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Cause-specific life years lost among persons diagnosed with schizophrenia: Is it getting better or worse?

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ABSTRACT

Background: People with schizophrenia have an increased risk of premature mortality compared to the general population. We aimed to quantify which types of causes of death contributed to the excess mortality, and to examine whether there has been an increase in the excess mortality among persons with schizophrenia in the period 1995 to 2015.

Method: We used a cohort design including the entire Danish population. We calculated life years lost of the cohort members compared to a set reference-age at 95 years old. Using a decomposition model we examined differences of cause-specific death among those with schizophrenia and the general population, including calendar trends during the last two decades.

Results: In the general population, as well as in persons with schizophrenia, we found improvements in life years lost during the last two decades. Men with schizophrenia lost 13.5 years more than the general population (women; 11.4 years). Compared to the general population, a large improvement in life years lost with respect to suicide and accidents was found in those with schizophrenia, but, this improvement was offset by an increasing number of life years lost in deaths from diseases and medical conditions.

Conclusion: Our findings highlight the urgent need for focused treatment of general medical conditions in those with schizophrenia. Without such an investment, it is probable that the life years lost among persons with schizophrenia (compared to the general population) will continue to worsen in future decades.

1. Background

People with schizophrenia have an increased risk of premature mortality compared to the general population (Brown, 1997; Osby et al., 2000; Tanskanen et al., 2018). The excess mortality has been demonstrated on several occasions over recent decades (Brown, 1997; Laursen et al., 2007; Liu et al., 2017) with some descriptions dating back to the first half of the 20th century (Odegard, 1951). Compared to the general population, it is unclear if the level of premature mortality is increasing, i.e. the differential gap is widening (Hayes et al., 2017; Saha et al., 2007), improving (Wahlbeck et al., 2011) or staying the same (Hjorthoj et al., 2017; Tanskanen et al., 2018) in recent years. Irrespective of changes over time, there is widespread consensus that the excess mortality in those with schizophrenia is unacceptable high (Liu et al., 2017; Thornicroft, 2011).

In order to close the mortality gap, we need a better understanding of the causes of death that are accountable for the excess mortality among those with schizophrenia. Once we have an understanding of these, we can explore causal pathways and modifiable risk factors. By convention, causes of death are divided into 'natural' (deaths from diseases and medical conditions; e.g. cancer and diseases of the circulatory system) and 'unnatural' causes of death (death from external causes; e.g. suicide and accidents). Natural causes are generally held responsible for most of the curtailed life expectancy (Brown, 1997; Laursen, 2011) linked to schizophrenia; mainly due to an increased risk of general medical conditions related to an unhealthy lifestyle (e.g. poor diet, smoking, alcohol use, and lack of physical activity), side effects from antipsychotic medication (especially weight gain), and suboptimal access to early diagnosis and treatment (Laursen et al., 2014). All of these factors are in

Abbreviations: MRR, mortality rate ratios; ICD8/10, International Classification of Diseases version 8/10; WHO, World Health Organization.

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principle modifiable, if not preventable; hence presenting an opportunity to act on these clear inequalities in the health care system. Unnatural causes account for a smaller part of the premature mortality associated with schizophrenia, although still with a substantial impact (Hellemose et al., 2018; Ko et al., 2018). Looking at all psychiatric disorders 20–30% of the curtailed life expectancy is due to unnatural causes (Erlangsen et al., 2017). Over the last two decades, a decline in the suicide rate of the general population has been observed, this was especially pronounced among persons with a psychiatric disorder (Nordentoft et al., 2011). A Danish study (Erlangsen et al., 2017) assessing the excess mortality related to psychiatric disorders in general (i.e. combined as one group, compared to those without any mental disorder), confirmed a decrease over recent years for both suicides and accidents.

People with schizophrenia belong to some of the most vulnerable groups in modern society, and are considered to be one of the most disabling disorders worldwide (Salomon et al., 2015). Thus, it is imperative to understand if the mortality gap (compared to the general population) is improving, remaining static, or worsening. There are several approaches for assessing mortality of specific groups. For example, standardized mortality ratios have been widely used in previous research, however, when addressing the impact of premature mortality associated with schizophrenia over the lifespan, the demographic approach of calculating Life Years Lost is a powerful tool (Andersen, 2017).

1.1. Aim

Our aim was to quantify which causes of death contributed to the excess mortality found among persons with schizophrenia. Furthermore, we wished to examine whether there has been an increase in the excess mortality during 1995 to 2015, with special focus to the contribution by different causes of death.

2. Methods

We used a cohort design including the entire Danish population. Every person in Denmark was followed from their 10th birthday, January 1st 1995 or immigration to Denmark (whatever happened last), until their 95th birthday, death, emigration from Denmark, or December 31st 2015 (whatever occurred first). We merged three registers with national coverage to create our research database; The Danish Civil Registration System (Pedersen et al., 2006) was used to define the cohort, the Psychiatric Central Research Register (Mors et al., 2011) to find those with schizophrenia, and lastly the Cause of Death Register (Helweg-Larsen, 2011) to define the cause of death. The Danish health register uses the WHO ICD10 classification (World-Health-Organization, 1994) from 1994 and onward. Prior to that, the WHO ICD8 classification (World-Health-Organization, 1967) was used. ICD9 was never implemented in Denmark.

2.1. Case definition

We considered a person as having schizophrenia from the date when a first diagnosis was recorded in the Psychiatric Central Research Register; either an ICD10 diagnosis of F20 or an ICD8 diagnosis of 295.xx excluding 295.79. As data on psychiatric diagnoses are available since 1969 (Mors et al., 2011), persons who had been recorded with a schizophrenia diagnosis prior to enrolment in the study, were considered as having schizophrenia from start of follow-up. Throughout the study, we have referred to these individuals as having schizophrenia.

2.2. Causes of death

Data on the underlying cause of death was obtained from the Causes of Death Register. We categorized causes of death into the following 10 discrete (non-overlapping) groups: Infectious diseases (ICD-10: A00–A09, A20–A99, B00–B89, B91–B99), neoplasms (ICD-10: C00–D09), diabetes mellitus (ICD-10: E10–E14), diseases of the circulatory system, including heart diseases (ICD-10: F03·9, I00–I25, I27, I30–52, I60–I84, I86-I99, R54), respiratory diseases, including pneumonia and influenza (ICD-10: J00–J99), digestive diseases (ICD-10: K00-K93), alcohol misuse (ICD-10: F10, I85, K70), suicide (ICD-10: X60–X84, Y87.0), accidents, including homicides (ICD-10: V01–X59, X85–Y09, Y10–Y86, Y87.1, Y87.2, Y88–Y89), and other causes of death (all remaining ICD-10 codes). These categories follow the official Danish cause of death list from the Danish Health Authority (Danish-Health-Authority, 2000); except for including a separate category of diabetes mellitus, as this is a common causes of death in people with schizophrenia (Ribe et al., 2014). Furthermore, we collapsed groups with few cases. Note, in keeping with standard conventions, a person could have one and only one underlying cause of death.

In a sub-analysis, we classified causes of deaths as unnatural (external causes of death), including suicide or accidents; or natural causes (deaths from diseases and medical conditions), which comprised all other causes of death.

2.3. Statistical methods

As a first step in our analysis, cause-specific mortality rates were described for persons with schizophrenia and the general population. Differences in mortality rates between persons with and without schizophrenia were estimated using cause-specific mortality rate ratios (MRRs). Sex-specific MRRs were obtained by means of Cox proportional hazards models with age as the underlying time scale and adjusting for calendar time, using the 'R' statistical software.

Secondly, to illustrate the difference in mortality between those with schizophrenia and the general population we calculated survival and cause-specific mortality curves at age 40 years for each of the groups (Andersen, 2013).

Thirdly, we calculated the main outcome, life years lost. This measure quantifies, for the group of patients with schizophrenia, the average remaining life expectancy from the age at disease onset subtracted from a set reference age, which we choose to be 95 years. For the general population, the measure quantifies the average remaining life expectancy subtracted from 95 years for subjects alive at ages corresponding to the age-at-onset distribution for those with schizophrenia (Andersen, 2017).

The difference between life years lost of the two groups, the general population and those with schizophrenia, we denote excess life years lost, and may be interpreted as the number of years that people with schizophrenia lose *in excess* of that found in the general population.

Life years lost were separated into loss attributable to specific causes of death using a decomposition model (Andersen, 2017; Erlangsen et al., 2017).

We calculated 95% confidence limits on the excess life years lost using bootstrapping with 500 resamples of the population with schizophrenia.

We undertook post-hoc analysis using the official UK definition of alcohol-specific deaths. We furthermore examined the impact of different ages at start of follow-up.

3. Results

3.1. Study period 1995–2015

We included all individuals aged 10–94 years living in Denmark at some point between January 1st 1995 and December 31st 2015 yielding 6,641,608 persons (3,312,111 men and 3,329,497 women). A total of 47,554 persons had schizophrenia (27,297 men; 20,257 women).

During the 21 years of follow-up 1,116,887 persons (561,233 men; 555,654 women) died. Of these, 12,417 (6988 men; 5429 women) had been diagnosed with schizophrenia.

The overall mortality rate ratio for schizophrenia was 3.55 (95% CI: 3.46–3.65) for men and 2.71 (2.63–2.79) for women. Mortality rates in persons with schizophrenia were higher than in the general population for all categories of causes of death, results ranging from an excess mortality rate ratio for cancer of 1.53 (1.43–1.65) for men with schizophrenia to a ratio of 15.84 (13.80–18.19) in women for dying by suicide, Table 1. Diseases of the circulatory system, neoplasms and the 'other' category were the most frequent causes of death both among those with schizophrenia as well as in the general population (Table 1). Among those with schizophrenia who died from 'other causes', 31.9% had a cause of death from the F chapter (mental and behavioural disorders). The equivalent number in the general population was 5.7%.

Looking at the survival curves for persons between age 40 and 95 a strikingly different pattern is seen for those with schizophrenia when compared to the general population. The value of the survival curve represents the percentage of the population who were alive at a given age, as read on the y-axis. The difference between the values of the coloured curves above the survival curve represent the share of the population that have died due to a specific cause of death where each colour represents a cause of death. For example, at age 60, approximately 10% of men in the general population had died, while approximately 30% had died among those with schizophrenia, with similar numbers for women.

The total area of Fig. 1, denotes the life span from age 40 to age 95 years on the x-axis. At any given age, the white area below the survival curve represents the average years lived up to that age while the total coloured area above the survival curve represents the total average years lost up to that age, each colour representing a given cause of death. Excess mortality among those with schizophrenia was found across all causes of death (Fig. 1).

In references to a life span of 85 years (between age 10 and 95), men in the general population on average lived 18.15 years short of reaching age 95 years (i.e. life years lost = 18.15) while women who on average lived longer than men had 14.07 life years lost, Table 2. The number of life years lost was considerably higher in persons with schizophrenia; men lost 31.62 years while women lost 25.46 years. The difference between life years lost for men with and men in general, i.e. the excess life years lost, was 13.48 years; the corresponding number for women was 11.39 year (Table 2).

In the general population, most life years were lost to cancer (men = 5.64 years, women = 4.92 years) followed by 'diseases of the circulatory system' and 'other causes'. In persons with schizophrenia, the category of 'other causes' of death resulted in most life years lost (men = 6.71, women = 5.55) and was followed by 'diseases of the circulatory system' and cancer. The only cause of death with less life years lost among persons with schizophrenia was in men with respect to cancer; −1.06 years compared to the general population, Table 2 and online Fig. O3. Also for women, negative excess life years lost from cancer mortality were noted; although, the difference in cancer mortality between those with schizophrenia and the general population diminished between 1995 and 2015. Nevertheless, it should be noted that we found a 1.5-fold (CI-95%: 1.43–1.65) higher mortality rate for cancer among those with schizophrenia when compared to the general population when looking at the entire period.

Post-hoc analysis using the official UK definition of alcohol-specific deaths instead of the one described above reviled only small differences, online Table O4. Different ages at start of follow-up showed a substantial excess number of life years lost in those with schizophrenia at all ages. At the age 75 years old the loss was 3.32 years for men and 3.24 for women, online Table O2.

3.2. Trends over calendar time

We subdivided the follow-up period into four different time-periods: 1995–1999, 2000–2004, 2005–2009, 2010–2015. Both in the general population as well as in persons with schizophrenia we found improvements in life years lost in each of the four time-periods. The improvement in total life years lost was at the same level in all four periods for men with schizophrenia and the general population, indicating that the mortality gap for men with schizophrenia remained static. However, for women the mortality gap had worsened over time by approximately 1.5 years (most recent versus earliest time-period), Table 3. Dividing the cause of death into natural and unnatural causes revealed a clear pattern; while the excess mortality related to unnatural causes of death decreased over time, an increasing gap was noted for natural causes from 1995 to 2000 through the periods to 2010–2015. This was true for both genders, Table 3 and Fig. O1.

Table 1
Overview of cause-specific mortality rates and adjusted mortality rate ratios in persons with schizophrenia and the general population, from 1995 to 2015.

	Schizophrenia (N)	Mortality rate per 1000 p-y	General Population (N)	Mortality rate per 1000 p-y	Mortality rate ratio (95% CI)[a]
Men					
Infectious diseases	68	0.22	2706	0.06	6.05 (4.59–7.97)
Neoplasms (cancer)	1021	3.33	162,479	3.39	1.53 (1.43–1.65)
Diabetes	216	0.71	14,020	0.29	4.40 (3.78–5.13)
Diseases of the circul. system	1409	4.60	183,383	3.83	2.85 (2.69–3.03)
Respiratory diseases	709	2.31	53,849	1.12	4.81 (4.42–5.24)
Digestive diseases	249	0.81	17,096	0.36	4.46 (3.86–5.14)
Alcohol misuse	434	1.41	19,675	0.41	3.21 (2.88–3.58)
Suicide	583	1.90	10,008	0.21	9.05 (8.22–9.96)
Accidents	799	2.61	21,889	0.46	8.00 (7.38–8.67)
Other causes of death[b]	1500	4.90	76,128	1.59	5.75 (5.42–6.09)
Women					
Infectious diseases	30	0.14	2819	0.06	2.99 (1.98–4.51)
Neoplasms (cancer)	975	4.43	154,155	3.14	1.54 (1.43–1.65)
Diabetes	144	0.65	11,708	0.24	3.35 (2.78–4.05)
Diseases of the circul. system	1345	6.11	195,846	3.99	2.13 (2.01–2.27)
Respiratory diseases	772	3.51	58,417	1.19	3.92 (3.62–4.26)
Digestive diseases	175	0.80	21,900	0.45	2.27 (1.92–2.70)
Alcohol misuse	137	0.62	7289	0.15	3.50 (2.88–4.24)
Suicide	284	1.29	3952	0.08	15.84 (13.80–18.19)
Accidents	352	1.60	16,924	0.35	5.75 (5.10–6.49)
Other causes of death[b]	1215	5.52	82,644	1.68	4.22 (3.95–4.50)

[a] Between persons with and without schizophrenia, adjusted for age and calendar time.
[b] In total N = 2715 persons with schizophrenia died from 'other causes' and N = 156,057 in the general population. Among those with schizophrenia who died from 'other causes', N = 865 (31.9%) had a cause of death from the F chapter (mental and behavioural disorders). The equivalent number in the general population was N = 8936 (5.7%).

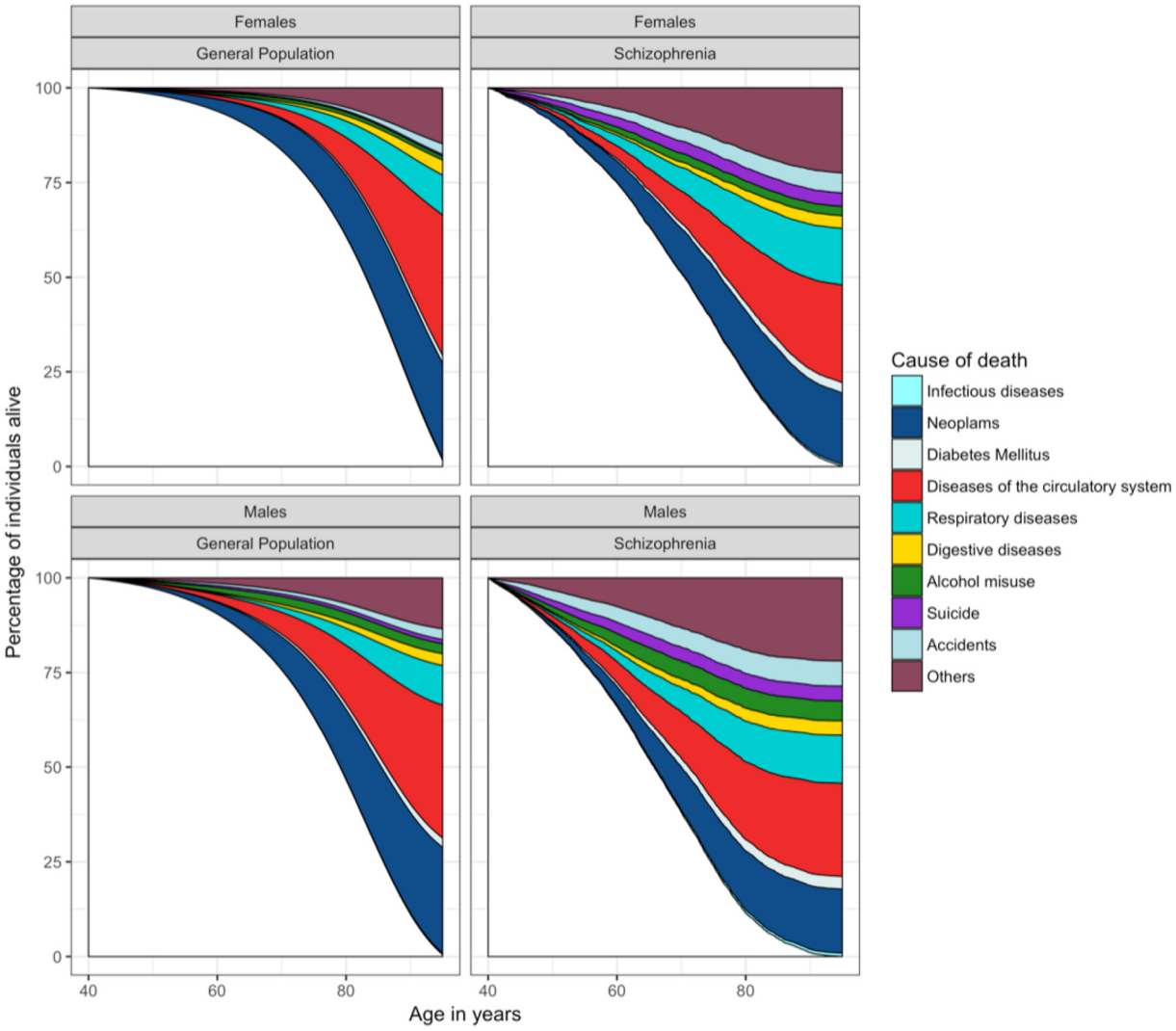

Fig. 1. Survival curves from age 40 in persons with schizophrenia and the general population, in the period 1995 to 2015, including life years lost by cause of death.

A finer granularity of causes of death showed that cancer and diseases of the circulatory system were responsible for an increasing share of the excess life years lost increase in the natural deaths over time, despite the fact that men with schizophrenia lost less life years to cancer than men in the general population throughout the period. In contrast, the excess mortality due to unnatural deaths, which predominantly consisted of suicides and accidents, was found to decrease over recent period; although persons with schizophrenia still had more life years lost due to unnatural deaths than the general population the difference diminished as seen in Fig. 2.

4. Discussion

Based on a new approach adapted from demography, we calculated life years lost. Over the last two decades, both men and women with schizophrenia have shown improvements with respect to life years lost. However, compared to the general population, women with schizophrenia had slightly higher number of excess life years lost in the later part of the period, i.e. an increasing mortality gap, while men with schizophrenia had the same number of life years lost throughout the period. Thus, persons with schizophrenia on average still live 11–13 years shorter. A clear tendency of a shift from unnatural causes towards natural causes of death as accountable for the 11–13 years of excess life years lost was seen in both men and women.

The good news of the results presented here is that people with schizophrenia in Denmark have greatly improved on their life years lost over the last two decades. Men with schizophrenia have even improved their life span at a similar pace as the general Danish population. The improvement in life years lost is impressive, when unnatural causes is examined, with almost 3 fewer years lost among men with schizophrenia and 2.5 years in women in 2010–2015 compared to 1995–2000.

The bad news is that the life span of Danish men and women with schizophrenia still is lagging behind with 11–13 life years lost compared to the general population, which is strikingly in a high-income country with equal access to health care through universal and free of charge health care coverage for all citizens. Furthermore, the improvements in the excess mortality for persons with schizophrenia seem to be attributable to improvement from unnatural causes of death, with no improvements observed for natural causes of death.

The latter implies that the three years gained in life expectancy from natural causes, which the general population have benefitted from during the studied period, have been completely missed out in the group of persons with schizophrenia. This suggests that those with schizophrenia are not benefiting to the same extend from the general improvements in treatment and prevention of medical conditions as the general population.

Our findings are consistent with those of other studies; while treatment for cancers and diseases of the circulatory system and subsequent survival have been greatly improved during recent decades in the

Table 2
Life years lost in persons with schizophrenia and the general population, in the period 1995–2015. Stratified by 10 causes of death. With 95% confidence interval.

	Life years lost		Excess life years lost[a]
	Schizophrenia	General population	Schizoph. – gen. pop.
Men			
Infectious diseases	0.31	0.10	0.21 (0.14–0.28)
Neoplasm (cancer)	4.58	5.64	−1.06 (−1.32 to −0.80)
Diabetes	0.96	0.47	0.49 (0.37–0.64)
Diseases of the circul. system	6.15	5.35	0.80 (0.50–1.10)
Respiratory diseases	3.10	1.53	1.57 (1.35–1.80)
Digestive diseases	1.11	0.54	0.57 (0.43–0.7)
Alcohol misuse	1.94	0.88	1.07 (0.87–1.26)
Suicide	2.89	0.43	2.47 (2.23–2.69)
Accidents	3.87	0.78	3.09 (2.83–3.34)
Other causes	6.71	2.43	4.28 (3.97–4.61)
All deaths	31.62	18.15	13.48 (13.21–13.77)
Women			
Infectious diseases	0.14	0.06	0.08 (0.03–0.14)
Neoplasm (cancer)	4.96	4.92	0.04 (−0.23–0.31)
Diabetes	0.65	0.30	0.36 (0.25–0.48)
Diseases of the circul. System	5.19	3.98	1.20 (0.92–1.46)
Respiratory diseases	3.31	1.45	1.86 (1.63–2.12)
Digestive diseases	0.79	0.53	0.27 (0.16–0.39)
Alcohol misuse	0.84	0.30	0.54 (0.40–0.69)
Suicide	1.96	0.15	1.81 (1.56–2.06)
Accidents	2.06	0.41	1.65 (1.44–1.87)
Other causes	5.55	1.97	3.57 (3.28–3.88)
All deaths	25.46	14.07	11.39 (11.06–11.73)

[a] Negative numbers implies that persons with schizophrenia have a lower loss of life-years due to that specific cause of death.

general population (Nichols et al., 2013), it appears that people with schizophrenia have not benefited from these improvements (Bitter et al., 2017; Correll et al., 2017; Jayatilleke et al., 2017). This is observable in Fig. 2, where the lines representing excess life years lost of cancer and diseases of the circulatory system have a clear upwards trend, indicating that those disorders account for an increasing share in the excess life years loss. Using a different approach, a Finish study reached the same results; longevity of persons with schizophrenia seems only to follow the general population. Furthermore, the shift in the excess life years lost, from unnatural to natural causes, was also noted (Tanskanen et al., 2018). Still, a Danish study found an increasing mortality gap between those with schizophrenia and the general population during 1980–2010 (Nielsen et al., 2013).

An explanation of the shift towards natural causes of death could simply stem from the lower rates of unnatural causes of death, which often occurs earlier in life, making more people with schizophrenia live to a higher age where cancer and diseases of the circulatory system are more common (Erlangsen et al., 2017).

4.1. Limitations

Our study was based on a single, underlying cause of death, as recorded by the doctor on the death certificate. Often, people have multiple disorders, each of which might contribute to the final cause of death. We have kept the cause of death 'mutually exclusive, comprehensively exhaustive' in order to build our models. This is of course a simplification of the real world, but necessary in order to calculate the health metrics of interest. The underlying cause of death used in this paper, is register-based from the Cause of Death Register (Helweg-Larsen, 2011). It has a high level of completeness and the validity of the date of death is excellent, though the causes of death are less valid. By keeping our definitions of causes of death to broad well-established ICD 10 categories, we aimed to minimize potential bias related to their validity, however, we cannot exclude a difference in the validity of the causes of death between those with schizophrenia and the population in general. Especially the substantial share of deaths in the 'other' group with an F-diagnosis is of concern. According to the directive from the Danish health authorities (Danish-Health-Authority, 2016), the F-diagnosis is only to be used if no other cause is found. The numbers reported in this study are so large that misclassification from the doctors part cannot be ruled out.

The overall loss of life years will however not be affected by the validity of causes of death as the date of death (and the actual occurrence of death) is extremely reliable (Helweg-Larsen, 2011).

While we have the date of the first diagnosis of schizophrenia, we do not have the exact time of onset of schizophrenia. In Denmark, a large proportion of people with schizophrenia have been in contact with the psychiatric health care prior to being diagnosed with schizophrenia. Six years before onset, 30% of the persons who later developed schizophrenia had been seen in the psychiatric health care system. One year before onset, 50% had been in contact with the psychiatric health care system (Norgaard et al., 2016). In this study, we have chosen to calculate the life years lost among persons with schizophrenia while accounting for the age at first diagnosis of schizophrenia. In a previous study based on Danish data (Laursen, 2011), the onset age was assumed to be at the age 15 years old and that resulted in somewhat higher number of life years lost. Thus, it should be kept in mind that the 13.5 life years lost for men (11.4 for women) found in this paper, are weighted averages and that later onset, results in fewer life years lost (and vice versa), as there is an obvious celling of how many years a person aged e.g. 75 can lose, see online Table O2.

4.2. Conclusion

Using an approach adapted from the field of demography; namely life years lost, we found that people with schizophrenia in Denmark have greatly improved on their life years lost over the last two decades. However, we found no improvement in how many life-years persons with schizophrenia lose compared to the general population. There is still an unacceptable high level of excess life years lost at 11–13 years.

Table 3
Life years lost per calendar time in persons with schizophrenia and the general population. Total and stratified by natural and unnatural causes of death.

	All causes of death			Unnatural causes of death			Natural causes of death		
	Schizophrenia	General population	Difference	Schizophrenia	General population	Difference	Schizophrenia	General population	Difference
Men									
1995–2000	33.53	20.30	13.23	8.62	1.47	7.15	24.91	18.82	6.09
2000–2005	32.80	19.05	13.75	6.76	1.25	5.50	26.04	17.79	8.24
2005–2010	32.43	17.83	14.60	7.77	1.18	6.60	24.66	16.65	8.00
2010–2015	29.99	16.21	13.78	5.60	0.99	4.62	24.39	15.23	9.16
Women									
1995–2000	26.64	15.85	10.79	5.67	0.75	4.92	20.97	15.10	5.87
2000–2005	26.16	14.90	11.26	4.15	0.57	3.57	22.01	14.32	7.69
2005–2010	25.70	13.88	11.82	3.61	0.51	3.10	22.09	13.36	8.73
2010–2015	24.86	12.46	12.40	3.25	0.42	2.82	21.61	12.03	9.58

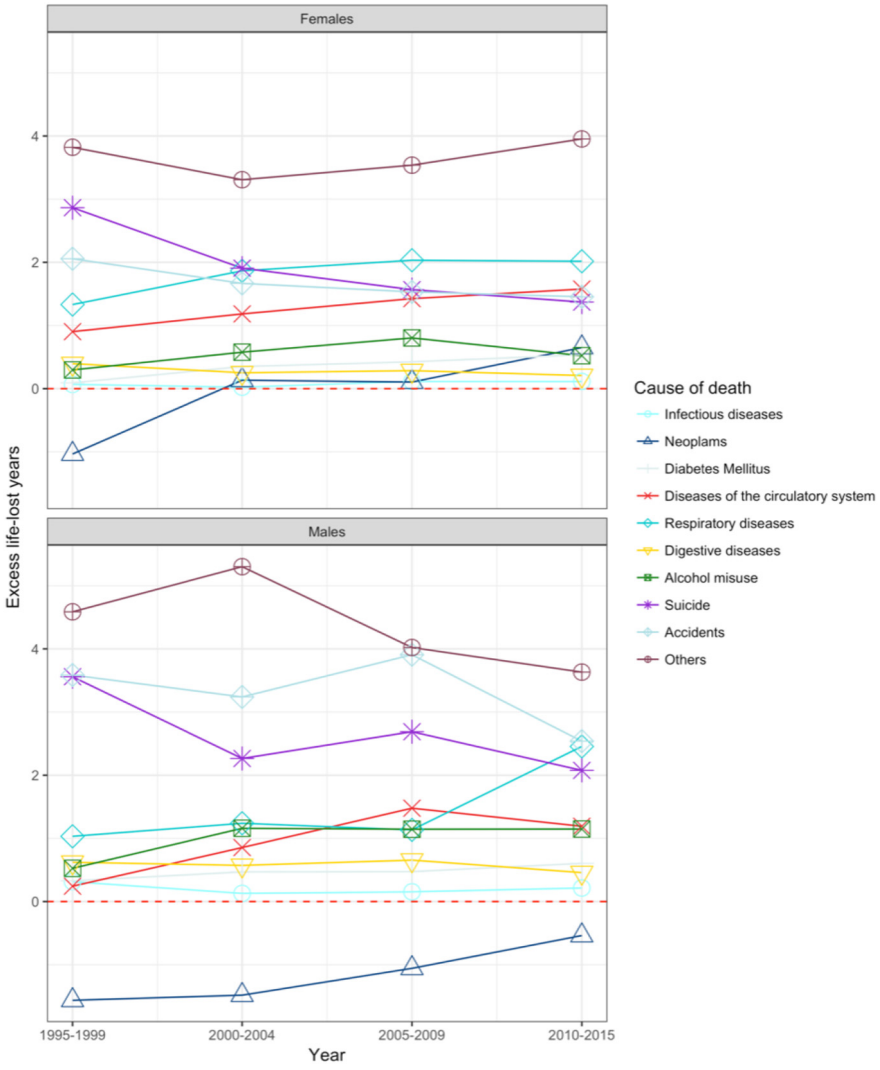

Fig. 2. Life years lost among persons with schizophrenia compared to the general population. Stratified by four calendar periods.

All the improvement found in death by suicide and accidents among persons with schizophrenia compared to the general population, was counteracted by an increasing difference in life years lost in deaths from diseases and medical conditions. The very positive trends of improvement in the two most common causes of death; death by diseases of the circulatory system and cancer found in the general population, have not been equally shared by those with schizophrenia.

Our findings highlight the urgent need for focused treatment of general medical conditions in those with schizophrenia. Without such an investment, it is probable that the life years lost among persons with schizophrenia (compared to the general population) will worsen in future decades.

Conflicts of interest

None.

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CRediT authorship contribution statement

Thomas Munk Laursen: Conceptualization, Writing - original draft, Writing - review & editing. **Oleguer Plana-Ripoll:** Conceptualization, Writing - review & editing. **Per Kragh Andersen:** Conceptualization, Writing - review & editing. **John J. McGrath:** Writing - review & editing. **Anita Toender:** Writing - review & editing. **Merete Nordentoft:** Writing - review & editing. **Vladimir Canudas-Romo:** Conceptualization, Writing - review & editing. **Annette Erlangsen:** Conceptualization, Writing - review & editing.

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The manuscript has been read and approved by all named authors, and all authors have approved the order of authorship. There are no other individuals who satisfied the criteria for authorship but are not listed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.11.003.

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