also a common adverse event associated with antipsychotics medications. The schizophrenia literature shows that many patients have untreated hypertension. Therefore it will be important to design studies in schizophrenia to accurately assess incidence, issues of management of hypertension and effectiveness of treatments and, in the long term, the

impact on morbidity and mortality. In theory this would be a simple project; however, in practice it would be a large epidemiological study.

Smoking. Tobacco is the second most important global mortality risk factor and accounts for 8.7% deaths globally (WHO, 2009). Patients with schizophrenia have higher rates of smoking than the general population (Catts et al., 2008; Tran et al., 2009). Recent studies in schizophrenia have shown that cardiac-related deaths are 12-fold higher in young smokers relative to non-smokers: hazard ratio (HR) = 12.4, $p = 0.0005$ (Kelly et al., 2009). Smoking approximately doubles the rate of cancer deaths (Tran et al., 2009). In the general population, smoking cessation has been associated with significant reduction in CVD risk and cancer deaths. However, the results of smoking cessation programmes to date in schizophrenia are poor (Campion et al., 2008). There is evidence demonstrating that excess cancer and cardiac mortality in schizophrenia is in part related to poor quality of physical treatments and late diagnosis (Kisely et al., 2007, 2008; Laursen et al., 2009; Mitchell et al., 2009). Smoking has also been linked with increased risk of suicide (Malone et al., 2003). Prospective studies are needed to unravel this complex area. Another issue which needs to be considered is the impact of smoking on heart rate variability, which has already been shown to be abnormal in schizophrenia (Jindal et al., 2009). It will also be important to establish whether two main carcinogenic components in cigarette smoke, polycyclic aromatic hydrocarbons and the tobacco-derived nitrosamines, have normal metabolism, as in the general population, or whether this is impaired in patients with schizophrenia, which will provide valuable insight into the risk of lung cancer. The histology of lung cancer in the general population has changed over the last 40 years from being predominantly squamous cell carcinoma to adenocarcinoma, but to date there is little information in the schizophrenia literature on the histology of lung cancer. Mortality rates for lung cancer are raised in schizophrenia (SMR = 2.65) (Brown et al., 2010). However, a meta-analysis suggested that the standardized incidence rates are lower in schizophrenia than in the general population, after controlling for smoking (Catts et al., 2008).

Blood glucose. High blood glucose is the third most important global risk factor for mortality and explains 5.8% of global deaths (WHO, 2009). It is well established that patients with schizophrenia and their families are at increased risk of diabetes mellitus. A US study showed that diabetes is an important risk factor for cardiac-related death in schizophrenia (Kilbourne et al., 2009). In the general population it has been shown that low birth weight is a risk factor for diabetes (Phillips et al., 1994). This study needs to be repeated in schizophrenia, as this may prove a useful risk signal. The management of diabetes in schizophrenia is less well established than in the general population. However, one study has reported that the management of diabetes in schizophrenia does not alter the course of the illness at 3 years (Ascher-Svanum et al., 2007). A community study showed better control of diabetes in patients with schizophrenia than controls (Dixon et al., 2004). However, some antipsychotic drugs have been shown to reduce the effectiveness of hypoglycaemic medication in older patients (Pham and Dickman, 2007). Kahn et al. found that first-episode patients with schizophrenia present with high levels of abnormal glucose (Kahn et al., 2008). Further, this study reported that antipsychotics were associated with significant worsening of glucose levels at 12 months. Piette et al. reported that 46% of patients with schizophrenia and comorbid diabetes were taking at least two or more medications to manage their diabetes (Piette et al., 2007). These findings support the view that it would be valuable to follow up patients with schizophrenia and monitor the relationship between their mental illness, their diabetes and treatment in relation to morbidity and mortality.

Physical fitness and inactivity. Physical inactivity accounts for 5.5% of global deaths (WHO, 2009). There are now several studies in the general population which show that low physical fitness, defined in terms of cardiorespiratory fitness (CRF), better predicts CVD mortality than traditional risk factors such as smoking, hypertension or diabetes in men (Kodama et al., 2009; Myers et al., 2002). Furthermore, a recent study of 22,817 patients with schizophrenia also found that low physical activity had a higher HR than smoking for heart disease mortality (HR = 1.66; 95% CI 1.59–1.74 versus HR = 1.32; 95% CI 1.26–1.39) (Kilbourne et al., 2009). High CRF and muscle strength are not only associated with a reduction in CVD mortality but also with all-cause mortality (Lee et al., 1999; Ruiz et al., 2008). A study in young adolescents with schizophrenia showed lower physical activity levels and CRF than their peers (Koivukangas et al., 2010), which supports the view that schizophrenia itself is linked to increased mortality vulnerability. Low CRF is associated with insulin resistance and other risk factors for CVD mortality (Leite et al., 2009).

These findings raise several important research questions in schizophrenia. For example, what is the best measure of fitness in patients with schizophrenia (resting heart rate, treadmill test or questionnaire?). As there are virtually no findings in schizophrenia, it will be important to mirror some of the studies already performed in the general population. These have examined long-term mortality and its association with fitness, pre and post training. This approach is important, as training people can improve their physical fitness and reduce their risk of CVD and all-cause mortality (Blair et al., 1995). The association between CRF and insulin resistance should also be explored in schizophrenia. The WHO report also highlights fitness as being highly protective against breast and colon cancer in the general population (WHO, 2009), so these cancers should be studied first.

Overweight and obesity. An increased body mass index (BMI) is the fifth most important global risk factor for mortality and accounts for 4.8% of global deaths (WHO, 2009). However, the Monica study (Tunstall-Pedoe et al., 1997) and an American study (Flegal et al., 2007) based on data analysis from 2.3 million deaths show that overweight patients have

significantly decreased all-cause mortality compared with those with ideal weight and the obese. Overweight and obesity are major issues for patients with schizophrenia, and it is important to establish how this impacts on all-cause and CVD mortality in schizophrenia. A study from Sweden found that, in the general population of 1.3 million army recruits followed up to 31 years, compared with those with a normal BMI, those who were overweight on recruitment had a 15% lower suicide rate and the obese had a 30% reduction subsequently (Magnusson et al., 2006). A population-based cohort study of 610,359 Norwegians, 1967–1976, found that low body weight was a significant risk factor for suicide (Gravseth et al., 2010). A prospective study, 1986–2002, of 46,755 men showed that a higher BMI was related to a reduced suicide mortality rate, from 52 per 100,000 person-years with a BMI of less than 21 to 13 per 100,000 person-years with a BMI of 30 or higher (Mukamal et al., 2007). The literature is speculative regarding the possible mechanisms associated with this lowered suicide risk. It may simply be correlational, with no causal link. However, as suicide and accidental death are associated with 40% of the deaths in schizophrenia, it is an important question to address regarding the risk balance of overweight and obese categories in schizophrenia. Moreover, suicides tend to occur in young patients, so this has potentially more impact on their family than later mortality. Two systematic reviews in schizophrenia show that modest intentional weight loss can be achieved in the short term, in both overweight and obese patients (Bushe et al., 2009; Faulkner et al., 2007). However, there are studies in older patients in the general population raising some concerns about intentional weight loss (Adams, 2009). One well-designed 18-year follow-up study shows a very significant increase in mortality (Sørensen et al., 2005). The relevance of this in schizophrenia should be evaluated as soon as possible, as most patients will be overweight secondary to antipsychotic medication use. We were unable to find studies in schizophrenia which examined the relationship between BMI and mortality.

Lipids. High cholesterol accounts for 4.5% of global deaths (WHO, 2009). In the general population, familial hypercholesterolaemia is a well-established risk factor for premature mortality. The role of statins in the management of diabetes and CVD are also well established in the general population. However, there are emerging data that in older patients low cholesterol may be associated with increased frailty and mortality (Okamura et al., 2008; Räihä et al., 1997). Recent research has linked the use of statins with increased risk of diabetes in the general population (Sattar et al., 2010), but to date there are few data in the schizophrenia literature. As patients with schizophrenia are at an elevated risk of developing diabetes, this may alter the risk–benefit balance of treatment with statins. Paradoxically, in patients who respond to clozapine it has been reported that a reduction in the positive and negative symptom score (PANSS) correlates with increases in lipid levels (Huang and Chen, 2005). Kilbourne's study in 22,817 patients with schizophrenia (Kilbourne et al., 2009) showed that hyperlipidaemia was protective for CVD mortality (HR for mortality from heart disease 0.86; 95% CI 0.82–0.89), whereas diabetes (HR = 1.51; 95% CI 1.44–1.57) and hypertension (HR = 1.38; 95% CI 1.32–1.46) both increased cardiac mortality risk. Moreover, if schizophrenia is a disease mimicking rapid ageing, it will be important to establish the best lipid levels by age and their impact on mortality in this population. To date there are only data from one study (Kilbourne et al., 2009).

Medical care. Patients with schizophrenia are not engaged with and tend to be treated poorly by health services (Kreyenbuhl et al., 2009; Rethink, 2010). There is evidence that people with schizophrenia are less likely to receive cancer screening and secondary care interventions even if identified with a disorder (Lawrence et al., 2000; Kisely et al., 2007, 2008). Even when a physical healthcare need is identified, treatment is less intensive than in the general population. Further research is needed to identify why this is so and how it may be remedied.

Antipsychotic medication

The primary theme of this paper is to explore whether the major risk factors for premature mortality in the general population are directly relevant and manageable in people with schizophrenia. However, treatments for schizophrenia may also affect physical health, which may lead to early mortality. This topic is complex, and here we present a summary of some the most recent findings. A systematic review examining the differential effects on mortality of second-generation antipsychotics compared with first-generation antipsychotics showed inconsistent findings (Weinmann et al., 2009). However, Tiihonen et al. describe one of the longest and largest studies, examining cause-specific mortality in 66,881 patients with schizophrenia versus the total population of Finland (5.2 million) between 1996 and 2006 (Tiihonen et al., 2009). 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, there were no signs of increased risk of death from ischaemic heart disease after 7–11 years of cumulative exposure to these agents. 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 study in patients with tardive dyskinesia found higher rates of mortality in older patients, particularly those on conventional antipsychotics (Dean and Thuras, 2009). Mortality studies which have not separated out the schizophrenia cohort from patients with other severe mental illnesses have not been included in this review, as interpretation of these findings is complex (Osborn et al., 2007; Ray et al., 2009).

Discussion

Patients with schizophrenia have an elevated incidence of the six leading global mortality risk factors described by the

WHO (WHO, 2009). If research findings from the general population are directly applicable to schizophrenia, this may account for the premature mortality associated with the illness. However, there is little evidence in the literature to support this assertion, or indeed refute it. Moreover, there are indications that schizophrenia is a metabolic disease with associated higher rates of diabetes, differing patterns of adiposity and elevated lipids. Furthermore, low birth weight, which is more common in those with schizophrenia, diabetes and CVD, may be an early common pathway for this excess mortality. Comorbidity is often associated with a poorer treatment response for a variety of factors including adherence, medication interactions and complications arising from the underlying disorders.

Currently, there is a dearth of basic data for these important parameters in schizophrenia. While some questions will require long-term prospective studies, others may be more amenable to shorter and less costly investigation. It will be important to establish appropriate measures of CRF, and how interventions to improve CRF impact on other risk factors in the short-to-medium term, such as insulin resistance, obesity (including disposition) and hypertension.

Interrogation of national prescribing databases should allow a retrospective view of the outcomes in treated hypertension, dyslipidaemia and diabetes, in order to ascertain whether results are the same or differ significantly from the general population. Given the chronic under-treatment of these disorders, some caution would have to be exercised in interpreting the findings. However, such studies could inform the design and feasibility of prospective longer-term studies of interventions aimed at both primary and secondary prevention.

There are suggestions that from the genetic perspective, schizophrenia may confer advantages and disadvantages in disease risk, such as elevated CVD but lower incidence of autoimmune disorders (Eaton et al., 2006). A greater understanding of the relationship between these disorders at a molecular level would be advantageous in advancing their treatment. Such molecular understanding would also allow us to understand whether carcinogens in cigarette smoke act in precisely the same way irrespective of whether the smoker has or does not have schizophrenia. Our review suggests that direct extrapolation of results from the general population to schizophrenia may not always be appropriate, and that optimum treatment may require a compromise between physical and mental health outcomes.

Since the introduction of atypical antipsychotics in the 1990s, there has been a debate about whether these drugs might be associated with increased cardiovascular mortality compared with typical antipsychotics, because of their tendency for causing greater weight gain and metabolic changes. Whereas smoking has now been strongly linked with a high risk of cardiovascular mortality in schizophrenia (Kelly et al., 2009; Kilbourne et al., 2009), the much larger study of antipsychotics with 7–11 years follow-up failed to show an increased all-cause mortality or increased CVD mortality with atypical antipsychotics compared with typicals (Tiihonen et al., 2009). This supports the view that if there is differential cardiovascular mortality risk between antipsychotic classes, it is likely to be small and may require even larger and longer studies to answer this question. These findings may be partially explained by the observation that weight gain in middle-aged and elderly individuals has a minimal impact on mortality at 14 years (Myrskylä and Chang, 2009). Further, Weiler et al. report that high-quality evidence is now available from large cohort studies confirming that physical inactivity, rather than obesity, is the causal factor for cardiovascular disease, coronary heart disease, type 2 diabetes, dyslipidaemias, hypertension, arrhythmias, increased inflammatory markers, myocardial infarction, stroke, cancer and ultimately death (Weiler et al., 2010). To date, there are few research findings on the impact of antipsychotics on physical activity levels or cardiovascular fitness in schizophrenia; these studies need to be completed urgently.

Suicide and accidental deaths account for up to 40% of all deaths in schizophrenia (Brown, 1997; Tran et al., 2009). However, the schizophrenia literature has largely ignored the impact of antipsychotics on suicide in the overall mortality risk balance equation for antipsychotics. A large Finnish study in first-admitted patients with schizophrenia showed significantly increased risk for suicide in patients not receiving antipsychotics (Tiihonen et al., 2006). Paradoxically, the literature in the general population supports the view that patients with a high BMI are at lower risk of suicide. This finding may partially explain lower suicide rates with clozapine (Hennen and Baldessarini, 2005) and may be relevant to all antipsychotics. Studies are required to examine the link between BMI and suicide risk in schizophrenia, which may provide understanding into the risk factors for suicide and improve management. A relatively simple population study may help to address this hypothesis. Patients with schizophrenia tend to have higher BMIs in the US as compared with Taiwan; as antipsychotics are used widely in both populations, by examining the rates of suicide in these countries it may be possible to see a differential impact of BMI on suicide risk by population. This will be an important test of hypothesis.

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References

Adams KF (2009) Understanding long-term effects of weight loss. *Epidemiology* 20: 849–850.

Ascher-Svanum H, Zhu B, Ernst FR, Faries DE, Jacobson JG and Doebbeling CC (2007) The 3-year clinical and functional course of schizophrenia among individuals with and without diabetes at

study entry. Primary care companion. *J Clin Psychiatry* 9: 122–128.

Blair SN, Kohl HW 3rd, Barlow CE, Paffenbarger RS Jr, Gibbons LW and Macera CA (1995) Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *JAMA* 273: 1093–1098.

Brown S (1997) Excess mortality of schizophrenia. A meta-analysis. *Br J Psychiatry* 171: 502–508.

Brown S, Barraclough B and Inskip H (2000) Causes of the excess mortality of schizophrenia. *Br J Psychiatry* 177: 212–217.

Brown S, Kim M, Mitchell C and Inskip H (2010) Twenty-five year mortality of a community cohort with schizophrenia. *Br J Psychiatry* 196: 116–121.

Bushe CJ, Bradley AJ, Doshi S and Karagianis J (2009) Changes in weight and metabolic parameters during treatment with antipsychotics and metformin: do the data inform as to potential guideline development? A systematic review of clinical studies. *Int J Clin Pract* 63(12): 1743–1761.

Campion J, Checinski K and Nurse J (2008) Review of smoking cessation treatments for people with mental illness. *Adv Psychiatr Treat* 14: 208–216.

Catts VS, Catts SV, O'Toole BI and Frost AD (2008) Cancer incidence in patients with schizophrenia and their first degree relatives – meta-analysis. *Acta Psychiatr Scand* 117: 323–336.

Dean CE and Thuras PD (2009) Mortality and tardive dyskinesia: long-term study using the US National Death Index. *Br J Psychiatry* 194: 360–364.

Dixon LB, Kreyenbuhl JA, Dickerson FB, Donner TW, Brown CH, Wohlheiter K, et al. (2004) A comparison of type 2 diabetes outcomes among persons with and without severe mental illnesses. *Psychiatr Serv* 55: 892–900.

Eaton WW, Byrne M, Ewald H, Mors O, Chen CY, Agerbo E, et al. (2006) Association of schizophrenia and autoimmune diseases: Linkage of Danish National Registers. *Am J Psychiatry* 163: 521–528.

Faulkner G, Cohn T and Remington G (2007) Interventions to reduce weight gain in schizophrenia (Review). *The Cochrane Library Issue* 3.

Fernandez-Egea E, Bernardo M, Heaphy CM, Griffith JK, Parellada E, Esmatjes E, et al. (2009) Telomere length and pulse pressure in newly diagnosed, antipsychotic-naive patients with nonaffective psychosis. *Schizophr Bull* 35: 437–442.

Ferrario CM and Levy P (2002) Sexual dysfunction in patients with hypertension: implications for therapy. *J Clin Hypertens* 4: 424–432.

Flegal KM, Graubard BI, Williamson DF and Gail MH (2007) Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA* 298: 2028–2037.

Gravseth HM, Mehlum L, Bjerkedal T and Kristensen P (2010) Suicide in young Norwegians in a life course perspective: population-based cohort study. *J Epidemiol Community Health* 64: 407–412.

Hennen J and Baldessarini RJ (2005) Suicidal risk during treatment with clozapine: a meta-analysis. *Schizophr Res* 73: 139–145.

Huang TL and Chen JF (2005) Serum lipid profiles and schizophrenia: effects of conventional or atypical antipsychotic drugs in Taiwan. *Schizophr Res* 80: 55–59.

Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. (2008) Cancer statistics, 2008. *CA Cancer J Clin* 58: 71–96.

Jindal R, Keshavan M, Eklund K, Stevens A, Montrose D and Yeragani V (2009) Beat-to-beat heart rate and QT interval variability in first episode neuroleptic-naive psychosis. *Schizophr Res* 113: 176–180.

Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, et al. (2008) Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet* 371: 1085–1097.

Kelly DL, McMahon RP, Wehring HJ, Liu F, Mackowick KM, Boggs DL, et al. (2009) Cigarette smoking and mortality risk in people with schizophrenia. *Schizophr Bull* [Epub ahead of print, Advance Access published on line December 17 2009, doi:10.1093/schbul/sbp152].

Kilbourne AM, Morden NE, Austin K, Ilgen M, McCarthy JF, Dalack G, et al. (2009) Excess heart-disease-related mortality in a national study of patients with mental disorders: identifying modifiable risk factors. *Gen Hosp Psychiatry* 31: 555–563.

Kirkpatrick B, Messias E, Harvey PD, Fernandez-Egea E and Bowie CR (2008) Is schizophrenia a syndrome of accelerated aging. *Schizophr Bull* 34: 1024–1032.

Kisely S, Sadek J, MacKenzie A, Lawrence D and Campbell LA (2008) Excess cancer mortality in psychiatric patients. *Can J Psychiatry* 53: 753–761.

Kisely S, Smith M, Lawrence D, Cox M, Campbell LA and Maaten M (2007) Inequitable access for mentally ill patients to some medically necessary procedures. *Can J Psychiatry* 176: 779–784.

Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. (2009) Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA* 301: 2024–2035.

Koivukangas J, Tammelin T, Kaakinen M, Mäki P, Moilanen I, Taanila A, et al. (2010) Physical activity and fitness in adolescents at risk for psychosis within the Northern Finland 1986 Birth Cohort. *Schizophr Res* 116: 152–158.

Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Duggan L, et al. (2010) Olanzapine versus other atypical antipsychotics for schizophrenia (Review). *Cochrane Library Issue* 3.

Kreyenbuhl J, Nossel IR and Dixon LB (2009) Disengagement from mental health treatment among individuals with schizophrenia and strategies for facilitating connections to care: a review of the literature. *Schizophr Bull* 35: 696–703.

Laursen TM, Munk-Olsen T, Agerbo E, Gasse C and Mortensen PB (2009) Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder. *Arch Gen Psychiatry* 66: 713–720.

Lawrence D, Holman CD, Jablensky AV, Threlfall TJ and Fuller SA (2000) Excess cancer mortality in Western Australian psychiatric patients due to higher case fatality rates. *Acta Psychiatr Scand* 101: 382–388.

Lee CD, Blair SN and Jackson AS (1999) Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. *Am J Clin Nutr* 69: 373–380.

Leite SAO, Monk AM, Upham PA, Chacra AR and Bergenstal RM (2009) Low cardiorespiratory fitness in people at risk for type 2 diabetes: early marker for insulin resistance. *Diabetol Metab Syndr* 1: 8.

Magnusson PK, Rasmussen F, Lawlor DA, Tynelius P and Gunnell D (2006) Association of body mass index with suicide mortality: a prospective cohort study of more than one million men. *Am J Epidemiol* 163: 1–8.

Malone KM, Waternaux C, Haas GL, Cooper TB, Li S and Mann JJ (2003) Cigarette smoking, suicidal behavior, and serotonin function in major psychiatric disorders. *Am J Psychiatry* 160: 773–779.

Mitchell AJ, Malone D and Carney Doebbeling C (2009) Quality of medical care for people with and without comorbid mental illness and substance misuse: systematic review of comparative studies. *Br J Psychiatry* 194: 491–499.

Mukamal KJ, Kawachi I, Miller M and Rimm EB (2007) Body mass index and risk of suicide among men. *Arch Intern Med* 167: 468–475.

Myers J, Prakash M, Froelicher V, Do D, Partington S and Atwood JE (2002) Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 346: 793–801.

Myrskylä M and Chang VW (2009) Weight change, initial BMI, and mortality among middle- and older-aged adults. *Epidemiology* 20: 840–848.

Okamura T, Hayakawa T, Hozawa A, Kadowaki T, Murakami Y, Kita Y, et al. (2008) Lower levels of serum albumin and total cholesterol associated with decline in activities of daily living and excess mortality in a 12-year cohort study of elderly Japanese. *J Am Geriatr Soc* 56: 529–535.

Osborn DPJ, Levy G, Nazareth I, Petersen I, Islam A and King MB (2007) Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Research Database. *Arch Gen Psychiatry* 64: 242–249.

Pham CB and Dickman RL (2007) Minimizing adverse drug events in older patients. *Am Fam Physician* 76: 1837–1844.

Phillips DI, Barker DJ, Hales CN, Hirst S and Osmond C (1994) Thinness at birth and insulin resistance in adult life. *Diabetologia* 37: 150–154.

Piette JD, Heisler M, Ganoczy D, McCarthy JF and Valenstein M (2007) Differential medication adherence among patients with schizophrenia and comorbid diabetes and hypertension. *Psychiatr Serv* 58: 207–212.

Räihä I, Marniemi J, Puukka P, Toikka T, Ehnholm C and Sourander L (1997) Effect of serum lipids, lipoproteins, and apolipoproteins on vascular and nonvascular mortality in the elderly. *Arterioscler Thromb Vasc Biol* 17: 1224–1232.

Ray WA, Chung CP, Murray KT, Hall K and Stein CM (2009) Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med* 360: 225–235.

Rethink (2010) *Stigma and health services*. Available at: http://www.rethink.org/living_with_mental_illness/everyday_living/stigma_mental_illness/stigma_and_1.html (Accessed 5 July 2010).

Ruiz JR, Sui X, Lobelo F, Morrow JR Jr, Jackson AW, Sjöström M, et al. (2008) Association between muscular strength and mortality in men: prospective cohort study. *Br Med J* 337: 92–95.

Saha S, Chant D and McGrath J (2007) A systematic review of mortality in schizophrenia. *Arch Gen Psychiatry* 64: 1123–1131.

Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. (2010) Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 375: 735–742.

Sørensen TIA, Rissanen A, Korkeila M and Kaprio J (2005) Intention to lose weight, weight changes, and 18-y mortality in overweight individuals without co-morbidities. *PLoS Med* 2: e171.

Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, et al. (2009) 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 374: 620–627.

Tiihonen J, Wahlbeck K, Lönnqvist J, Klaukka T, Ioannidis JP, Volavka J, et al. (2006) Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder. *Br Med J* 333: 224–227.

Tran E, Rouillon F, Loze JY, Casadebaig F, Philippe A, Vitry F, et al. (2009) Cancer mortality in patients with schizophrenia: an 11-year prospective cohort study. *Cancer* 115: 3555–3562.

Tunstall-Pedoe H, Woodward M, Tavendale R, Brook RA and McCluskey MK (1997) Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish heart health study: cohort study. *Br Med J* 315: 722–729.

Weiler R, Stamatakis E and Blair S (2010) Should health policy focus on physical activity rather than obesity? Yes. *Br Med J* 340: c2603.

Weinmann S, Read J and Aderhold V (2009) Influence of antipsychotics on mortality in schizophrenia: systematic review. *Schizophr Res* 113: 1–11.

WHO (2009) *Global health risks: mortality and burden of disease attributable to selected major risks*. Geneva: World Health Organization.