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Excess Early Mortality in Schizophrenia

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Abstract

Schizophrenia is often referred to as one of the most severe mental disorders, primarily because of the very high mortality rates of those with the disorder. This article reviews the literature on excess early mortality in persons with schizophrenia and suggests reasons for the high mortality as well as possible ways to reduce it. Persons with schizophrenia have an exceptionally short life expectancy. High mortality is found in all age groups, resulting in a life expectancy of approximately 20 years below that of the general population. Evidence suggests that persons with schizophrenia may not have seen the same improvement in life expectancy as the general population during the past decades. Thus, the mortality gap not only persists but may actually have increased. The most urgent research agenda concerns primary candidates for modifiable risk factors contributing to this excess mortality, i.e., side effects of treatment and lifestyle factors, as well as sufficient prevention and treatment of physical comorbidity.

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INTRODUCTION

Schizophrenia is often described as a severe mental disorder. However, the degree of severity is frequently difficult to determine. To get a perspective of the psychiatric disorder schizophrenia, it is necessary to compare it to other psychiatric disorders as well as other somatic disorders, and a measurement of severity is therefore needed. One way of measuring the severity of a disorder is to calculate a disability weight for the individual disorder. In a large study with data from all over the world, 220 disorders or disorder states were assigned a disability weight from 0 to 1, with 0 implying no loss of health and 1 implying a health loss equivalent to death (Salomon et al. 2012). A mild infection had a score of 0.005, whereas a more severe event such as losing an arm had a score of 0.13. Very severe somatic disorders such as cancer with metastases had a score of 0.48. However, the most severe of all 220 disorders was schizophrenia in an acute state, with a score of 0.76. Such a ranking is obviously subject to several limitations, but the data nevertheless indicate that schizophrenia is one of the most severe and disabling disorders worldwide.

One major reason that schizophrenia is one of the most severe disorders is the very high mortality rates that are present in persons with the disorder. More than 60 years ago, Odegard (1951) showed an excess mortality in patients admitted to a Norwegian mental hospital in the period 1916 to 1941, with a follow-up period from 1926 to 1941. The mortality rate for men with schizophrenia was 3.2 times higher than that for the general Norwegian population, and the corresponding number for women was 4.8. During recent decades, mortality in schizophrenia has been extensively studied. A cornerstone study was the extensive review Harris & Barraclough (1998), which

documented excess mortality among psychiatric patients, especially patients with schizophrenia. It is well established that suicide contributes to the excess mortality; a recent meta-analysis estimated that the risk of suicide was approximately 13-fold higher for persons with schizophrenia as compared to the general population (Saha et al. 2007). However, mounting evidence suggests that most of the excess mortality is explained by natural causes of death (Laursen 2011), and this calls for an increased focus on physical illness to understand the observed excess mortality.

In this article, we review the literature on excess early mortality in persons with schizophrenia and suggest possible steps to reduce it.

HISTORICAL DEVELOPMENT

Symptoms of schizophrenia have been described for centuries, but the modern concept of schizophrenia was developed in the late-nineteenth century. In the 1890s, the German psychiatrist Emil Kraepelin developed a classification system in which he dichotomized patients with severe mental disorder including psychotic symptoms in two categories: manic-depressive illness (later named bipolar disorder) and dementia praecox (later named schizophrenia). According to Kraepelin's dichotomization, patients with bipolar disorder would eventually improve, whereas patients with schizophrenia were prone to deterioration and would eventually get dementia. The prognosis and outcome in persons with schizophrenia tended to be worse (including higher mortality rates) than the outcome in persons with bipolar disorder (Shorter 1997). The key difference in Kraepelin's classification compared to earlier classification concepts was that the prognosis—not the cause—of the disorder was the single most important feature (Shorter 1997).

Kraepelin's dichotomization proved later not to be entirely true because some patients with schizophrenia recovered completely, and thus outcome measures as a key component in the diagnosis had to be questioned (Angst 2002). Other key features in Kraepelin's dichotomization have also been questioned, in particular in connection with Jacob Kasanin's introduction of the concept of schizoaffective disorder in 1933. Overall, patients with schizoaffective disorder were characterized by a good prognosis, but with both schizophrenic and affective symptoms.

As a natural consequence of these inconsistencies, alternative classifications to the Kraepelinian dichotomization have been proposed, especially in Europe (Kelly & Murray 2000). These include the developmental theory (Murray et al. 2004), which suggests a genetic overlap between bipolar affective disorder and schizophrenia, and the continuum theory (Angst 2002, Moller 2003, Torrey 1999, Varma et al. 1997), which suggests that the major psychiatric disorders constitute a continuum ranging from unipolar depressive disorder, to bipolar affective disorder, to schizoaffective disorder, to schizophrenia, with increasing severity across the spectrum.

However, in the World Health Organization's *International Classification of Diseases* (ICD-10; World Health Organ. 1994a), which is used in most of the world (except the United States) at present, schizophrenia is still defined as a distinct entity separate from bipolar disorder. It is described in the following way: "The schizophrenic disorders are characterized in general by fundamental and characteristic distortions of thinking and perception, and affects that are inappropriate or blunted. Clear consciousness and intellectual capacity are usually maintained although certain cognitive deficits may evolve in the course of time" (World Health Organ. 1994b). It is important to note that schizophrenia is a syndrome, and thus the definition of the disorder can vary from one classification system to another.

INCIDENCE OF SCHIZOPHRENIA

How many persons have a schizophrenia diagnosis? From Danish population registries, we know that approximately 1.5% of the population will get a diagnosis of schizophrenia at some point

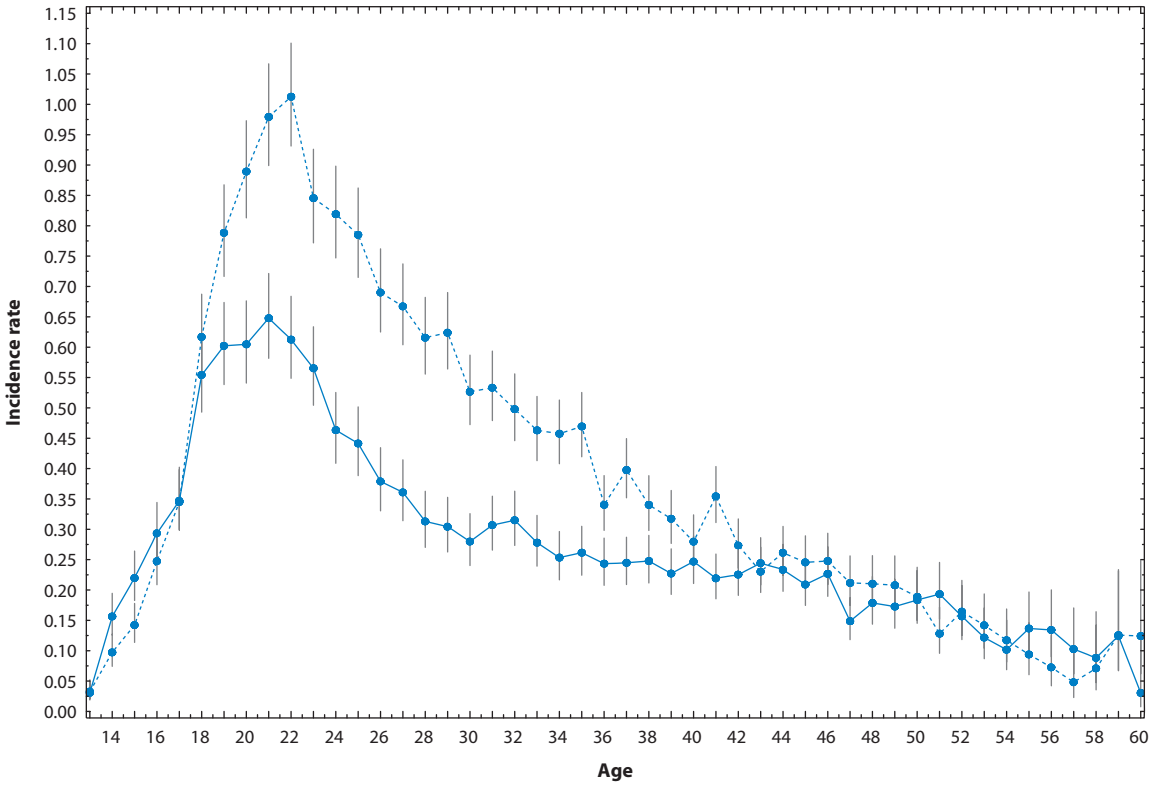

Figure 1

Incidence of schizophrenia among women (*solid line*) and men (*dotted line*), ages 13 to 60, per 1,000 years under risk in Denmark in the period 1995 to 2011.* Vertical lines represent 95% confidence limits. *X*-axis = age, *Y*-axis = incidence of schizophrenia per 1,000 years under risk.

*Note: Calculations include all persons born in Denmark after 1950. Incidence onset of schizophrenia defined as first psychiatric contact (in or outpatient) with a diagnosis of schizophrenia in 1995 to 2011 (both years included); thus, 61 is the maximum age of the cohort members. All persons with a contact with a schizophrenia diagnosis from 1970 to 1994 are deleted to ensure a washout period resulting in incident cases. Numbers calculated on the basis of a merging of the Danish Psychiatric Central Research Register (Mors et al. 2011) and the Danish Civil Registration System Register (Pedersen et al. 2006). Mortality and immigration out of Denmark were taken into account in the calculations. The merging of the registers was approved by the Danish Data Protection Agency. No informed consent from participants was needed because data were analyzed anonymously. Because the data are entirely based on register information, no specific ethical permission is required according to Danish law.

in their life (Thorup et al. 2007). This percentage may be slightly lower in other countries, but schizophrenia occurs worldwide (McGrath et al. 2008). Population subgroups have different incidences of schizophrenia; e.g., males have a higher incidence of schizophrenia, males have an earlier onset (van der Werf et al. 2012), and persons living and/or born in the city have a higher incidence (Pedersen & Mortensen 2006), as do immigrants (Cantor-Graae et al. 2003). In Denmark, the incidence (i.e., new cases of schizophrenia per 1,000 years under risk in each age group) peaks in the early twenties. **Figure 1** shows the incidence of schizophrenia in Denmark among the total population ages 13 to 61 years. A sharp peak occurs in the late teens and early twenties and is more pronounced among males than females. The incidence declines steadily after the age of 22, and at the maximum age of this cohort, 60 to 61 years, the incidence is 0.1 new cases of schizophrenia per 1,000 years under risk in both men and women.

The results from Denmark are similar to those of studies from other countries, although some differences are noted. A review by Messias et al. (2007) found the incidence of schizophrenia to be 0.2 per 1,000 years under risk, with a range from 0.11 per 1,000 years to 0.70 per 1,000 years. In the same study, prevalence was found to be approximately 5 per 1,000 years (Messias et al. 2007).

A paper from the AeSOP study (Kirkbride et al. 2006) found an overall incidence of schizophrenia of 0.128 per 1,000 persons; the incidence per 1,000 years under risk was around 0.4 for men in the young age groups and 0.1 in the older age groups. Women had a lower rate in the young age groups (Kirkbride et al. 2006).

A systematic review by Saha et al. (2005) found a lifetime morbidity risk of 7.2 per 1,000 persons; the 10% and 90% quantiles were 3.1 and 27.1, respectively. However, as the 10% and 90% quantiles suggest, there was a huge difference in lifetime risk across the different studies.

The overall picture is that the incidence of schizophrenia varies significantly not only across different groups within a population but also between countries. Although it is not a common disorder, more than 1% of a population has schizophrenia.

EXTENT OF THE EXCESS MORTALITY

How to Measure Mortality

The excess mortality in persons with schizophrenia has traditionally been described by mortality rate ratios (MRRs). The MRRs are found by calculating the mortality rate in all persons with schizophrenia and then dividing that rate by the mortality rate in a comparison group. Another concept very similar to the MRR is the standardized mortality rate (SMR), which is found by dividing the mortality rate in the group of persons with schizophrenia by the rate in the general population. Since the time that Odegard (1951) and Alström (1942) conducted studies, the MRR (or SMR) between persons with schizophrenia and the general population has been shown to decrease with increasing age. This phenomenon, termed "effect modification by age" is very important to take into account when calculating MRRs. The explanation for the effect modification by age is that the mortality in the general population is very low in the young age groups. **Figure 2** shows the MRR in Denmark among persons with schizophrenia compared to the general population. It clearly demonstrates that with increasing age, the MRR decreases between persons with schizophrenia and the general population. An exception from this trend is in the age group 18 to 19. The extremely high MRR in the young age groups should be interpreted with caution because of the very low number of deaths in the general population. For example, the lower MRRs among the 18- to 19-year-olds (compared to the 20- to 36-year-olds) probably appears because young men from the general population are more often involved in traffic accidents than are young men with schizophrenia.

Because MRRs decrease with older age, when analyzing data it is crucial that the age distributions of the populations compared are the same. Comparisons of MRRs between groups or countries are very difficult if the age of the groups is not fully taken into account, and this could bias the results. Another pitfall in the calculation of MRRs is unequal detection of deaths in the two groups. If the general mortality rate in a country is used in one group, it is very important to include all deaths in the group of persons with schizophrenia to prevent an underestimation of the MRRs.

An alternative approach to measuring the excess mortality among people with schizophrenia is to calculate the differences in number of years that a person with schizophrenia lives compared to a person in the general population. If a person dies at age 55, and the expected age of death in the population is 75, a total of 20 years of life are lost. Calculating the excess mortality as differences in the number of years that persons with schizophrenia live compared to the general population

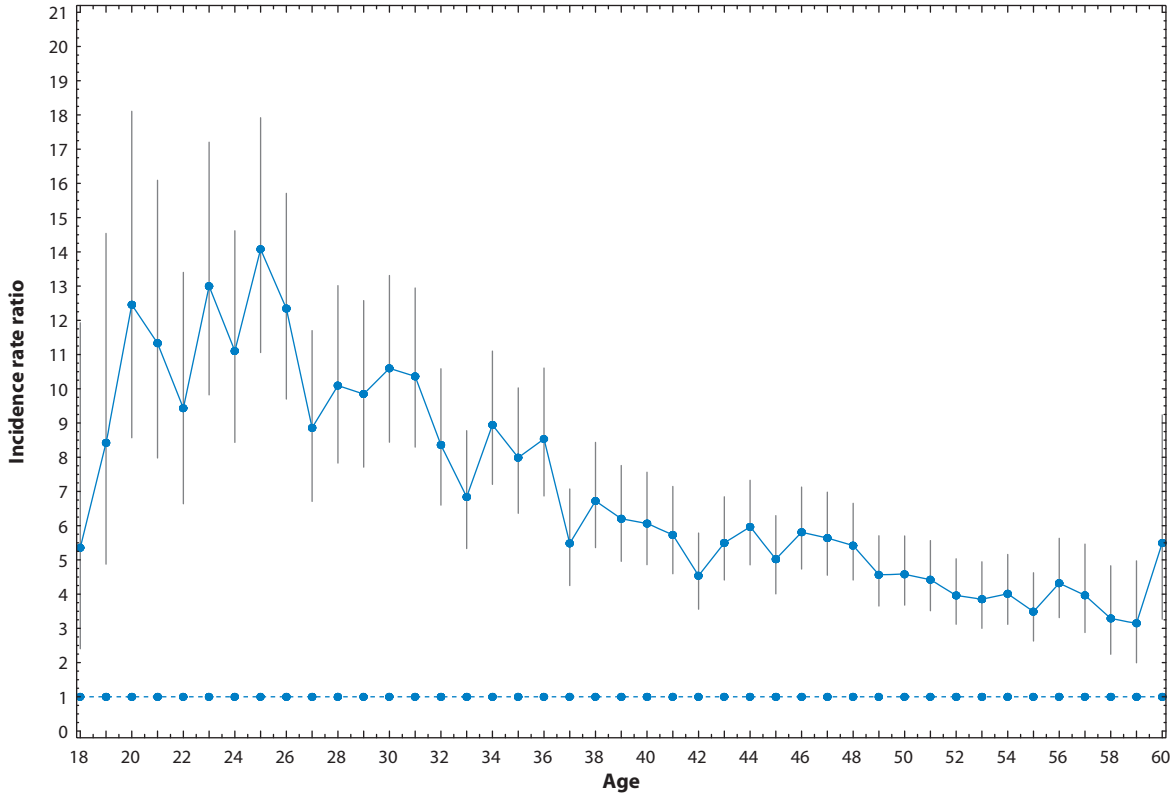

Figure 2

Mortality rate ratio for persons with schizophrenia (*solid line*) in Denmark compared to the general population (reference group; *dotted line*).* Vertical lines represent 95% confidence limits.

*See **Figure 1** for study details. In **Figure 2**, follow-up time is expanded to include the period from 1970 to 2010, and only persons 18 years or older are included. Standardized mortality rate is adjusted for gender and calendar time.

presents several advantages compared to the MRR. These advantages include that the method takes into account the effect of very common causes of death with relatively low excess mortality, it gives more weight to deaths occurring among younger persons (which are more common among persons with severe mental disorders than the general population), and it presents a straightforward and understandable measure of the magnitude of the excess mortality.

Most mortality studies on calculation of life expectancy are based on record linkage. Persons with schizophrenia are identified through recorded contacts to psychiatric treatment facilities, and data are subsequently linked to registers of cause of death. Studies in general use two different ways of calculating the number of years that persons with schizophrenia live in comparison with the general population. The first method is to calculate life expectancy from mortality rates in different age groups. In this method, the mortality rate is calculated for all age groups (e.g., in one-year bands). Life expectancy at a given age represents the average number of years of life remaining if a group of persons at that age had similar mortality rates for a particular year over the course of their remaining lives. Life expectancy is a summary measure of the age-specific all-cause mortality rates in an area in a given period. The second method uses only information on the persons who died and calculates the average age in which persons in the cohort died. This method has several shortcomings compared to life expectancy calculations, e.g., if the compared

Table 1 Life expectancy among patients with schizophrenia in Denmark, Sweden, and Finland compared to the general population

Population	Denmark		Finland		Sweden	
	Life expectancy	Difference	Life expectancy	Difference	Life expectancy	Difference
Men						
General population	75.7	–	75.7	–	78.2	–
Patients with schizophrenia	55.7	20.0	58.6	17.1	59.3	18.9
Women						
General population	80.3	–	82.5	–	82.6	–
Patients with schizophrenia	63.8	16.5	66.9	15.6	65.7	16.9

Adapted from "Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophrenia in the Nordic countries" (Laursen et al. 2013b). Note that we have assumed no mortality in the age group 0–15 years old.

groups of persons do not have the same average age, then it would appear as if the group with the highest average age had the highest mortality, simply because mortality is higher in older people.

In the following sections, we describe the literature on life expectancy and MRR/SMR.

Life Expectancy

A recent study using information from the entire population in Denmark, Sweden, and Finland calculated life expectancy among the general population and compared it to persons with a psychiatric hospital admission for a diagnosis of schizophrenia and found life expectancies to be 15.6 to 20 years shorter in this patient group in these three countries (see **Table 1**).

A Danish study used age at death among persons with schizophrenia as an indication of length of life expectancy compared to the general population and found that a person with schizophrenia died 11.2 years earlier than the general population (Nielsen et al. 2013b). The same method was used in a study from Sweden that found that persons with schizophrenia died 15 years (men) and 12 years (women) earlier than the general population (Crump et al. 2013). A study from Israel found life expectancy to be 12 years lower among persons with schizophrenia (Kodesh et al. 2012), and a Welch study found that persons admitted with schizophrenia to an asylum from 1875 to 1924 died 10.8 years earlier than the general population (Healy et al. 2012). A recent study from the United Kingdom (Chang et al. 2011) found that life expectancy was reduced by 14.6 years among persons with schizophrenia. A study focusing on patients with schizophrenia and substance abuse, i.e., a dual diagnosis (Schmidt et al. 2011), found that age at death for these patients was particularly low (49 years). A Finnish study found life expectancy to be 10 to 15 years shorter for persons with a diagnosis in the schizophrenia spectrum (Westman et al. 2011). An even shorter life expectancy was found during 11 years of follow-up in a Finnish study; life expectancy at age 20 was found to be 25 years shorter in 1996 and 22.5 years shorter in 2006 (Tiihonen et al. 2009).

In conclusion, all studies find a significant and very low life expectancy in persons with schizophrenia. However, some of the studies use only information on the persons with schizophrenia who died, and results should therefore be interpreted with caution. With that caution in mind, studies indicate that the lives of persons with schizophrenia are between 10 and 25 years shorter than those of the general population.

Mortality Rate Ratios

In 1997, Brown completed a comprehensive meta-analysis of the SMR in persons with schizophrenia (Brown 1997). The SMR in persons with schizophrenia was found to be 1.51, i.e., the mortality rate was on average 51% higher than that of the general population. In a study from Sweden (Osby et al. 2000), the excess mortality in patients who had been admitted with schizophrenia was 2.8 for men and 2.4 for women. In a Finnish study (Joukamaa et al. 2001), the excess mortality in schizophrenic patients was 3.3 for men and 2.3 for women. Another Finnish study that included only persons with schizophrenia older than 65 found a SMR of 2.69 (Talaslahti et al. 2012). A recent systematic review by Saha et al. (2007) identified 37 studies examining the SMR for persons with schizophrenia compared to the general population. The overall SMR was 2.58, with 10% and 90% quantiles of 1.18 and 5.76, respectively. An elevated mortality rate among persons with schizophrenia was indicated by cause-specific SMRs that were higher than 1, except for the SMR for cerebrovascular disease, which was based on only three studies. Notably, the SMR for cancer was only 1.37, which has also been observed in other studies (Laursen et al. 2007; Mortensen & Juel 1990, 1993). Another interesting result was that the SMRs increased significantly during three recent decades, i.e., the seventies, eighties, and nineties; from 1.84, to 2.98, to 3.20, respectively. The cardiovascular mortality gap between persons with schizophrenia and the general population has also grown during the past few decades, according to a Danish register-based study (Laursen & Nordentoft 2011); the mortality rate ratio has increased from around 2.0 in 1994 to 3.5 in 2006 compared to the general population. The study suggests that the overall improvement in cardiovascular treatment and lifestyle experienced by the general population has not been experienced by persons with schizophrenia. The same widening of the mortality gap was found in another Danish study (Nielsen et al. 2013b) and in a study from the United Kingdom (Brown et al. 2010). In the British study, an MRR of 2 to 3 was found. In contrast, a study from Finland (Westman et al. 2011) found that the difference in mortality among women with schizophrenia compared to the general population has diminished during recent years. Finally, a study from Africa found higher mortality among all patients at a Nigerian psychiatric hospital (Abiodun 1988).

In conclusion, the mortality among persons with schizophrenia is between two and three times higher than that of the general population when all age groups are included.

WHY THE EXCESS EARLY MORTALITY?

Why do persons with schizophrenia have a higher mortality? A recent paper identifies four main reasons (Laursen et al. 2012):

- Physical illnesses in persons with schizophrenia are common but are diagnosed late and treated insufficiently.
- Antipsychotic medicine may have negative side effects.
- Persons with schizophrenia tend to have an unhealthy lifestyle (poor diet, smoking, excess alcohol consumption, and lack of exercise).
- The risk of suicide and accidents among patients with schizophrenia is high.

In the following sections, we examine all four factors.

Poor Physical Health and Health Care

The Charlson Comorbidity Index is sometimes used to measure somatic comorbidity in schizophrenic patients. The index includes 19 severe chronic disorders that are assigned a weighted

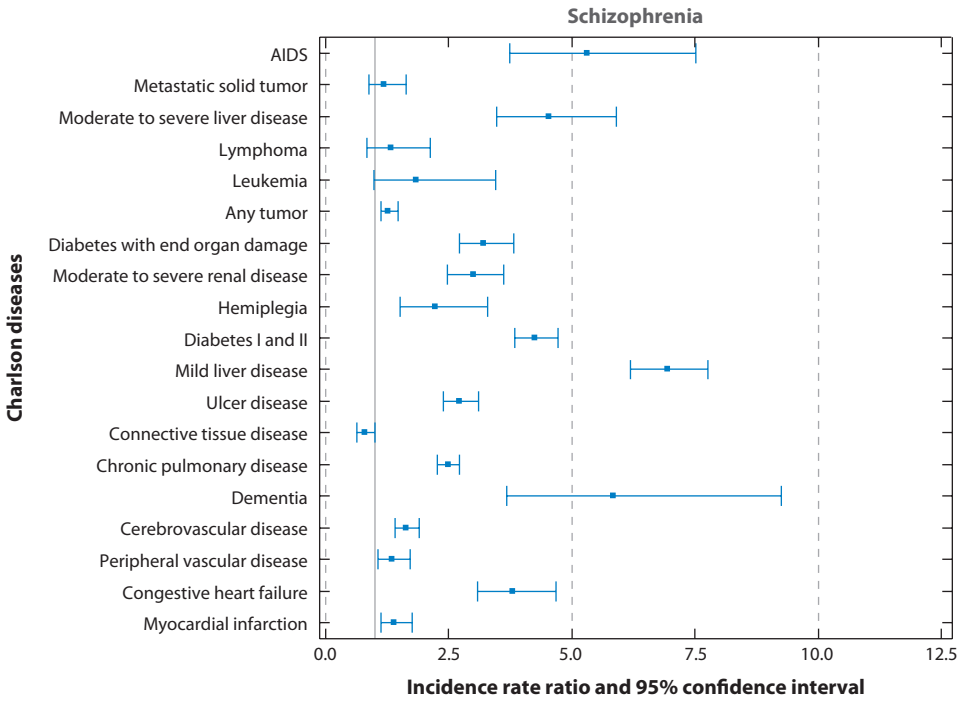

Figure 3

Incidence rate ratios of 19 somatic chronic diseases included in the Charlson Comorbidity Index among persons previously admitted with schizophrenia to a Denmark psychiatric hospital compared to the general population without psychiatric hospital contact. Solid vertical line crossing at 1.0 is the reference and includes all persons never admitted to psychiatric hospital.

score according to severity. The index was originally constructed to quantify the impact of comorbidity on mortality in a hospital setting among breast cancer patients (Charlson et al. 1987) and later was adapted to ICD-10 diagnoses (Sundararajan et al. 2004). A high Charlson index indicates a high comorbidity with somatic disorders and thus poor somatic health. A Danish study showed excess incidence in persons with schizophrenia in all but one of the somatic disorders from the Charlson index (Laursen et al. 2011) (see **Figure 3**). Furthermore, the paper showed that the Charlson index is twofold higher among persons with schizophrenia compared to the general population, which suggests there is an increased occurrence of somatic disorders in these individuals. Although there is increased somatic comorbidity among persons with schizophrenia, the study also showed that mortality from natural causes is extremely high in patients with schizophrenia, and this suggests that the excess mortality may be partly rooted in higher rates of somatic disorders and partly in underdetection or undertreatment of chronic disorders (Laursen et al. 2011).

Underdiagnosis of somatic disorders in schizophrenic patients has been described in many other studies (Frayne et al. 2005, Laursen et al. 2009, Osborn et al. 2008). Briskman et al. (2012) compared two groups of patients admitted to a hospital: patients with schizophrenia (and a few with bipolar disorder or schizoaffective disorder) and patients without a psychiatric disorder. They found that comorbid somatic disorders, e.g., diabetes, hypertension, and dyslipidemia, were underdiagnosed and undertreated in the patients with co-occurring schizophrenia.

Cardiovascular drug use has also been reported to be lower among patients with schizophrenia. A reduced use of cardiovascular drugs has been reported in several studies (Druss et al. 2001, Hippisley-Cox et al. 2007, Petersen et al. 2003, Weiss et al. 2006). A study from Helsinki (Lahti et al. 2012) found a 0.37-fold use of antihypertensive drugs and a 0.47-fold use of lipid-lowering drugs compared to the general population. A study from Denmark (Laursen et al. 2013a) also found reduced use of nearly all cardiac drugs. Lawrence et al. (2010) concluded that insufficient health service for schizophrenic patients with cardiovascular disease may explain part of the increased mortality from natural causes. Mitchell & Lord (2010) reviewed papers on invasive cardiac procedures and medication and concluded that evidence supports that deficits in quality of care contribute to higher-than-expected mortality in people with schizophrenia. However, some studies did not find a reduction in cardiovascular drug use (Desai et al. 2002, Plomondon et al. 2007).

Studies from Australia and Canada also report higher levels of somatic admissions in individuals with schizophrenia compared to the general population (Kisely et al. 2007, Lawrence et al. 2003). Furthermore, a higher prevalence of chronic medical conditions among patients with psychotic disorders has been shown in the United States (Carney et al. 2006, Carney & Jones 2006).

Several studies have found that risk factors for cardiovascular disorders were more common in patients with severe mental disorders (Birkenaes et al. 2007, Newcomer & Hennekens 2007) than in patients without such disorders. A Danish study has found that the rates of invasive procedures were considerably lower and the survival after first contact to a hospital for heart disease was reduced in persons with schizophrenia compared to the general population (Laursen et al. 2009).

Recently, it has been suggested that persons with schizophrenia are more vulnerable to chronic physical diseases; the risk of medical disease is higher, and the prognosis is poorer (Laursen et al. 2012). Furthermore, patients with a psychiatric disorder tend to use medical services to a lesser degree, which could lead to an increased mortality (Cradock-O'Leary et al. 2002). Therefore, diagnosis, treatment, and care management of chronic physical illnesses in persons with schizophrenia must be optimized, but providing optimal care for this group of patients is complex because they need coordinated and combined vertical, and especially horizontal, integration of care.

A few somatic disorders seem to be underrepresented in persons with schizophrenia. A consistent finding is the negative relationship between schizophrenia and autoimmune diseases. Rheumatoid arthritis in particular has been shown to have a negative correlation with schizophrenia (Eaton et al. 1992, 2006; Oken & Schulzer 1999). A Danish study showed that rheumatoid arthritis was the only somatic disorder (out of 19 common chronic somatic disorders) with a lower rate in persons with schizophrenia (Laursen et al. 2011), and another Danish study also found that individuals with schizophrenia had a highly reduced risk for being admitted to a hospital with rheumatoid arthritis [odds ratio 0.44 (CI 0.24–0.81)]. The authors concluded that the association could be explained by the reduced tendency of patients with schizophrenia to report musculoskeletal pain (Mors et al. 1999). Although the prevalence of some somatic disorders (and causes of death) seems to be the same or even lower among schizophrenic patients, the risk from early death caused by other somatic disorders or suicide and accidents should be kept in mind. High mortality rates caused by other sources would lower the risk of getting a disease (or dying from it), especially if the disease has a late onset, as is common with some cancers, for example.

In the same way, the different causes of mortality do not contribute equally or work independently. This is illustrated in a Danish study in which the rate of mortality from different causes of death in persons with schizophrenia is substituted with the rate from the general population (Laursen 2011). The results are not as clear-cut as expected because high mortality rates (from, e.g., cancer and heart disease) "eat" away the expected beneficiary impact of lowering a specific mortality rate. This is obviously just a mathematical thought experiment, but it nevertheless illustrates that the lowering of somatic disorders must be a combined effort of all somatic specialties.

Side Effects of Antipsychotic Medicine

Antipsychotics, in particular atypical antipsychotics, have been associated with weight gain, dyslipidemia, diabetes, and other cardiac risk factors (Newcomer 2007). Evidence has suggested that antipsychotics are responsible for some of the excess mortality among persons with schizophrenia, especially since the introduction in the late 1990s of second-generation antipsychotics (Saha et al. 2007). Raedler (2010) reviewed the effect of antipsychotic drugs and concluded that antipsychotics increased the risk of metabolic syndrome, sudden cardiac death, and myocarditis/cardiomyopathy. However, no evidence suggested that the risk varied by type of antipsychotic drugs. Antipsychotic medication may cause adverse effects, which may negatively affect mortality, but it is unclear how different antipsychotic drugs may affect the excess mortality. A randomized trial including 18,154 patients with schizophrenia compared the effects of ziprasidone and olanzapine (Strom et al. 2011). The study identified no differences in mortality rates between the groups after one year.

A multinational randomized study of 9,858 patients with schizophrenia compared sertindole and risperidone (Thomas et al. 2010). The study showed no difference in all-cause mortality rates between the two groups, but sertindole users specifically had an increased cardiac mortality. A cohort study including 1,686 persons examined two antipsychotic drugs; risperidone and clozapine (Kelly et al. 2010). Despite known differences in risk profile for weight gain and metabolic side effects, the study found no differences in cardiac mortality between the users of the two different drugs.

Goff et al. (2005) compared patients with schizophrenia included in the Clinical Trials of Antipsychotic Treatment Effectiveness (CATIE) study with matched controls and found a higher risk of cardiovascular disease among the patients. The excess risk was concluded to be partly explained by a higher frequency of cigarette smoking, although the relative contributions to cardiac risk of specific antipsychotic agents, diet, exercise, and quality of medical care remain to be clarified. Daumit et al. (2008) analyzed changes in 10-year coronary heart disease risk estimates during the 18-month CATIE trial by antipsychotic treatment, and they found that treatment with olanzapine and quetiapine was associated with a higher long-term risk of cardiovascular disease than was treatment with perphenazin, risperidone, and ziprasidone.

The FIN11 study from Finland (Tiihonen et al. 2009) examined mortality in more than 66,000 persons with a broad definition of schizophrenia and had a special focus on antipsychotic medication use. No increase in the excess mortality in persons with schizophrenia was found in the 11-year period from 1996 to 2006, which was the period when second-generation antipsychotics were introduced, although a very high mortality was found.

In a recent meta-analysis based on FDA data from placebo-controlled studies, the investigators found, contrary to their expectation, that antipsychotic medication did not increase the risk of death from diseases and medical conditions (Khan et al. 2013).

The number of studies on the adverse effect of antipsychotics is substantial. We have included only a few of the most recent papers to illustrate the lack of studies on long-term outcomes in persons using antipsychotic drugs, which impedes the establishment of clear guidelines in the use of the drugs.

Lifestyle Factors

Lifestyle factors that contribute to early mortality in persons with schizophrenia include smoking, physical activity, and diet and weight.

Smoking. One of the risk factors most likely to contribute substantially to reduced life expectancy in schizophrenia is smoking. In the general population in Denmark, smoking-related illnesses

account for a reduction in life expectancy of 3.5 years for men and 3.0 years for women (Juel & Sørensen 2006). National statistics on smoking habits among people with schizophrenia are not available, but surveys indicate that smoking occurs more frequently among people with schizophrenia than in the general population. A national Danish survey found that 38.8% of people who declared they suffered from "long-lasting mental disorder" were daily smokers, and 19.8% of those who did not suffer from long-lasting mental disorder were daily smokers. The extent of heavy smoking (more than 15 cigarettes daily) among people with long-lasting mental disorder was 25.9% versus 10.1% for those without such disorder. Note that the classification of the dichotomy "long-lasting mental disorder" is based on self-report and is therefore not likely to be specific to schizophrenia (Nordentoft et al. 2012). Another Danish survey carried out among users of drop-in centers or institutions for people who were homeless showed that 80% of people with mental disorders in this population were daily smokers (Pedersen et al. 2012). In the American CATIE study, 58% of the included patients with schizophrenia were smokers (Daumit 2008). A large study from Spain found that 55% of nearly 2,000 outpatients with schizophrenia were smokers (Bobes et al. 2010). In a systematic review, Compton et al. (2006) concluded that people with mental disorders belonging to different diagnostic groups in the United States were twice as likely to be smokers. Even though we lack national statistics on smoking habits for people with schizophrenia, a number of studies indicate that smoking is far more frequent among people with schizophrenia and contributes substantially to the reduced life expectancy in this patient group.

Several studies have investigated factors affecting the success of smoking cessation among people with schizophrenia, and some evidence suggests that both bupropion and varenicline can increase the chances of quitting smoking. Smoking cessation programs and nicotine substitution seem to support smoking cessation among people with schizophrenia. A Cochrane review based on 11 trials including 685 daily smokers with schizophrenia (Tsoi et al. 2013) concluded that bupropion improved the chances of quitting smoking by 2.8 fold (95% CI: 1.02–7.58). Treatment with varenicline also increased the chance of smoking cessation, although the evidence is weaker than for bupropion (Williams et al. 2012). No studies have compared smoking cessation programs with no intervention, but one study has compared a specialized smoking cessation program for patients with schizophrenia with an ordinary program developed for people in the general population and found no differences in cessation rates between the two programs (Baker et al. 2006).

Based on the above-mentioned studies, information on smoking habits should be systematically collected. Likewise, smoking cessation programs should be offered to people with schizophrenia. More studies on the efficacy of different smoking cessation methods are needed, but current evidence suggests that bupropion, varenicline, nicotine substitution, and smoking cessation programs are effective.

Physical activity. Three randomized clinical trials with a total of 103 participants evaluated the effect of exercise therapy on physical fitness (VO_2 max) (Beebe et al. 2005, Scheewe et al. 2013, Skrinar et al. 2005). All three studies evaluated the effect of aerobic training and included outpatients. The largest study was a Dutch study including 63 patients who were randomized to either physical training ($n = 31$) or occupational therapy ($n = 32$) (Scheewe et al. 2012). The training was twice a week for six months, and the authors concluded that the training could prevent VO_2 max from declining. However, 38% of participants were excluded from the study because they had less than 50% attendance.

The effect of physical activity on body weight is reported in two small studies. Beebe et al. (2005) found a nonsignificant decline of 1.27 kg/m^2 in body mass index (BMI) in the training group versus 0.14 kg/m^2 in the control group. Skrinar et al. (2005) found a nonsignificant decline in BMI of 0.7 kg/m^2 versus an increase of 0.5 kg/m^2 in the control group.

Thus, only weak evidence supports the theory that participation in training programs will lead to weight loss among people suffering from schizophrenia. A major challenge for further studies in this field is recruitment of participants with mental illness for lifestyle programs focusing on physical activity.

Diet and weight. Several studies have indicated that dietary habits are partly responsible for weight gain in schizophrenia, but medication can also independently cause weight gain. A retrospective study based on the South Carolinas Medicaid program included 2,231 patients with schizophrenia who were recently prescribed antipsychotic medication for the first time. Weight gains resulting in a BMI of 30 or more occurred among 2.73% of these patients per year during the first three years of treatment (Jerrell et al. 2010). A large randomized clinical trial of first-episode patients treated with different antipsychotic drugs (Kahn et al. 2008) found that all antipsychotic drugs were associated with a greater than 7% increase in weight during the trial; proportion of patients affected ranged from 37% (ziprasidone) to 86% (olanzapine).

However, weight management programs have proven to be effective in preventing weight increase (or weight loss) during treatment with antipsychotic medication. Two meta-analyses (Bonfioli et al. 2012, Caemmerer et al. 2012) indicated that weight management programs could impede weight gain during antipsychotic treatment and could also be effective for weight loss. Moderate evidence suggests that it is possible to counteract weight loss or to prevent weight increases of 3.12 kg on average (or 0.94 kg/m^2 measured as BMI) in obese mentally ill people undergoing antipsychotic treatment. Note that large differences exist between the effects achieved in the studies (Bonfioli et al. 2012, Caemmerer et al. 2012). In addition to the effect on weight, significant changes have been linked with other clinically relevant somatic risk factors, including the levels of body fat percentage, fasting plasma glucose, and blood fat as well as waist measurement. A modest dropout rate is found in the lifestyle intervention groups that focus on weight loss or weight stability compared with the control groups (15% versus 17%). This indicates that the lifestyle interventions are not only effective but are also achievable for the participants. Data also indicate that it is possible to maintain a weight loss after completion of the intervention since the achieved weight loss is still significant after 3.6 months.

After the publication of the meta-analyses (Bonfioli et al. 2012, Caemmerer et al. 2012), Daumit et al. (2013) found further support in a randomized controlled trial for weight loss through weight management programs.

Suicide

Schizophrenia and other mental disorders are associated with an increased risk of suicide (Caldwell & Gottesman 1990, Dutta et al. 2010, Harris & Barraclough 1997, Lonnqvist et al. 1995, Mortensen et al. 2000, Qin & Nordentoft 2005); this risk is often reported as the increased relative risk or odds ratio for death by suicide for people with mental disorders compared to people without health services contact for a mental disorder. The absolute risk of dying by suicide, which is often referred to as the lifetime risk of suicide following onset of mental disorders, can be estimated as the percentage of a cohort expected to die by suicide before extinction. Even though no studies have actually conducted lifetime follow-up, lifetime risk is mentioned in many scientific papers (Guze & Robins 1970, Miles 1977) and textbooks (Goodwin & Jamison 2007). One of the most cited papers is the review written by Miles (1977), which estimated that 15% of persons with unipolar affective disorder, 15% with alcoholism, and 10% with schizophrenia would die from suicide. However, this review was based on rather small studies with selected samples and brief follow-up periods. Several investigators later concluded that Miles's estimates were most likely too

high for various reasons (Blair-West et al. 1997, 1999; Bostwick & Pankratz 2000; Inskip et al. 1998; Palmer et al. 2005). Meta-analyses that were based on more sophisticated statistical methods and included large long-term follow-up studies found lower figures (Bostwick & Pankratz 2000, Inskip et al. 1998, Palmer et al. 2005). Inskip et al. (1998) estimated the lifetime risk to be 6% for affective disorder, 7% for alcohol dependence, and 4% for schizophrenia, whereas Palmer and colleagues (2005) estimated the lifetime risk to be 5.6% for schizophrenia. Recently, Dutta et al. (2010) estimated a lifetime risk of suicide of 3.23% for patients 20 years after the first psychotic diagnosis. In an analysis of the absolute risk of suicide in a total national cohort of 176,347 individuals, who were followed from first psychiatric contact up to 36 years after first psychiatric contact, Nordentoft et al. (2011) found the absolute risk of suicide in schizophrenia to be 6.55% (95% CI: 5.85–7.34) among men and 4.91% (95% CI: 4.03–5.98) among women. The co-occurrence of deliberate self-harm increased the risk approximately twofold (Nordentoft et al. 2011). These estimates are lower than reported in the most cited papers in the field, but the figures are still substantial and emphasize the continuous need for prevention of suicide among people with schizophrenia.

It is beyond doubt that the risk of suicide is high in schizophrenia, and suicide preventive measures should be a mandatory part of treatment programs (Hawton & Saunders 2009). It is also evident that a history of deliberate self-harm markedly increases the risk of suicide in schizophrenia and other diagnostic groups (Nordentoft et al. 2011). In addition, suicide attempt should be considered a very important risk factor among patients with schizophrenia and other mental disorders, as underlined by the recent findings in a large Swedish study (Runeson et al. 2010).

The steepest increase in suicide risk occurs during the first few years after initial contact with mental health services; thus, early intensive intervention initiatives are needed. By establishing closer communication with the patient and increased monitoring of symptoms, such initiatives would help reduce suicide risk in this period and thereby positively influence the long-term risk of suicide.

Accelerated Aging

The common process of a parallel course of biological and calendar aging, with biological age antedating calendar age, has been coined "accelerated aging" (Fernandez-Egea et al. 2011, Kirkpatrick et al. 2008). An alternative explanation of the early excess mortality in persons with schizophrenia has been the theory of accelerated aging. According to this theory, physiological changes associated with aging occur at an earlier age in people with schizophrenia compared to the general population (Kirkpatrick et al. 2008). A study in age-dependent cognitive tests found a discrepancy of 20 years between persons with schizophrenia and the general population (Fernandez-Egea et al. 2011), in accordance with the 20 years' shorter life expectancy. If persons with schizophrenia experience accelerated aging as an integrated part of the illness, it could be very difficult to prevent the excess mortality. Cardiovascular morbidity and mortality in schizophrenia often occur before age 50. The European guidelines for prevention of cardiovascular disease primarily target older people because individuals under the age of 50 have a very low risk of cardiovascular morbidity and mortality (Perk et al. 2012). If persons with schizophrenia have accelerated aging, a lower age threshold for starting drug therapy to decrease cardiovascular risk factors could be a way to reduce the high mortality.

FURTHER STUDIES AND RANDOMIZED CONTROLLED TRIAL INITIATIVES

Although excess mortality, and to some extent excess physical morbidity, has been amply documented, only a few studies have documented the causes of this excess mortality. However, several highly plausible candidates seem obvious.

First, difficulties in diagnosing somatic comorbidities, undertreatment of diagnosed disorders, or even untoward effects of the treatment of schizophrenia (e.g., diabetes, obesity) are likely to contribute and could suggest possible avenues for prevention. Second, lifestyle factors such as excess alcohol consumption and tobacco use and little attention to a healthy diet are more prevalent in psychiatric patients. The general socioeconomic background is also strongly related to mortality gradients, even in Scandinavian countries with relatively modest socioeconomic differences and universal access to free health care (Diderichsen et al. 2012). Furthermore, schizophrenia has a very strong impact on income, educational attainment, marital status, and other indicators associated with health and mortality.

However, it is worth noting that no solid epidemiological studies to date have tested to which extent any or all of the above-mentioned factors can explain the excess mortality in schizophrenia. Further explanations may exist, as one could hypothesize that factors contributing to the etiology of schizophrenia may also be risk factors for other disorders that reduce longevity.

For example, shared familial or genetic factors could exist. Laursen et al. (2005) have documented an excess mortality in the parents of patients with schizophrenia, a finding that could suggest both shared environmental and genetic factors but may also reflect an impact of the stress associated with caring for a severely ill family member. More insight into the genetic architecture underpinning schizophrenia may in the future allow studies in which the association between longevity and hundreds or thousands genetic variants linked with schizophrenia risk can be tested empirically. Studies identifying subgroups of patients who are likely to develop severe side effects of neuroleptic treatment, such as obesity, diabetes, or agranulocytosis, may be of direct clinical use.

Shared environmental risk factors affecting fetal development may also contribute to the excess mortality, as fetal growth restriction has been associated with both schizophrenia (Nielsen et al. 2013a) and multiple somatic health outcomes (Risnes et al. 2011).

All of these hypotheses could inspire further studies, but by far the most urgent research agenda is to address the obvious candidates for modifiable risk factors that may contribute to the excess mortality, i.e., side effects of treatment, lifestyle factors, access to adequate prevention, and treatment of physical comorbidity. There seems to be a historical parallel between now and 70 years ago, when the documentation of excess mortality from tuberculosis among psychiatric patients (Alstrøm 1942) helped introduce specific interventions and treatment facilities that contributed to the reduction of this major source of excess mortality. However, the major sources of excess mortality have changed over the past 70 years.

An editorial headline in the *Lancet* in 2011 read "No mental health without physical health" (Tiihonen et al. 2011), suggesting that physical health should be made one of the cornerstones in the treatment of patients with schizophrenia. The diagnosis, treatment, and care management of chronic physical illnesses in persons with schizophrenia need to be optimized. Provision of optimal care for persons with schizophrenia is often a complex task, and therefore a coordinated and collaborating health care system is essential. Multiple specialists from psychiatric as well as somatic departments must collaborate to ensure that people with schizophrenia encounter an integrated health care system with a single point of entry. More research is needed to identify the most effective clinical and organizational interventions and the best way to implement these. A possible step is to use care coordinators to bridge the gap between mental health and physical care teams. Another possibility is to increase coordination of different treatment initiatives through primary care physicians. Primary care physicians could provide profound care through patient-focused consultations at regular intervals and thereby identify patients' new physical, mental, or social needs, including comprehensive follow-up.

Previous studies indicate that excess mortality (whether caused by disease or external factors) peaks during the first year after patients are discharged from the hospital (Nordentoft et al.

2013), which has been previously documented for suicide (Nordentoft et al. 2004; Osby et al. 2000, 2001). Excess death following hospitalization for a mental disorder indicates not only that a current mental disorder is a risk factor contributing to death from a physical disorder, but also that the health system fails to prevent, identify, and treat physical diseases during hospitalization for a mental disorder. This interpretation is supported by studies documenting that patients with psychiatric disorders receive less treatment for physical conditions than do people without psychiatric disorders (Kisely et al. 2009, Laursen et al. 2009, Lawrence et al. 2000).

A randomized clinical trial called CHANGE, in which staff members are employed in a multidisciplinary team, is currently under way. CHANGE treatment involves lifestyle coaching, education in diet and physical activity (Cent. Prev. Board Health. 2006), networking, and smoking cessation programs. The team members act as lifestyle coaches for 10 patients at a time, and their activities include mapping lifestyle and exploring and eliciting patients' motivation for change (Miller & Rollnick 1991, Prochaska & Diclemente 1992). To allow sufficient time to implement changes in individual habits, each patient is offered affiliation with the team for one year. Patients are supported in developing a desire for change; an important element is identification of attainable and realistic goals. Small changes are better than no changes; many small steps in combination create important landmarks. The lifestyle coaches must support the patient in setting up individual goals that take into account the patient's personal values, life conditions, and priorities. This involves the systematic exploration of possibilities for physical activity in daily life and selection of activities at hand that are realistic and appealing to the patient. Dietary changes require not only a close examination of the patient's dietary habits, food purchases, and cooking practices, but also the identification of financially realistic and appealing possibilities for change. Systematic monitoring of health status and risk factors (HbA1c, waist circumference, weight, blood pressure, and step count) serves as a motivating instrument. Personal and professional networks as well as a participant network can form part of the individual plans. A smoking cessation program suited to the patient population is offered in order to elicit and enhance motivation and maintain smoking cessation. Continued motivation is ensured through support such as offering counseling to prevent relapses and providing nicotine substitution products and craving-reducing medication.

A similar approach focusing on obesity has been evaluated by Daumit et al. (2013), who report a 3.2 kg weight loss in a randomized controlled trial that examines the outcome of a tailored weight management program versus standard treatment in a group of patients with schizophrenia and other severe mental disorders and with a mean body mass index of 36.3 kg/m^2.

WHICH EXISTING KNOWLEDGE CAN BE IMPLEMENTED IN CLINICAL PRACTICE? ARE CLINICAL GUIDELINES REQUIRED?

Mounting evidence suggests that people suffering from schizophrenia have increased morbidity and mortality. We also know that a significant share of this excess mortality, which shortens life by 15 to 20 years, is caused by somatic illness linked with an unhealthy lifestyle. New nationwide Danish data show that obesity, smoking, unhealthy diet, and sedentary behavior are seen approximately twice as frequently in people who self-report that they have a mental illness as compared with the general population. However, the data also show that these individuals want to stop smoking, eat more healthily, and be more physically active just as much as the general population does.

The lifestyle of people with mental illness can be changed, and to a great extent these individuals also want this change. People suffering from mental illness encounter a number of barriers to lifestyle changes, including illness symptoms, adverse drug effects, and life situations. Therefore, individual consideration and support by both professional and personal networks are crucial for a successful outcome of lifestyle interventions.

The American Schizophrenia Patient Outcomes Research Team recommends weight management for patients with schizophrenia and a BMI higher than 25 (Dixon et al. 2010); however, it is not clear how these weight management programs should be administered. Thus, more randomized clinical trials should be carried out to investigate the effectiveness of programs that aim to improve treatment of medical conditions and facilitate lifestyle changes.

Smoking

Moderate evidence indicates that nicotine substitution treatment increases cessation of smoking among people with previous or ongoing depression. The effect of nicotine substitution on persons with depression is the same as that on smokers without depression, corresponding to a cessation success rate of 14% to 22% after a six-month smoking cessation intervention. Moderate evidence also suggests that counseling to help quit smoking works for people with previous or ongoing depression. If behavioral mood management therapy is included, smoking cessation counseling increases the chance of smoking cessation by approximately 1.5 times compared with no counseling. Evidence of the effect of bupropion and other antidepressant drugs to promote smoking cessation is not as clear but findings indicate a slightly higher tendency of smoking cessation among people with depression who took these drugs. In the case of people with schizophrenia, moderate evidence suggests that bupropion can nearly triple the chance of smoking cessation after six months, with no negative effects on psychotic symptoms. The effect of varenicline is not as clear, but the literature indicates that people with schizophrenia tolerate it, which can increase the chance of smoking cessation, at least in the short term. Weak evidence also indicates that payment for participation in a smoking cessation program has a positive effect, but it is uncertain whether this also applies to the long term. In general, it has proven difficult to recruit people with bipolar disorders and ongoing depression for smoking cessation interventions, and only a very limited number of studies focus on long-term maintenance of achieved smoking cessation.

Diet and Weight

We find moderate evidence that it is possible to take actions leading to weight loss or prevention of weight increases of an average of 3.12 kg or a BMI equaling 0.94 kg/m^2 in obese mentally ill people undergoing antipsychotic treatment. Large differences exist between the effects achieved in the studies. In addition to the effect on weight, significant changes have been found in other clinically relevant somatic risk factors, including the levels of body fat percentage, fasting plasma glucose, and blood fat. We find a modest dropout rate in the lifestyle interventions that focus on weight loss or weight stability compared with the control groups (15% versus 17%). This indicates that study participants are able to carry out the lifestyle interventions and that the interventions are effective. Some data also indicate that it is possible for participants to maintain a weight loss after completion of the intervention since the achieved weight loss was still significant after 3.6 months. Outcomes are not known for nonmotivated psychiatric patients in lifestyle interventions that focus on diet.

Barriers and Motivation for Lifestyle Changes

Our results indicate that people with mental illness have the same interest as control groups do in changing their lifestyle with regard to smoking, diet, and physical activity. They associate better health with a more meaningful daily life and better quality of life. The most significant barriers to changing their lifestyle are the symptoms of the mental illness and the adverse drug effects of medical treatment, but individuals with mental illness are also challenged by a life situation

characterized by social isolation and difficulties with creating a structured life. The lifestyles of the mentally ill are generally influenced by a number of dilemmas and conflicting feelings, and this implies that good intentions for a healthier lifestyle may not always result in taking action. Individual consideration is the key to successful planning and completion of lifestyle interventions and activities. The support provided by professionals, family, and friends is also crucial. A number of studies indicate that health care employees with negative attitudes may actually form a barrier for lifestyle changes among people with mental illness. Studies also confirm that the provided support must exercise a balance not only between pressure and encouragement, but also between support and autonomy in daily life.

Future Research Directions

Our knowledge about the lifestyle habits of people suffering from mental illness in Denmark is primarily based on a large Danish self-reported survey, the National Health Profile 2010. This survey does not allow identification of differences on the basis of psychiatric diagnoses but rather provides a combined category: long-term mental illness. Therefore, it is necessary to obtain a better overview of the state of health and lifestyle conditions among people suffering from mental illness in Denmark as well as in other countries.

We also need more knowledge about long-term maintenance of smoking cessation after completion of an intervention. Therefore, future research should include a focus on this particular area. Investigation of smoking cessation among people suffering from bipolar disorder has so far been fairly limited, and currently we cannot identify the most effective interventions for this group of patients on the basis of existing data. Consequently, more research in this area is required.

Until now, research on the effect of physical activity among people with mental illness has focused on the positive outcomes that physical activity may have on the symptoms of mental illness. Future research should also focus on the beneficial somatic effects of physical activity and suggest goal-oriented strategies for increased participation in training programs. We also need more knowledge on how to sustain achieved improvement in fitness and muscular strength after completion of training programs. In addition, there is a need for further research on the effects of lifestyle programs including dietary changes; in particular, how patients can change their dietary habits and maintain such changes on a long-term basis.

Finally, more research is needed on identification of the barriers and motivating factors people suffering from mental illness experience in connection with lifestyle changes. Both the international and national qualitative literature in the area is limited and does not allow us to draw conclusions about the extent to which special barriers and motivating factors may exist for the individual diagnoses.

CONCLUSION

The concept of schizophrenia was originally defined to include patients with especially poor outcomes. This group of patients still has an exceptionally short life expectancy because of very high mortality in all age groups. Not only do persons with schizophrenia have a short life expectancy, but evidence also suggests that they may not have experienced the same improvement in life expectancy as the general population has during the past decades. Thus, the mortality gap not only persists but may actually even be increasing.

It is well known that the excess risk of suicide contributes to the shorter life expectancy in patients with schizophrenia. Prevention of suicide—especially in the early phases of the illness—should therefore have high priority.

We cannot continue to disregard the physical health needs of people with schizophrenia. No international standards of effective somatic treatment exist for this patient group. The most urgent research agenda is to address primary candidates for modifiable risk factors contributing to this excess mortality, i.e., lifestyle factors and side effects of treatment, as well as access to health care for sufficient prevention and treatment of physical comorbidity.

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