Increasing mortality gap for patients diagnosed with schizophrenia over the last three decades — A Danish nationwide study from 1980 to 2010

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ABSTRACT

Objective: The objective of this study is to describe secular trends in the average age of death in patients with schizophrenia and to compare these with the general population.
Methods: This is a longitudinal linkage study from 1 January 1980 to 31 December 2010 using the Danish Psychiatric Research Register and the Danish Cause of Death Register. Data were analyzed using descriptive statistics and survival analysis.
Results: The average age of death in the schizophrenia population (62.2 years; 95% CI, 61.9–62.5) was lower compared to the general population (73.4 years; 95% CI, 73.4–73.4), $P < 0.001$. In the general population we found, for men, an average increase in the age of death of 0.28 years (95% CI, 0.27–0.28) per calendar year, and for women an increase in age of death of 0.31 years (95% CI, 0.31–0.32) per calendar year (both $P < 0.001$). In contrast, age of death decreased in the schizophrenia population: the change in average age of death for males was 0.04 years (95% CI, -0.09 to 0.00) per calendar year ($P < 0.05$), and the comparable estimate for females was -0.05 years (95% CI, -0.09 to 0.01) per calendar year ($P < 0.05$). A similar pattern existed after acts of self-harm as cause of death were excluded from the analyses. Patients diagnosed with schizophrenia had an increased mortality rate compared with the general population (hazard ratio, 2.05; 95% CI, 2.01–2.09).
Conclusions: On average, patients with schizophrenia die younger than the general population, independent of intentional self-harm as cause of death.

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1. Introduction

Patients diagnosed with schizophrenia have an increased mortality compared with the general population (Saha et al., 2007; Laursen, 2011; Beary et al., 2012; Morden et al., 2012; Ratliff et al., 2013). Although some excess mortality is explained by intentional self-harm, cardiovascular diseases appear to be a major contributor to the increased mortality in schizophrenia, followed by cancer-related deaths (Morden et al., 2012).

While the findings with respect to the increased risk of mortality in schizophrenia are cause for concern, there is also worrying evidence to suggest that the differential mortality gap is worsening over time. This secular trend has been examined with several different mortality-related measures (Hosmer et al., 2008), for example standardized mortality ratios (SMRs), comparing mortality rates in a given population with the general population (Saha et al., 2007), Kaplan–Meier plots and related survival analyses, which are particularly suited to 'censored'

data owing to early death (Tiihonen et al., 2012). However, from a general clinical perspective the most requested and readily understood estimate related to mortality in schizophrenia is the average age of death, or the average gap in expected lifespan compared with the general population.

With respect to SMRs, Saha et al. (2007) reported a median SMR of 2.58 in a meta-analysis consisting of 37 studies from 25 different countries in the period 1980–2006, with an increase in SMR over the last three decades. Studies from Norway (Hoye et al., 2011) and the UK (Hoang et al., 2011) have also suggested that SMRs associated with schizophrenia have increased over time. This worsening in relative mortality over time has not been found everywhere, though, as shown by Finnish studies (Rantanen et al., 2009; Tiihonen et al., 2009; Salokangas et al., 2011).

With respect to the differences in age of death, the results are less consistent. Morden et al. (2012) showed an increase (i.e. worsening) of the mortality gap from 12.8 to 15.4 years in a sample of 65,362 patients diagnosed with schizophrenia, all followed by the Veterans Affairs Medical System in the USA, over the period from 2000 to 2007 (Morden et al., 2012). The FIN11 study of 66,881 patients in Finland diagnosed with schizophrenia followed for an average period of 7.8 years

showed a non-significant improvement in the mortality gap, with an initial gap of 25.0 years in 1996 to 22.5 years in 2006 compared with the general population (Tiihonen et al., 2009).

The generally worsening secular trends in mortality-related estimates associated with schizophrenia are in contrast to the general population, where life expectancy has increased over the last few decades in all European countries, as well as in the USA and Japan, with the exception of former communist countries having a decrease or stagnation in life expectancy in the period from 1970 to the end of the 1980s (Leon, 2011).

We examined the average age of death in those diagnosed with schizophrenia compared with the general population. We wished to examine secular changes in the average age of death between the two groups. Based on the literature, we predicted that while the average lifespan of the general population has increased in Denmark (Leon, 2011), the average lifespan for those with schizophrenia would, at least, remain unchanged. Owing to age of death as an outcome measure being sensitive to changes in treatment options over time, we also investigated the hazard ratio (HR) of mortality for patients diagnosed with schizophrenia compared to five control participants matched on year of birth and gender.

2. Methods

2.1. Design

This is a nationwide register-based study of the average age of death of patients diagnosed with schizophrenia and a representative sample of the Danish population, excluding persons diagnosed with schizophrenia, termed the 'general population', covering the period from 1 January 1980 to 31 December 2010 for analysis of average age of death. The 'general population' was randomly selected from the Danish population by Statistics Denmark as a representative control group for several epidemiological and pharmaco-epidemiologic studies.

In the second analysis of survival, utilizing Cox regression and Kaplan–Meier plots, every patient diagnosed with schizophrenia was matched by Stata's sample function to five birth-year and sex-matched control participants from the aforementioned general population.

2.2. Sample

We examined the changes in mortality over time by utilizing two different statistical methods. First, we investigated age of death over the last three decades. Our initial sample consisted of all patients diagnosed with an ICD-8 schizophrenia (300) in the period from 1980 to 1993 or an ICD-10 schizophrenia (F20) in the period from 1994 to 2010 (the ICD-9 was not introduced in Denmark) (World Health Organization, 1992). The sample was extracted from the Danish Psychiatric Central Research Register (Mors et al., 2011).

Data on age of death for the general population were retrieved from the Danish Register of Causes of Death (Helweg-Larsen, 2011). The Danish Register of Causes of Death is coded according to World Health Organization rules; the cause of death and contributory causes are stated on the death certificate, and are registered in the Danish Register of Causes of Death (Helweg-Larsen, 2011).

As we wished to examine average age at death, patients diagnosed with schizophrenia, who died in the study period, were included in the 'schizophrenia population'. Data on age of death were retrieved from the Danish Cause of Death Register (Helweg-Larsen, 2011). The main causes of death were divided into cardiovascular disease (ICD-8: 330–334 + 400–467; ICD-10: G45–G46 + I00–I99 + K55); cancer (ICD-8: 140–239; ICD-10: C00–C97 + D00–D48); infection (ICD-8: 000–136 + 470–513 + 575 + 605 + 622–624 + 630 + 690–698; ICD-10: A00–A99 + B00–B99 + G00–G09 + J00–J04 + J06–J22 + J36 + J39.0–J39.2 + J85–J86 + K35–K36 + K61 + K63.0 + K65 +

K67 + K75.0 + L00–L08 + M00–M01 + M60.0 + N10 + N30 + N34 + N70 + N76); diabetes (ICD-8: 250; ICD-10 E10–E14); intentional self-harm (ICD-8: E950–959 + E970–E979; ICD-10: X60–X84); epilepsy (ICD-8: 353; ICD-10: G40–G41), lower respiratory disease (ICD-8: 518–527; ICD-10: J40–J84 + J90–J99); and other (including remaining ICD-8 and ICD-10 diagnoses).

Second, we matched each patient, independent of death or not in the study period, to five controls on sex and year of birth, and performed a survival analysis. Controls were drawn from our control sample used in the first statistical analysis, and consisted of a representative sample of the Danish population, excluding persons diagnosed with schizophrenia. Data on age of death for the controls were retrieved from the Danish Register of Causes of Death (Helweg-Larsen, 2011).

The Danish Data Protection Agency, National Board of Health and Statistics Denmark approved the use of the data.

2.3. Statistical analysis

Descriptive analyses were performed using a Z-test, two-sample t-test and chi-squared test.

Simple plots of the average age of death were constructed for the schizophrenia population and the general population. A line was fitted by utilizing linear regression analysis, and slopes were calculated.

The matched control versus schizophrenia analysis was done as survival analysis, with entry defined as time of birth and Kaplan–Meier plots were obtained. Log-rank test and Cox regression were employed. P-values <0.05 were generally considered statistically significant. Statistical analyses were performed with Stata 12 (StataCorp, College Station, TX, USA) on the Statistics Denmark server with remote access.

3. Results

A total of 14,974 patients [male: 54% (n = 8148); female: 46% (n = 6826)] diagnosed with schizophrenia who died in the period 1980–2010 were included in the study. The average age of death (in years) for male patients diagnosed with schizophrenia was 57.3 years (95% CI, 56.9–57.7) compared with 68.1 (95% CI, 67.7–68.5) for females, ($P < 0.001$). Causes of death for both populations are shown in Table 1.

The general population consisted of 1,311,419 persons [male: 42% (n = 549 316); female: 58% (n = 762 103)] who died in the period 1980–2010. The average age of death (in years) for male norms was 69.6 years (95% CI, 69.6–69.6) compared with 76.2 years (95% CI, 76.2–76.2) for females ($P < 0.001$), as shown in Table 2.

The average age of death (in years) for the schizophrenia population was significantly lower than the general population both in total, when divided by sex and when divided into all three decades, as shown in Table 2. The average difference in age of death between the schizophrenia and general populations was 11.2 years (95% CI,

Table 1
Cause of death.

Cause of death	General population		Schizophrenia population		P
	n	%	N	%	
Cardiovascular disease	452,526	34.5	3634	24.3	<0.001
Cancer	297,331	22.7	1737	11.6	<0.001
Infection	160,933	12.3	1709	11.4	<0.005
Diabetes	23,606	1.8	308	2.1	<0.001
Self-harm	24,501	1.9	1542	10.3	<0.01
Epilepsy	5141	0.4	143	1.0	<0.001
Lower respiratory disease	48,736	3.7	589	3.9	n.s.
Other	298,645	22.8	5312	35.5	<0.001
Total	1,311,419		14,974		