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a Danish nationwide cohort study

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Title

Increased mortality from somatic multimorbidity in patients with schizophrenia: a Danish nationwide cohort study

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Abstract

Objective

To investigate the association of single- and multimorbidity with mortality rates in patients with schizophrenia compared to the general population.

Method

A nationwide cohort study including residents in Denmark between 1995 and 2015. The cohort was dichotomously divided by a diagnosis of schizophrenia. Somatic diseases included infections, cancer, endocrine, neurologic, cardiovascular, respiratory, digestive, skin, musculoskeletal, and urogenital diseases. Hazard ratios (HRs) and population attributable fractions (PAFs) were calculated.

Results

The cohort included 30,210 patients with schizophrenia (mean age(SD)=32.6(11.4), males=57.2%), and 5,402,611 from the general population (mean age(SD)=33.0(14.5), males=50.4%). All number of somatic diseases were associated with an increased mortality in schizophrenia (HR=16.3 (95%CI=15.4-17.3) for 1 disease to 21.0 (95%CI=19.1-23.0) for ≥5 diseases), using the general population with no somatic disease as reference. Across all somatic diseases, patients with schizophrenia showed a HR>2, compared to the general population, and respiratory (PAF=9.3%), digestive (PAF=8.2%) and cardiovascular (PAF=7.9%) diseases showed largest contributions to death.

Conclusions

Patients with schizophrenia showed higher mortality on all levels of multimorbidity, and a doubled mortality rate across all somatic diseases, compared to the general population. The findings suggest that the clusters and trajectories of symptoms associated with schizophrenia is the main driver of the excess mortality.

Keywords

Physical health

Physical illness

Comorbidity

Mortality

Clinical aspects

Significant outcomes

- In this nationwide cohort study, we found an increased mortality rate across all levels of somatic multimorbidity in patients with schizophrenia, compared to the general population.
- Different somatic disease systems contribute to the increased mortality in patients with schizophrenia, however, the results point towards the signs and symptoms associated with schizophrenia as the main driver of the excess mortality.

Limitations

- We were not able to adjust for important confounders, such as cigarette smoking, diet habits as well as physical activity, as these variables are not available in the Danish registers.
- Information on the severity of the somatic condition was lacking.

Introduction

Patients with schizophrenia have a general reduced life expectancy of up to 20 years compared to the general population (1). The main causes of death are somatic diseases, such as cardiovascular, respiratory and cancer diseases (2). These causes of death are similar to the main causes of death observed in the general population, although, the developments within somatic treatments have resulted in an improved survival following these and other somatic diseases (3), but data do not support similar improved survival following somatic diseases in patients diagnosed with schizophrenia (4,5).

Numerous studies have reported increased mortality following a range of different individual somatic diseases in patients with schizophrenia, compared to the general population (6–8). This is supported by the established increased risk of somatic morbidity in patients with schizophrenia, which is mainly explained by inadequate lifestyle behavior (e.g. excess smoking, poor diet intake, and limited physical activity) and adverse effects from antipsychotic treatment (e.g. increased

cardiometabolic risk) (9,10). Despite the established increased somatic morbidity in patients with schizophrenia (11,12), limited studies have reported outcomes related to somatic multimorbidity (≥2 diseases in the same individual) in patients with schizophrenia (13,14).

In the general population, somatic multimorbidity is associated with functional decline, decreased quality of life, higher healthcare costs as well as an increased risk of premature mortality, with most research on somatic multimorbidity focusing on older people in the general population (15,16). Few recent studies have reported an increased risk of somatic multimorbidity in patients with schizophrenia (17,18), thus understanding the potential contributing effect of somatic multimorbidity to mortality rates in patients diagnosed with schizophrenia is essential. Moreover, identifying which somatic disease categories contribute the most to increased mortality rates will enable targeted preventive health care strategies.

Aims of the Study

We examined the association of number of somatic diseases with mortality in patients with schizophrenia, as compared to the general population. Secondary, we calculated the population attributable fraction (PAF) for all-cause mortality for different disease categories in patients with schizophrenia as well as in the general population. Lastly, we compared mortality rates of all specific somatic disease categories directly between patients with schizophrenia and the general population.

Material and Methods

Study design

A nationwide Danish register-based cohort study with follow-up from 1 January 1995 to December 31 2015.

Data source

Data were derived from several Danish nationwide registers; 1) the Danish Psychiatric Central Research Register (DPCRR) which was established in 1969 and contains information on every admission to the psychiatric hospital in Denmark. Valid data are available from 1970, which is the year all psychiatric departments at Danish hospitals were obligated to report to the DPCRR. From 1995, all patients attending psychiatric outpatient services and emergency room were included (19). 2) the Danish National Patient Register (NPR) which was established in 1977, and initially contained somatic hospitalizations, but since 1995; all hospitalizations and outpatient treatments in Denmark were also registered (20). 3) The Danish Register of Causes of Death which was established in 1970 and includes cause and date of deaths among Danish citizens. All deaths are coded in line with the rules for World Health Organization (WHO) (21).

Study population

Residents born in Denmark between 1 January 1930 and 31 December 1997 were included (individuals were between 18 and 85 years old in 2015). We identified and created a cohort of all patients diagnosed with schizophrenia (ICD-8; 295 or ICD-10; F20) from the initiation of the DPCRR to the end of study period. Those who received a schizophrenia diagnosis after 1 January 1995 were included from their 18th birthday (thereby contributing to risk time to the general population) until time of schizophrenia diagnosis, and then followed until end of study period. The remaining

individuals not diagnosed with schizophrenia were considered as the cohort of people from the general population. Those who turned 18 years after 1 January 1995 in the general population were followed from their 18th birthday until end of follow-up. We included both prevalent and incident somatic diseases.

Measure and outcome

From the NPR, we identified whether individuals from the two cohorts had any somatic hospitalizations or outpatient contacts during the follow-up period. Each individual somatic diagnostic code were grouped into broader disease categories in accordance with the chapters defined by WHO (22). The following chapters were included; infection (ICD-10: A00-B99, ICD-8: 001-139), cancer (ICD-10: C00-D49, ICD-8: 140-239), endocrine (ICD-10: E00-E89, ICD-8: 240-279), neurologic (ICD-10: G00-G99, ICD-8: 320-359), cardiovascular (ICD-10: I00-I99, ICD-8: 390-459), respiratory (ICD-10: J00-J99, ICD-8: 460-519), digestive (ICD-10: K00-K95, ICD-8: 520-579), skin (ICD-10: L00-L99, ICD-8: 680-709), musculoskeletal (ICD-10: M00-M99, ICD-8: 710-739), and urogenital (ICD-10: N00-N99, ICD-8: 580-629). The primary study endpoint was time to all-cause mortality. The follow-up began on 1 January 1995 or on the cohort member's 18th birthday, whichever came last. The follow-up ended on 31 December 2015, the day of death, or the day of emigration, whichever came first. Time of schizophrenia diagnosis (if entry after January 1, 1995) and time of somatic hospitalization (if entry after January 1, 1995) were considered as time-dependent covariates during follow-up.

Explanatory variables

Demographic covariates included sex, age at study entry and calendar year (1995-1999, 2000-2004, 2005-2009, 2010-2015) of the index date were included. The total number of somatic diseases categories was included and divided into the following groups; 0, 1, 2, 3, 4, or ≥5.

Statistical analysis

Descriptive analyses were conducted initially to report population characteristics of the two cohorts included. Data were reported as mean±SD and n (%) for continuous and categorical variables, respectively. Population characteristics were compared between the two cohorts using independent sample t-test or chi-square test.

Second, we utilized a Cox proportional hazards regression model to investigate the individual impact of number of somatic diseases on mortality rates in both cohorts, using those from the general population with no somatic diseases as the reference, adjusted for age, sex, and calendar period. The mortality rates were calculated in a time-dependent manner, so each person could contribute to time at risk in each number of disease categories investigated.

Third, we conducted a Cox proportional hazards regression model to investigate the individual impact of somatic disease categories on mortality in both cohorts separately. The HRs were estimated as being diagnosed within that specific disease category versus not being diagnosed within that specific disease category within their individual cohort. This allowed us to calculate the PAF in both cohorts to understand which somatic disease categories affected mortality rates mostly. The PAF (expressed as percentage (95%CI)) is a measure of proportion of deaths that might be prevented if the exposure (in this case the somatic disease) was not present. We calculated the PAF using “punafcc” function in STATA based on the fully adjusted regression model, as previously done by others (23).

A sensitivity analysis excluding individuals with somatic hospitalization before January 1, 1995 was performed to allow only incident patients with somatic diseases.

All models using Cox proportional hazards regression fulfilled the assumption of linearity. Statistical significance was accepted at p-value of <0.05. All statistical analyses were performed with STATA 14 at the Statistics Denmark server with remote access.

Ethics

Register-based research in Denmark does not require approval from the Ethics Committee, although, all data extracted from the Danish nationwide registers involves personal information, thus processing of any personal data were anonymized before analysis. The Danish Data Protection Agency (2008-58-0028) approved the use of these data to this current research project.

Results

Population characteristics

The cohort included 5,432,821 individuals of which 30,210 (0.6%) had a diagnosis of schizophrenia and the remaining 5,402,611 (99.4%) served as controls from the general population, yielding 415,236 and 79,607,446 person-years, respectively. The mean age (SD) at entry in the schizophrenia group was 32.6 (11.4) years and 57.2% were males, whereas the mean age (SD) in the general population was 33.0 (14.5) years and 50.4% were males.

There were fewer individuals who did not develop any somatic disease in patients diagnosed with schizophrenia (11.6%) as compared to the general population (33.5%), p<0.001. Patients diagnosed with schizophrenia had significant higher levels of one (25.1% vs. 21.7%), two (16.5% vs. 13.3%), three (12.6% vs. 9.7%), four (9.1% vs. 6.8%), and more than five (25.1% vs. 15.1%) somatic diseases,

compared to the general population (P < 0.001 for all) (Table 1). Total number of deaths were 3658 (12.1%) among patients with schizophrenia compared to 281,108 (5.2%) deaths in the general population, p<0.001. In the cohort of patients diagnosed with schizophrenia, the most frequently observed somatic disease categories were the digestive system (38.5%), musculoskeletal system (34.5%), and urogenital system (27.3%). In the general population, musculoskeletal (32.5%), digestive (22.3%), and urogenital (21.0%) disease categories were most frequent observed. The frequency of all somatic disease categories (except cancer) were significantly higher in patients with schizophrenia compared to the general population, all p<0.001. Cancer disease had higher frequency in the general population as compared to patients with schizophrenia, p<0.001.

Association of number of somatic disease categories with mortality rates

In patients diagnosed with schizophrenia, the largest relatively increase in mortality was observed from no somatic disease (HR: 4.65, 95%CI, 4.20-5.15) to a single somatic disease (HR: 16.34, 95%CI, 15.41-17.32), and all other number of diseases showed increased mortality compared to the corresponding number of disease in the general population. Individuals from the general population had a dose response increase in mortality associated with an increasing number of somatic diseases, as observed by the relative increased mortality from no somatic disease to a single somatic disease (HR: 3.94, 95%CI, 3.89-4.00), and the additional increased mortality rate associated with two somatic diseases (HR: 4.81, 95%CI, 4.74-4.88).

The relative increase in mortality rates from zero to one disease category was 3.51 for patients diagnosed with schizophrenia compared to 3.94 for the general population, with corresponding number for one to two, two to three, and three to four disease categories being 0.90 vs 1.22, 1.03 vs 1.18 and 1.19 vs 1.25, respectively.

Mortality and population attributable fraction of specific somatic disease systems

In the cohort of patients with schizophrenia, the somatic disease category with the largest mortality rate was respiratory (HR: 1.49, 95%CI, 1.38-1.61), followed by cardiovascular diseases (HR: 1.39, 95%CI, 1.29-1.51), and cancer diseases (HR: 1.36, 95%CI, 1.25-1.49). However, respiratory diseases showed the highest PAF (9.29%, 95%CI, 7.81-10.74), as compared to digestive (8.19%, 95%CI, 5.96-10.34) and cardiovascular (7.89%, 95%CI, 6.28-9.48) diseases. In the general population, cancer (HR: 2.02, 95%CI, 2.00-2.04), respiratory (HR: 1.66, 95%CI, 1.65-1.68) and cardiovascular (HR: 1.56, 95%CI, 1.55-1.57) disease categories showed significant highest all-cause mortality, but PAF estimates showed that cancer (17.26%, 95%CI, 17.12-17.40), cardiovascular (14.15%, 95%CI, 13.93-14.36), and respiratory diseases (9.08%, 95%CI, 8.95-9.21) had largest impact on the overall mortality.

Comparing mortality rates of each somatic disease between patients with schizophrenia and the general population

In a Cox regression model adjusted for age, gender, calendar year, and number of diseases, the highest mortality rates were observed in skin disease (HR: 2.85, 95%CI, 2.64-3.08), musculoskeletal disease (HR: 2.85, 95%CI, 2.67-3.04), and digestive disease (HR: 2.79, 95%CI, 2.65-2.94), but across all somatic disease categories, patients with schizophrenia had a HR≥2 compared to the general population, see table 4.

The sensitivity analysis excluding patients with somatic diseases prior to index to allow only incident patients with somatic diseases showed nearly similar results to the primary findings. Cancer disease had a larger contribution to mortality in patients with schizophrenia in the sensitivity analysis, as compared to the main findings.

Discussion

In this nationwide retrospective cohort study of 5.4 million Danish individuals with a total follow-up of 80.0 million person-years, we found that compared to the general population, patients with schizophrenia were more likely to have both single as well as somatic multimorbidity. Patients with schizophrenia had an increased mortality independent of the number of somatic diseases diagnosed, as compared to the general population, with increased mortality differences increasing with somatic morbidities, and the largest mortality rate ratio was observed in those not diagnosed with any somatic disease between patients with schizophrenia and the general population. Lastly, in an analysis adjusted for age, gender, calendar year, and number of disease categories, patients with schizophrenia had a more than doubled HR for all individual somatic disease categories. The somatic disease categories associated with largest impact on mortality were respiratory, digestive and cardiovascular diseases.

Earlier studies have reported an excess mortality of somatic diseases in patients with schizophrenia.(4,5,8,24) Our results indicate that the largest difference in mortality rates between patients with schizophrenia and the general population is observed before the development of somatic multimorbidity. Laursen et al. (8) previously showed that a Charlson Comorbidity Index score of zero was associated to an almost 13-fold increase in mortality rates in patients diagnosed with schizophrenia, as compared to people without any contact to a psychiatric hospital, and the difference in mortality rates between these populations diminished with increasing comorbidity score. Our data showed an initial increase in mortality from zero to one somatic disease in patients with schizophrenia, but this mortality rate increase was negated when two, three, four and five somatic diseases were added. This finding is consistent with a study by Correll et al. (25) who showed that each additional cardiometabolic comorbidity did not significantly increase mortality. Once patients with schizophrenia had a single cardiometabolic disease, the addition of another comorbid disease did not result in an additive or multiplicative effect on the mortality rates.

Together, these findings could indicate a ceiling effect in patients with schizophrenia, particularly in prediction of mortality in those who suffer from more than two somatic diseases. The results are probably also affected by competing risk, as many patients with schizophrenia die before having the chance to develop somatic diseases, and as a consequence the mortality rates will appear higher in the lower levels of somatic diseases. For example, the high risk of unnatural deaths in patient with schizophrenia might interfere with the results observed. Although, previous studies have suggested underdiagnoses and under-treatment of somatic diseases in patients with schizophrenia, as compared to the general population (11,26). Our finding, that nearly all somatic disease categories (except cancer disease) were more prevalent in patients with schizophrenia, suggests that patients with schizophrenia in general do have more somatic disease, and does not directly support previous studies that have reported a general lack of somatic disease diagnostics in these patients (18,24). However, antipsychotics, antidepressants, and anxiolytics have weight gain properties that interferes with the number of patients who develop diseases such as cardiovascular, endocrine, and neurologic diseases in patients with schizophrenia. Instead, our results of a doubled mortality risk within all somatic disease categories in patients with schizophrenia, adjusted for number of disease categories, and demographic variables, could point towards the clusters of signs and symptoms associated with schizophrenia as the primary driver of the excess mortality. Several studies have reported that patients with SMI receive less medical prophylaxis (27) as well as fewer invasive procedures during hospitalization as compared to people without SMI (28). However, a recent observational study showed that exposure to secondary preventive cardiovascular treatment was associated to a reduced excess mortality in patients with schizophrenia (29). This association is not necessarily causal due to the risk of residual confounders, although it suggests that some interventions might work to reduce some of the excess mortality in patients with schizophrenia. Previous studies have suggested a delayed initiation of somatic treatment in patients with mental illnesses as a result of patient-related barriers or a general negative attitudes towards these patients by health care professionals (11,30). We believe that patients diagnosed with schizophrenia have a

poorer treatment seeking behavior and undergo fewer primary prophylactic treatments at GPs, which could even worsen the outcomes on multimorbidity, as compared to the general populations

Earlier findings have suggested that specific somatic diseases, such as cardiovascular, infection, cancer, endocrine, and respiratory, contribute to the excess mortality in patients with schizophrenia (24,31). To the best of our knowledge, our study is the first to investigate the contribution of each somatic disease category for all-cause mortality and the associated PAF estimates in a nationally representative data sample. Since no others have used PAFs in this population, it makes comparison difficult, but the use of PAF is highly relevant to understand the proportion of deaths that can be prevented if the specific somatic disease category was not present (a theoretical improvement). Our results showed that respiratory (9.3%), digestive (8.2%), and cardiovascular (7.9%) diseases had largest PAFs in patients with schizophrenia. The sensitivity analysis showed that cancer, cardiovascular, and respiratory diseases had largest PAF in patients with schizophrenia. This is probably a result of the current data, as it is restricted to individuals born between 1930 and 1997, and since cancer appear later in life, not many patients had the chance to develop cancer before index. Recent findings from Danish nationwide studies have reported that cancer, cardiovascular, and respiratory causes of death have largest impact on life-years lost in people with schizophrenia (32,33). Erlangsen et al. (32) reported that up to 20% of the excess life-years lost in mental disorders were related to respiratory diseases. However, the PAFs in patients with schizophrenia were lower than the PAFs observed in the general population for these disease categories. Therefore, residual confounding needs to be considered to our finding, such as tobacco use as well as substance- or alcohol abuse, which is much more prevalent in patients with schizophrenia than in individuals without (34), and have shown a large contribution to mortality in patients with schizophrenia (35). Lack of healthy diet intake (36), less physical activity (37) as well as a higher impact of unnatural deaths in patients with schizophrenia (33) might also skew the results towards a lower contribution of somatic diseases in patients with schizophrenia. Together, poor health seeking behavior from patients as well as insufficient quality of care provided by caregivers could contribute to the excess

mortality observed. There is an urgent need to identify and understand the possible barriers in our healthcare system, and future research should aim to focus on interventions and treatment within general somatic health, which will enable us to deliver a better-targeted intervention in patients with schizophrenia (from a healthcare perspective). The results also suggested that the signs and symptoms associated with schizophrenia is the primary driver of the excess mortality, thus, future research should focus on general health behavior challenges in patients with schizophrenia to identify the barriers that patients are experiencing.

Strengths and limitations

A major strength in the current study is the nationwide database including inpatient- and outpatient somatic diagnoses, which allows the inclusion of less severe cases of somatic disease than studies limited to hospitalized cases. However, our study is limited by the lack of data from primary care, which would have allowed us more reliable risk estimates than those observed in the current study. Our large sample size in combination with the number of events and long follow-up time provide strong evidence to understand the impact of different somatic diseases to mortality in patients with schizophrenia. However, the large sample size increases the probability to find significance even at small differences, thus all results should be interpreted in terms of clinical importance of the difference. Important confounders for increased mortality, including cigarette smoking, diet habits as well as physical activity, are not available in the Danish registers, thus we were not able to adjust for these confounders in the regression models. These confounders are known to have a high impact on survival outcomes and is a major concern in patients with schizophrenia due to the limited ability to adhere to these healthy lifestyle behaviors. Even though, it is believed that a large fraction of the excess somatic morbidity and mortality in patients with schizophrenia is related to their poor lifestyle related behavior, it might be difficult to include such variables in the regression models due to the relative close association of these variables to the diagnosis of schizophrenia. The differences

are believed to be linked specifically to the cluster of signs and symptoms in patients with schizophrenia, and as such adjusting for these variables would make results more difficult to apply in the general clinical practice. We were not able to assess the severity of the somatic disease, as well as we acknowledge that there are variations in outcome within each somatic disease category. Previous studies on this topic often report cause of death as the primary outcome, which are limited to identify a single cause of death, which does not represent the real-life setting, as people most often develop different somatic diseases along their life course up until time of death. Also, the large uncertainty associated with death certificates do challenge previous reports (21). Thus, we believe the current methodology is a major strength that adds valuable knowledge to the current literature regarding this topic.

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Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Table 1. Population characteristics.

Characteristics	Schizophrenia	General population	*P*
Number of subjects, N	30,210	5,402,611	
Number of person-years, y	415,236	79,607,446	
Age at entry, mean (SD), y	32.59 (11.42)	33.03 (14.49)	<0.001
Entry year in calendar periods, n (%)			<0.001
1995-1999	23,936 (79.23)	4,258,533 (78.82)	
2000-2004	1445 (4.78)	409,569 (7.58)	
2005-2009	2197 (7.27)	404,583 (7.49)	
2010-2015	2632 (8.71)	329,926 (6.11)	
Gender, n (%)			<0.001
Male	17,288 (57.23)	2,725,052 (50.44)	
Female	12,922 (42.77)	2,677,559 (49.56)	
Number of deaths, n (%)	3658 (12.11)	281,108 (5.20)	<0.001
Number of somatic diseases			
0	3508 (11.61)	1,811,302 (33.53)	<0.001
1	7589 (25.12)	1,172,963 (21.71)	<0.001
2	4994 (16.53)	717,017 (13.27)	<0.001
3	3794 (12.56)	521,863 (9.66)	<0.001
4	2758 (9.13)	366,227 (6.78)	<0.001
≥5	7567 (25.05)	813,239 (15.05)	<0.001
Somatic disease categories			
Infection	5185 (17.16)	401,404 (7.43)	<0.001
Cancer	4457 (14.75)	837,739 (15.51)	<0.001
Endocrine	5689 (18.83)	491,661 (9.10)	<0.001
Neurologic	5486 (18.16)	548,004 (10.14)	<0.001
Cardiovascular	6973 (23.08)	994,839 (18.41)	<0.001
Respiratory	7973 (26.39)	723,289 (13.39)	<0.001
Digestive	11,620 (38.46)	1,207,012 (22.34)	<0.001
Skin	6544 (21.66)	509,584 (9.43)	<0.001
Musculoskeletal	10,429 (34.52)	1,755,026 (32.48)	<0.001
Urogenital	8234 (27.26)	1,135,584 (21.02)	<0.001

Data are represented as N (%) for categorical variable and mean (SD) for continuous data.

Table 2. Number of somatic diseases and mortality rates in patients with schizophrenia compared to the rates in the general population

Number of diseases	Crude mortality, HR (95% CI)		Adjusted mortality, HR (95% CI)*		MRR†
	Schizophrenia	General population	Schizophrenia	General population	
0	4.31 (3.89-4.77)	1.0 (ref.)	4.65 (4.20-5.15)	1.0 (ref.)	4.7
1	13.60 (12.82-14.42)	4.91 (4.84-4.98)	16.34 (15.41-17.32)	3.94 (3.89-4.00)	4.2
2	12.77 (11.88-13.73)	6.91 (6.81-7.02)	14.72 (13.69-15.83)	4.81 (4.74-4.88)	3.1
3	13.74 (12.59-15.01)	9.34 (9.20-9.49)	15.21 (13.39-16.61)	5.65 (5.56-5.74)	2.7
4	16.53 (14.86-18.39)	12.45 (12.25-12.66)	17.68 (15.90-19.67)	6.66 (6.55-6.77)	2.7
≥5	21.12 (19.25-23.17)	17.63 (17.34-17.92)	21.00 (19.14-23.04)	8.30 (8.16-8.44)	2.5

*Adjusted for age, gender, calendar year, and all individual disease systems
Abbreviations: HR; Hazard Ratio, MRR; Mortality Rate Ratio

Table 3. Specific disease systems and mortality rates as well as population attributable fraction in patients with schizophrenia and the general population.

Disease category	Mortality, HR (95% CI)*		PAF, % of death (95% CI)†	
	Schizophrenia	General population	Schizophrenia	General population
Infection	1.14 (1.02-1.26)	1.31 (1.29-1.33)	1.53 (0.36-2.68)	1.97 (1.88-2.06)
Cancer	1.36 (1.25-1.49)	2.02 (2.00-2.04)	4.96 (3.73-6.17)	17.26 (17.12-17.40)
Endocrine	1.19 (1.09-1.31)	1.46 (1.44-1.48)	2.61 (1.33-3.88)	4.84 (4.73-4.96)
Neurologic	1.17 (1.07-1.29)	1.31 (1.30-1.32)	2.34 (1.06-3.59)	3.34 (3.23-3.47)
Cardiovascular	1.39 (1.29-1.51)	1.56 (1.55-1.57)	7.89 (6.28-9.48)	14.15 (13.93-14.36)
Respiratory	1.49 (1.38-1.61)	1.66 (1.65-1.68)	9.29 (7.81-10.74)	9.08 (8.95-9.21)
Digestive	1.27 (1.18-1.36)	1.28 (1.27-1.29)	8.19 (5.96-10.34)	7.88 (7.65-8.11)
Skin	1.26 (1.15-1.38)	1.26 (1.24-1.27)	3.84 (2.52-5.14)	2.23 (2.13-2.34)
Musculoskeletal	0.90 (0.82-0.98)	0.87 (0.86-0.88)	#	#
Urogenital	0.98 (0.91-1.07)	0.95 (0.94-0.96)	#	#

*Calculated separately for each cohort, and adjusted for age, gender, and calendar year
†Calculated based on the corresponding cox regression model from their respective cohorts
#Estimates only for diseases with a significant increased effect on mortality

Table 4. Crude and adjusted mortality rates for individual somatic disease categories in schizophrenia versus the general population.

	Schizophrenia vs. General population		
Disease category	**Crude HR (95% CI)**	**Adjusted HR (95% CI)***	**Adjusted HR (95% CI)†**
Infection	1.55 (1.41-1.70)	2.38 (2.17-2.62)	2.22 (2.02-2.45)
Cancer	1.42 (1.32-1.54)	2.19 (2.03-2.36)	2.17 (2.02-2.35)
Endocrine	1.38 (2.27-1.50)	2.24 (2.06-2.43)	2.16 (1.99-2.34)
Neurologic	1.54 (1.42-1.67)	2.58 (2.37-2.80)	2.44 (2.25-2.65)
Cardiovascular	1.53 (1.44-1.63)	2.61 (2.45-2.78)	2.48 (2.33-2.64)
Respiratory	1.83 (1.72-1.94)	2.91 (2.73-3.09)	2.78 (2.61-2.96)
Digestive	1.71 (1.62-1.80)	2.99 (2.84-3.16)	2.79 (2.65-2.94)
Skin	1.94 (1.80-2.10)	3.13 (2.90-3.38)	2.85 (2.64-3.08)
Musculoskeletal	1.91 (1.79-2.04)	3.39 (3.17-3.61)	2.85 (2.67-3.04)
Urogenital	1.94 (1.82-2.07)	3.13 (2.94-3.34)	2.77 (2.60-2.95)

*Adjusted for age, gender, and calendar year
†Adjusted for age, gender, calendar year, and number of disease categories