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Excess medical comorbidity and mortality across the lifespan in schizophrenia. A nationwide Danish register study

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ABSTRACT

Introduction: People with severe mental illness have greater risk of un-detected and inadequately treated medical disorders, adding up to the risk of premature death. This study investigated how chronic medical comorbidity evolved across the lifespan in schizophrenia and the associated impact on mortality.
Method: A register-based retrospective nested case-control study was conducted, identifying incident cases of cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), cancer and diabetes, as well as mortality due to these diseases, across the lifespan in schizophrenia.
Sample: A schizophrenia cohort consisting of 4924 individuals aged 18–40 years registered with a diagnosis of schizophrenia (ICD-8: 295.0–3 + 295.9) during admission to a psychiatric hospital unit in 1970–79. Schizophrenia cases were age and gender matched with 22,597 controls in the general population.
Results: Rate ratio (RR) of CVD and cancer were similar to controls. The RR of COPD and diabetes were increased across the lifespan.
The probability of having been diagnosed prior to dying from CVD, cancer, pulmonary diseases or diabetes was markedly reduced in schizophrenia cases compared to controls. The RR of all-cause mortality and mortality from CVD, COPD and diabetes remained elevated in all age groups in schizophrenia. Registration of medical comorbidity was associated with increased survival.
Conclusion: Excess medical comorbidity persists across the lifespan and into older age. No age-related decrease in incidence of major chronic medical comorbidities in schizophrenia was found except for diabetes.
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1. Introduction

People with schizophrenia have a shorter life expectancy than the general population (Hjorthoj et al., 2017). This excess mortality is mainly due to medical comorbidity, in particular cardiovascular disease (CVD) (Cohen et al., 2015; Correll et al., 2017; Crump et al., 2013; Laursen et al., 2013). Comorbid medical illnesses among people with severe mental illness may be un-detected (Crump et al., 2013; Laursen et al., 2011; Ward and Druss, 2015) and inadequately treated (Crump et al., 2013; Lahti et al., 2012a; Laursen et al., 2014a; Vahia et al., 2008), adding up to the risk of premature death. It has been argued that reasons for this could be patients showing reduced or different healthcare-seeking behaviour (Berren et al., 1999; Brink et al., 2017; Munk-Jørgensen et al., 2000). Nonetheless, increased contact with the healthcare system among people with schizophrenia indicates that they benefitted less from this compared to those without schizophrenia (Crump et al., 2013; Norgaard et al., 2016). Unhealthy lifestyle and adverse effects due to antipsychotic medication adds to an increased risk of metabolic syndrome and medical comorbidity (Cohen et al., 2015). Smoking, highly prevalent among people with serious mental illness, plays a particularly important role in increasing morbidity and mortality (Dickerson et al., 2016). Associations of excess CVD in schizophrenia have not been entirely consistent (Carney et al., 2006; Crump et al., 2013; Hendrie et al., 2013), but a recent large scale meta-analysis established an increased risk of CVD and CVD-related mortality in people with severe mental illness (Correll et al., 2017). Associations with cancer in schizophrenia compared to people without schizophrenia have been less consistent (Catts et al., 2008; Crump et al., 2013), whereas excess diabetes and chronic obstructive pulmonary disease

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(COPD) have been consistent findings (Carney et al., 2006; Crump et al., 2013; Hendrie et al., 2014; Ward and Druss, 2015).

The excess mortality in schizophrenia appears to continue into later life, but at a lower level than in younger age groups (Kredentser et al., 2014; Talaslahti et al., 2012). A survivor effect describes a selection process such that those who remain alive tend to be healthier than those who have died during an observation period. This may play a role since higher functioning patients displaying healthier lifestyles most likely stand a better chance of surviving into old age (Meesters et al., 2013), a notion supported by other studies (Brink et al., 2017; Hendrie et al., 2013).

In light of increased medical comorbidity and premature death in younger age groups (Hendrie et al., 2014), additional knowledge about how medical comorbidity develops over the life course in people with schizophrenia would help inform the design of approaches to the management of chronic medical conditions in this vulnerable group.

The aim of this longitudinal study was to examine how risk of major medical comorbidities and mortality changes through adult life and their associations in people with schizophrenia compared to people without schizophrenia.

2. Methods

We conducted a register-based retrospective nested case-control study in order to identify incident cases of CVD, COPD, cancer and diabetes as well as mortality due to these diseases. This was done according to age groups across the lifespan in schizophrenia. By comparing adults with and without schizophrenia, the objectives of this longitudinal study were to examine: 1) To what extent the relative risk of CVD, COPD, cancer and diabetes develops as age increases. 2) Overall and cause-specific mortality due to natural causes across the lifespan. 3) The association between medical comorbidity and corresponding cause-specific mortality as well as overall mortality due to natural causes.

2.1. General setting

Universal healthcare, including admission to hospital and outpatient healthcare, is available to all residents in Denmark.

The system of assigning unique ID numbers to all Danish citizens allows for record linkage across the various administrative registries on an individual level (Frank, 2000). The registers used in this study were the Danish National Patient Register (Lynge et al., 2011), the Psychiatric Central Register (Loffler et al., 1994), Statistics Denmark (Statistik, 2013), the Register of Causes of Death (Juel and Helweg-Larsen, 1999) and the Danish Civil Registration System (Pedersen, 2011). Statistics Denmark contains sociodemographic data, such as marital status, educational level, income and residence, whereas the other registers contain health related data, such as in- and outpatient contacts, diagnosis and also cause and time of death. See Appendix A for specification of applied register variables.

Diagnostic criteria: The International Classification of Diseases and Related Health Problems (ICD) was used for recording diagnoses. Until 1994, the 8th revision of ICD (ICD-8) was applied; thereafter the ICD-10 was implemented. The ninth revision was never used in Denmark (Bertelsen, 1996). In this article, the term medical is used for all non-psychiatric health conditions.

2.2. Sample

The study population consisted of all individuals aged 18–40 years residing in Denmark who were registered with a diagnosis of schizophrenia (ICD-8: 295.0–3 + 295.9) during admission to a psychiatric hospital unit in the ten-year period 1970–79. Each individual in the schizophrenia cohort was matched by age and gender with 4.97 control subjects using propensity scores (please see Section 2.4 statistical analyses). The matched controls were nested in a larger random sample of 40,708 controls drawn from the general population. This larger random sample will be referred to as the parent cohort and was generated by using the Danish Civil Registration System and the Psychiatric Central Register. The observation period started 1 January 1980, when individuals were aged 18–50 years old, and ended 31 December 2012, with the highest ages reaching 51–83 years accordingly. Register data was collected over the entire observation period, spanning more than three decades. Variables of interest and sources of data exist equally for cases and controls and were thus comparable.

In total, 4924 people were registered with schizophrenia in the period of 1970–1979 in Denmark. Some of these cases were excluded from analysis due to deaths ($n = 305$) and emigration ($n = 75$) before 1980. The remaining cases ($n = 4544$) were age- and gender-matched with 22,597 controls. Fifty-six controls were censored after onset of schizophrenia.

2.3. Measures

Data on sociodemographic variables, medical comorbidity and cause and time of death were linked. Data were obtained from all in- and outpatient healthcare settings nationwide. Four categories of medical diagnoses were defined (CVD, cancer, COPD and diabetes) and grouped by applying the ICD-8 and ICD-10 codes used in the Charlson Comorbidity Index (Charlson et al., 1987). Modifying the index slightly, some groups were merged (e.g. diabetes with and diabetes without complications grouped as one). Thus the ICD codes used were as follows: CVD: ICD8 410; 427.09–427.11; 427.19; 428.99; 782.49; 440–445; 430–438. ICD10 I21-I23; I50; I11.0; I13.0; I13.2; I70–74; I77; I60-I69; G45; G46. Cancer: ICD8 140–199; 204–207; 200–203; 275.59; ICD10 C00-C75; C91-C95.COPD: ICD8 490–493; 515–518. ICD10 J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3. Diabetes: ICD8 249.00; 249.06; 249.07; 249.0; 250.00; 250.06; 250.07; 250.09; 249.01–249.05; 249.08; 250.01–250.05; 250.08. ICD10 E10.0; E10.1; E10.9; E11.0; E11.1; E11.9; E14.0; E14.1; E14.9; E10.2-E10.8; E11.2-E11.8; E14.2-E14.8.

Cohorts: A series of cohorts were constructed based on the age of the participants. A participant was included in a given cohort when he or she turned 30, 40, 50, 60, and 70 and did not have one of the diagnostic categories registered at that time. Each cohort was followed for 10 years. Participants were excluded at the time when one of the diagnostic categories was registered or censored if participants did not register with any of the diagnoses categories mentioned above during their time of observation in a given age cohort. If participants were registered with a diagnosis, they were excluded from that particular diagnose category only. Participants who did not register with any of the diagnoses were included in more than one cohort as they grew older. For example, a participant without any diagnoses was included in the cohort of 30–39 year olds and censored the day he or she turned 40, and subsequently immediately included in the cohort of 40–49 year olds. If the participant registered with a diagnosis of interest at the age of 42, then he or she was excluded from that particular diagnose category at that time and ceased to be a candidate for the 50–59-year cohort when he or she turned 50. Thus, only incident diagnoses were registered.

Prior diagnosis had to be registered at least 30 days before death. This timespan was chosen to exclude individuals who were diagnosed very shortly before their death and who did not greatly benefit from potential lifesaving treatment. Cause of death was defined according to the Danish list-49 grouping of diseases and diagnoses covering CVD, cancer (malignant neoplasms), pulmonary diseases (COPD, lung infections e.g. pneumonia) and diabetes were used (see Appendix B for specific ICD8 and ICD10 codes).

Even though mortality in schizophrenia has been extensively examined, analyses on mortality were here performed so as to allow

comparison with the development of chronic medical comorbidity across the lifespan.

2.4. Statistical analyses

We matched the schizophrenia group with a control group without schizophrenia using propensity scores with a caliper threshold of 0.05 instead of exact matches on gender and age. The propensity score approach enabled us to achieve a higher ratio (1 to 4.97), while minimizing the age and gender differences in a context of a limited availability of potential controls ($n = 40{,}708$) in the parent cohort. Therefore, adjusting for gender was still required. The case and control groups were compared on background variables using two-way tables and χ^2 tests. Incidence rates of CVD, cancer, COPD and diabetes, cause-specific mortality and all-cause mortality across age groups, according to each of the cohorts described above, were compared using crude and adjusted Poisson models. We relaxed the assumption of $\lambda = \sigma^2$, using cluster robust variance estimation where person years represent observations nested in individuals. Absolute numbers of relevant events and person years were tabulated across age groups for cases and controls. The association between the Charlson Comorbidity Index and mortality was modelled using the same Poisson approach.

The association between schizophrenia and being diagnosed with, prior to dying from, CVD, cancer, pulmonary diseases or diabetes was modelled using logistic regression producing odds ratios (OR).

The rate ratios (RR) in this study represent the outcome risk among schizophrenia patients relative to the control group. They were adjusted for gender and calendar year, for Charlson Comorbidity Index score and, lastly, for marital status and highest educational level, since these are potential confounders of outcome risk of medical comorbidity and mortality. All statistical tests were two-sided. Alpha level of 0.05 was used.

Patients with schizophrenia may be less likely to have been diagnosed with medical comorbidities prior to death. Therefore, we combined Charlson Indexed diagnoses of CVD, COPD, cancer and diabetes, regardless of whether the diagnosis appeared for the first time as a diagnosis in the Danish National Patient Register or as the cause of death on the death certificate. This was done for both cases and controls and was an attempt to assess "true" incidence of medical disease.

We included missing observations categories for some sociodemographic covariates to avoid losing observations. As variables with missing values were time-varying, missing values were only temporary. Time-varying covariates were refreshed yearly.

3. Results

In total, 4544 people between 18 and 51 years old with a diagnosis of schizophrenia in 1970–79 were matched with 22,597 controls in the general population without schizophrenia.

The average age at baseline (January 1, 1980) was 34.3 years for the schizophrenia cohort and 33.9 years for controls. Compared to controls, people with schizophrenia were more likely to be less educated, unemployed or retired, and living in an urban area, as presented in Table 1. Also, they were less likely to be married or to have been married. Women with schizophrenia were less likely to have children compared to controls. Information on parenthood was not available for men.

Table 1
Sociodemographic characteristics of people with and without schizophrenia, January 1, 1980.

	Schizophrenia		Control		*P*-value
	N	%	N	%	
N	4544		22,597		
Age					
19–29	1272	28.0	6360	28.1	
30–39	2130	46.9	10,779	47.7	0.356
40–51	1142	25.1	5458	24.2	
Gender					
Female	1527	33.6	7254	32.1	0.048
Male	3017	66.4	15,343	67.9	
Educational status					
Primary	2576	57.6	8266	36.9	
Secondary	1389	31.0	9772	43.6	<0.001
Tertiary	379	8.5	3927	17.5	
Missing	200	4.4	632	2.8	
Employment status					
Currently employed	1057	23.3	20,523	90.8	
Retired	2912	64.1	437	1.9	<0.001
Unemployed	551	12.1	1636	7.2	
Missing	24	0.5	<5	–	
Marital status					
Never married	3185	70.1	5202	23.0	
Married	619	13.6	15,323	67.8	<0.001
Divorced	712	15.7	1918	8.5	
Widowed	28	0.6	154	0.7	
Children (only females)					
No	849	55.6	1125	15.5	<0.001
Yes	678	44.4	6129	84.5	
Residence					
Rural	3389	74.6	18,597	82.3	
Urban	1144	25.2	3981	17.6	<0.001
Missing	11	0.2	19	0.1	

The *P*-value shows differences between schizophrenia and controls. Significance level 0.05.

3.1. Chronic medical diseases

As depicted in Fig. 1, the risk of having a diagnosis of CVD was not significantly different between cases and controls when stratified in age cohorts. Cases between the ages of 50–59 years had increased risk of having a diagnosis of cancer (RR 1.42, 95% CI 1.17 to 1.71) compared to controls. The risk of having a diagnosis of COPD was increased for cases 1.5–2-fold at any age above 50 years and the diagnosis of diabetes increased 1.6–2.1-fold for the age intervals 30 to 59 years relative to controls.

Results on age group 20–29 years were omitted throughout the study due to very small numbers of individuals.

Combining Charlson Indexed registrations of CVD, COPD, cancer and diabetes diagnoses (alive) with similar cause of death in one binary outcome did not alter results (data not shown). For absolute numbers of events see Appendix C. The unadjusted and adjusted rate ratios are presented in Appendix D. Adjusting for Charlson Comorbidity Index changed the increased risk of CVD diagnoses among 50–79 year olds with schizophrenia from being significant to being non-significant. Adjusting for education and marital status did not alter results significantly.

3.2. Diagnosis of chronic medical diseases prior to death

The probability of having been diagnosed prior to death caused by CVD, cancer, pulmonary diseases or diabetes was markedly reduced among people with schizophrenia compared to the control group (see Table 2). These estimates did not change significantly when comparing OR across age groups.

3.3. Mortality

The risk of all-cause mortality remained significantly elevated at all ages in schizophrenia compared to controls, but the difference decreased with age. Thus, the age and gender-adjusted risk ratio (RR, 95% CI) was 5.95 (4.89 to 7.23) at age 30–39 years, and decreased to 2.73 (2.34 to 3.19).

The risk of mortality due to natural causes compared to controls was highest among schizophrenia cases who did not have any of the 19 groups of chronic medical conditions in the Charlson Comorbidity Index (RR 5.54, 95% CI 5.03 to 6.10) (see Table 3). The risk was almost halved when comparing cases and controls with one score on the

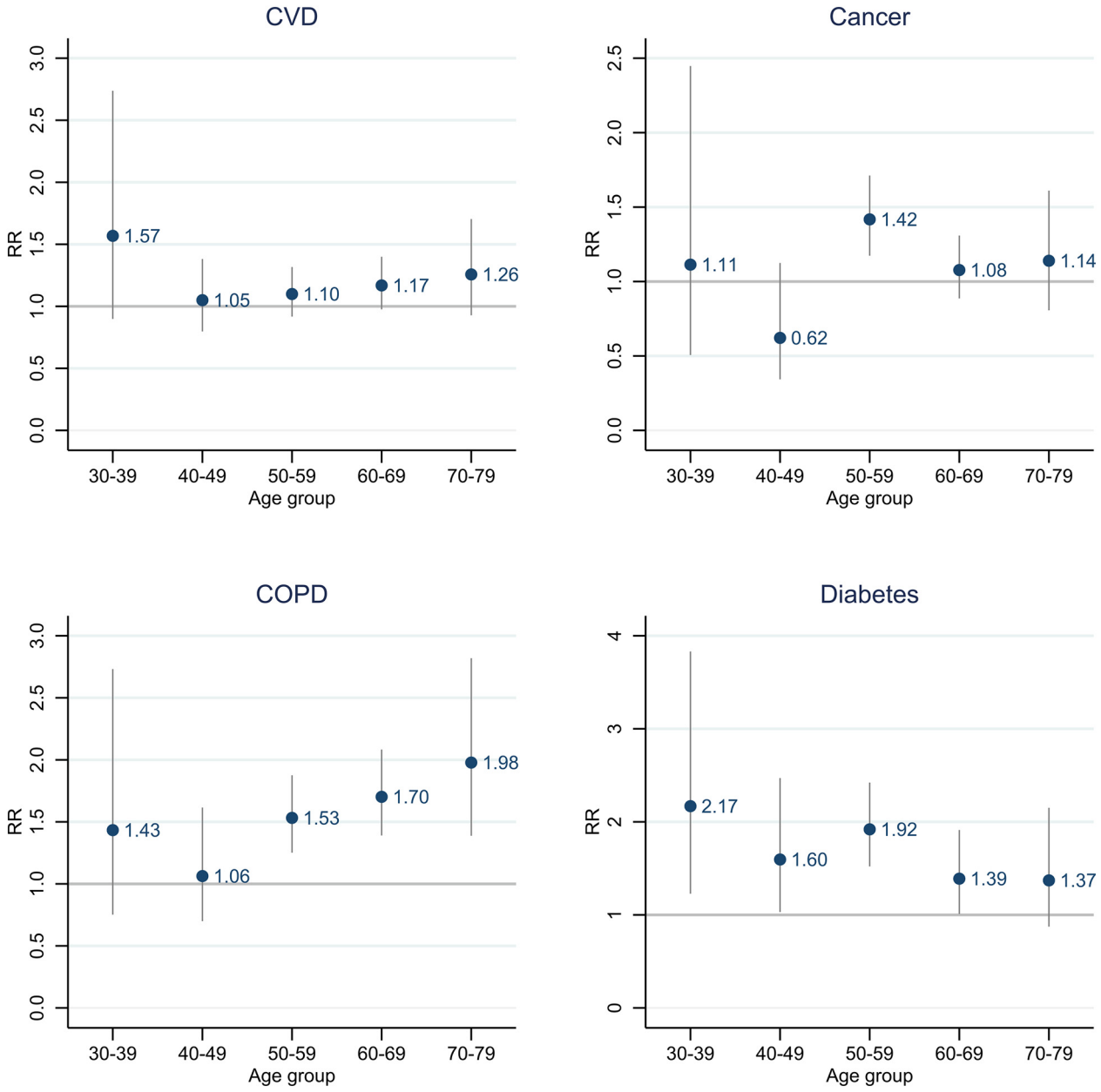

Fig. 1. Rate ratios (RR) across age intervals for incident cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), cancer and diabetes in schizophrenia compared to controls in the general population. Adjusted for age, gender, calendar year, Charlson Comorbidity Index score, education and marital status. 95% confidence intervals.

Charlson Comorbidity Index. Mortality due to natural causes decreased relative to controls with increasing Charlson score, being lowest among cases with scores of three or more (RR 1.7, 95% CI 1.5 to 1.8). All estimates were statistically significant.

Compared to the general population, people with schizophrenia had increased risk of mortality from CVD at 30–39 years (RR 3.42, 95% CI 1.17 to 10.0) and at any age above 50 years, COPD at any age above 40 years, cancer in 50–69 year olds and diabetes among 60–69 year olds (RR 4.07, 95% CI 2.21 to 7.47), as shown in Fig. 2. For absolute numbers of events see Appendix C.

Changes in mortality risk ratios were mostly seen after adjusting for education and marital status, especially for COPD where risk ratios were almost halved in age groups 40–69 years. Changes according to age

Table 2
Probability of having been diagnosed >30 days prior to death caused by cardiovascular disease, cancer, pulmonary disease or diabetes.

	Odds ratio	95% CI
Cardiovascular disease	0.55	0.44; 0.68
Cancer	0.38	0.27; 0.55
Pulmonary disease	0.42	0.30; 0.60
Diabetes	0.36	0.18; 0.71

Adjusted for age and gender. CI = confidence interval.

Table 3
Rate ratios (RR) of death due to natural causes stratified according to Charlson Comorbidity Index score in 30–84 year old people with schizophrenia relative to controls without schizophrenia in the general population.

Charlson Comorbity Index score	RR	95% CI
0	**5.54**	5.03, 6.10
1	**3.42**	3.95, 4.96
2	**2.56**	2.24, 2.92
3	**1.66**	1.51, 1.83

RR = rate ratio. All risk estimates reached significance, $p < .001$. Risk years = 786,329. Number of subjects = 27,141. Adjusted for age and gender.

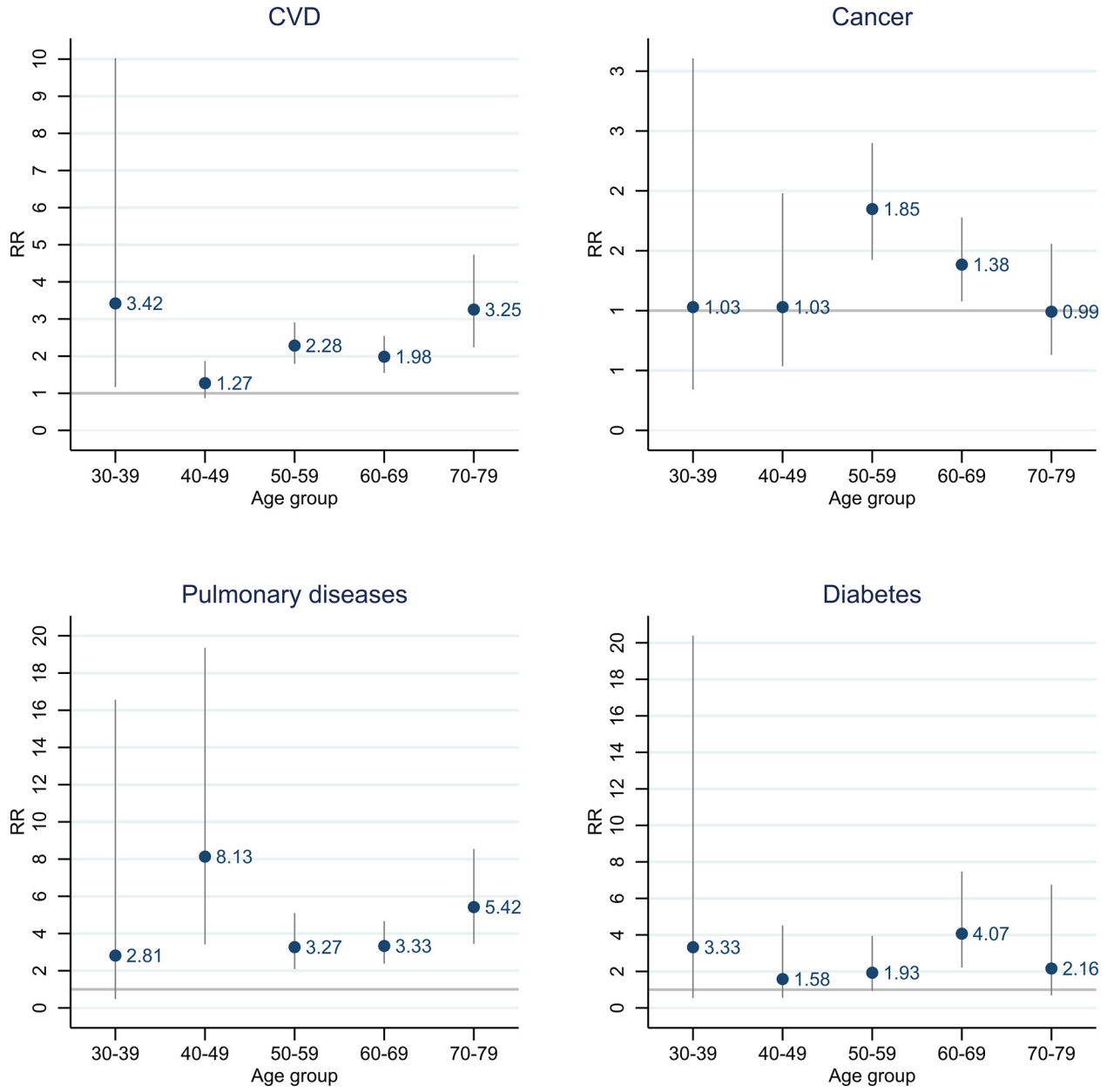

Fig. 2. Rate ratios (RR) across age intervals for mortality due to cardiovascular disease (CVD), pulmonary disease, cancer and diabetes in schizophrenia compared to controls in the general population. Adjusted for age, gender, calendar year, Charlson Comorbidity Index score, education and marital status. 95% confidence intervals.

group were: 40–49 years RR 14.66 (adjusted 8.91); 50–59 years RR 5.67 (adjusted 3.00); 60–69 years RR 5.59 (adjusted 3.40) (Appendix E).

4. Discussion

Increased overall incidence of medical comorbidity and mortality continued across the lifespan and into older age in this longitudinal study following a cohort of 4544 people with schizophrenia compared to controls without schizophrenia. More specifically, schizophrenia cases had increased incidence of registered COPD and diabetes in most age groups, but did not differ significantly in incidence of registered cancer and CVD.

Excess mortality in schizophrenia, although present across the lifespan, diminished with ageing. In addition, increased risk of undetected medical comorbidity was also found in this patient group. Thus, compared to controls, participants with schizophrenia who died during follow-up were less likely to be diagnosed prior to death with the medical disease that was stated as their cause of death. Schizophrenia cases registered with any medical comorbidity were associated with reduced excess mortality relative to controls.

Compared to controls in the general population there was no difference in risk of registered CVD in schizophrenia, which contrasts with the finding of a 2–3-fold increase in death by CVD in this patient group compared to controls. These discrepancies of reduced registration and increased mortality have been described before (Correll et al., 2017; Crump et al., 2013; Laursen et al., 2014b; Nielsen et al., 2013; Talaslahti et al., 2012).

According to a meta-analysis, there was no increase in the pooled overall cancer incidence rate in schizophrenia compared to the rest of the population (Catts et al., 2008). This was also the case in another register study (Crump et al., 2013), corroborating the results reported here.

Similarly the excess medical comorbidity from COPD and diabetes has been reported before (Carney et al., 2006; Crump et al., 2013; Hendrie et al., 2014; Osborn et al., 2008; Ward and Druss, 2015), as well as in the over 65 year-olds with schizophrenia (Hendrie et al., 2013) compared to those without schizophrenia. The finding of a steady

decrease in diabetes incidence supports the notion of a possible survivor effect.

Consistent with other studies, overall mortality in schizophrenia decreased with age relative to the general population, but remained elevated over the entire lifespan (Kredentser et al., 2014; Meesters et al., 2016; Talaslahti et al., 2012), as did specific causes of death due to CVD, COPD and diabetes. Cancer mortality was only increased in schizophrenia among the 50–69 year-olds and was consistent with a large meta-analysis showing a significantly increased risk of cancer mortality compared to the general population (Zhuo et al., 2017). Thus, excess mortality continues to be a major issue across the lifespan.

In this study, the high proportion of patients with CVD and COPD registered as cause of death but without a corresponding diagnosis registered prior to death indicates that these chronic medical diseases in patients with schizophrenia went under-detected and under-treated, as also shown in other studies. (Ayerbe et al., 2018a; Crump et al., 2013; Lahti et al., 2012b; Laursen et al., 2014a; Laursen et al., 2009; Laursen et al., 2011; Vahia et al., 2008; Ward and Druss, 2015). Therefore, the number of actual incident medical comorbidities in all age groups is possibly higher. Thus, it appears that undiagnosed patients missed potential treatment opportunities, with concomitant reduced likelihood of survival.

Under-detection may arise due to provider bias or bias related to patient behaviour. Providers may be more focused on psychiatric symptoms than on general medical issues, or affected by negative preconceptions. In addition, people with schizophrenia are offered treatment to a lesser extent than people without schizophrenia adding to the increased risk of premature death; especially treatment for myocardial infarction has been in focus (Attar et al., 2017; Ayerbe et al., 2018a; Ayerbe et al., 2018b; Druss et al., 2000; Laursen et al., 2009; Vahia et al., 2008), Patients may tend to avoid seeking healthcare until a certain illness severity (Munk-Jørgensen et al., 2000; Oud and Meyboom-De Jong, 2009), and may also have cognitive difficulties in communicating their needs, or be less aware of physical symptoms (Cohen et al., 2015; Hert et al., 2011).

Patients may also avoid or miss healthcare appointments and fail to adhere to treatment recommendations due to adverse effects of medications, financial reasons or reduced disease insight (Cohen et al., 2000). Under-detection of important causes of mortality in people with schizophrenia, despite universal healthcare, suggests that this may be an even greater problem in countries without universal healthcare (Crump et al., 2013).

Registration with a chronic medical disease is a consequence of having been in contact with inpatient or outpatient healthcare services in Denmark. Provided that schizophrenia cases were selectively underdiagnosed with medical comorbidity, these patients would in reality be suffering from medical comorbidity to a greater extent than the control group. Consequently, they would probably have greater mortality; in particular, those not registered with any comorbidity at all, and missing out on potentially lifesaving medical treatment.

The association of decreasing excess mortality with increasing degree of registered medical comorbidity in schizophrenia relative to controls would appear to indicate a protective effect of healthcare contact. This finding is in line with findings in another Danish register study (Laursen et al., 2011). Thus, healthcare contact, and thereby possibilities of treatment, underscores the importance of help-seeking behaviour (Leucht et al., 2007) and access to care. This association was similar to yet another Danish register study, which found that receiving diagnoses of CVD and cancer within the healthcare system, be it by general practitioner or any hospital contact, decreased the excess mortality in patients with schizophrenia compared to the general population (Laursen et al., 2014a).

Denmark's easily accessible and universal healthcare is geared to provide optimal opportunities to schizophrenia patients seeking healthcare. Even so, help-seeking appears to remain a challenge in this patient group (Brink et al., 2017; Munk-Jørgensen et al., 2000). More joined-up healthcare with mental health and general healthcare services in close proximity could increase the chance of recognition and treatment of physical diseases in this group. Good examples have included co-locating psychiatric outpatient clinics and pharmacy services to increase medication adherence (Rubio-Valera et al., 2014), introducing physicians into psychiatric outpatient settings (Hansen et al., 2016) or combining psychiatric and general medical casualty rooms (Jensen, 2016).

There are indications that the differential mortality gap has worsened over time (Hjorthoj et al., 2017; Nielsen et al., 2013; Saha et al., 2007). Apparently people with schizophrenia have not seen the same reduction in mortality due to CVD over time as the general population, who have experienced an overall improvement in CVD treatment and lifestyle (Brown et al., 2010; Laursen and Nordentoft, 2011). In addition, it has been suggested that people with schizophrenia may have more severe forms of general medical conditions (Cohen et al., 2015; Munk-Jørgensen et al., 2000), potentially leading to increased mortality.

Some survivor effect would have been expected in the schizophrenia group inasmuch as higher functioning patients would most likely stand a better chance of surviving into old age. In this study we failed to find an age-related decrease in incidence of major chronic medical diseases, except for diabetes. Along with the continued excess mortality into older age, this was a concerning finding, especially when inadequate detection and treatment of medical diseases in schizophrenia has been known for decades (Cohen et al., 2000; Jeste et al., 1996; Koranyi, 1979).

Reasons for survival into old age have been suggested in part to be due to the correlation between psychotic symptoms and physical health. As psychotic symptoms tend to diminish with age, patients may become more alert to their medical problems and also be better received by other healthcare professionals (Leucht et al., 2007; Vahia et al., 2008). Also, remission has been associated with lower mortality in older individuals with schizophrenia (Talaslahti et al., 2012).

Lifestyle factors and adverse effects of antipsychotic medication seen in schizophrenia have been held partly responsible for the increased prevalence of metabolic syndrome and medical comorbidity, but this may also be partly inherent to the disorder itself (Cohen et al., 2015; Jeste et al., 2011). Accelerated physical ageing in schizophrenia has been suggested (Jeste et al., 2011). Treatment with cardiovascular medication (Laursen and Nordentoft, 2011) or antipsychotics (Crump et al., 2013; Tiihonen et al., 2009) has also been associated with lower all-cause mortality in this patient group.

5. Limitations and strengths

As in other register studies, individual data on smoking, exercise or other direct lifestyle measurements, level of cognition, data on living alone or with others and age of illness onset were unavailable in this study. Adjusting for sociodemographic data may serve as an indirect proxy for smoking and other unhealthy lifestyles, since these are more common in less educated populations (Lee et al., 2009; Osler et al., 2001), as is seen in schizophrenia. Thus this may be part of the cause of the markedly reduced risk ratios in COPD that were found when adjusting for education and marital status. Adjusting for confounders did not change the overall result, but may have diminished the contribution of schizophrenia to premature mortality. Smoking, in particular, is known to contribute significantly to COPD, CVD and cancer, and is highly prevalent in schizophrenia (Crump et al., 2013). Thus, this would be expected to affect risk estimates. One register study ran a sensitivity analysis to assess the potential mediating effect of smoking and found up to 30% attenuation of risk estimates in lung cancer, CVD and respiratory diseases. However risk estimates remained significantly elevated (Crump et al., 2013).

The diagnosis of schizophrenia outside hospital settings was not registered in the 1970s and thus not possible to include in the setup of our study. Leaving out individuals with schizophrenia who did not need clinical admission during their disease course in 1970–79 was a

limitation, in that less severe cases were thereby excluded from the study. The opposite limitation arose from the 305 people with schizophrenia who were excluded due to death before baseline, and possible examples of more severe cases.

In Denmark substance and alcohol use disorders are mostly treated in specialized outpatient clinics where patients are not registered, because they can present for treatment anonymously. Any registration of diagnoses of substance or alcohol use disorder happens only in connection with inpatient or other outpatient contact in Denmark. Only few events were registered, most likely due to under-registration and inconsistency due to changes in registration practices. Therefore, data on alcohol and substance use disorder diagnoses were not used for adjusting risk estimates.

Register studies are powerful in being able to include large numbers of individuals and making long observation periods possible while avoiding recall bias. Danish registers have a high degree of validity and completeness (Kildemoes et al., 2011; Lynge et al., 2011; Pedersen, 2011; Statistik, 2013). Nonetheless, with only predefined variables being available, missing values and problems with changing practices of registration set limits on the use of registers. The incidence rates reported here were dependent on the individual entering into secondary care through contact with inpatient or outpatient services (Munk-Jørgensen et al., 2014). Register research in schizophrenia is challenged in this respect as this patient group appears to display a different pattern in the use of healthcare services (Berren et al., 1999; Brink et al., 2017; Munk-Jørgensen et al., 2000).

The validity of the schizophrenia diagnosis using ICD-8 was lower than today (Loffler et al., 1994; Uggerby et al., 2013), but even if some of the patients in the schizophrenia cohort turned out to have been wrongly diagnosed, our results would ultimately tend to be even more significant in the case of significant differences.

We strived to generate a homogenous cohort with lifelong illness by recruiting only early onset (<40 years) patients comprising 75–80% of all schizophrenia cases (Cohen et al., 2015). Inclusion of outpatient data (since 1995) increased the possibility of registering milder forms of medical diseases not requiring hospital admission, and so providing a more robust and generalizable estimate of medical comorbidity and avoiding the bias that could result from use of inpatient data only. Nordic countries have a tradition of universal healthcare services for all citizens. Thus health data from these populations potentially would have the highest inclusion of the economically disadvantaged compared to other countries. The results of this study may be generalized to people with schizophrenia in other developed countries.

6. Conclusions/perspectives

The overall incidence of four major medical comorbidities were increased to some extent for some age groups, but more worrying was the noticeable excess mortality due to these comorbidities across the lifespan. This showed that people with schizophrenia suffered and died from these diseases to a greater extent than those without schizophrenia. The findings in this study indicate inadequate detection and/or treatment of medical comorbidity in schizophrenia at any time in mid- and later life, thus causing continued excess mortality in this patient group. Heightening awareness among healthcare professionals and patients is critical in this regard. Further investigation into the causes and mechanisms are needed to identify measures on how to address these potentially remediable problems.

Practice as well as research needs to be targeted in terms of improving healthcare utilization and accessibility in ways that will appeal to people with schizophrenia – while also ensuring successful implementation. Intensive case management with a general health focus in improving the medical care and health outcomes is likely to play a role. Mobile mental health technology, e.g. mental health apps, comprises a whole host of possibilities, including symptom tracking, reminders of appointments and psycho-educational approaches/games that may help improve health in this patient group. And yet, although mental health technology is viewed as a promising modality to extend the reach of mental healthcare beyond the clinic, current supporting literature regarding its efficacy remains limited (Van Ameringen et al., 2017).

Although increasingly more people with schizophrenia survive into older age, they remain vulnerable and in need of targeted and sustained focus on the detection and treatment of medical diseases through life.

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Conflict of interest

None of the authors have any conflicts of interest to declare.

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CRediT authorship contribution statement

Maria Brink: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing - original draft, Writing - review & editing. **Anders Green:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation, Writing - review & editing. **Anders Bo Bojesen:** Data curation, Formal analysis, Methodology, Software, Visualization, Writing - review & editing. **J. Steve Lamberti:** Methodology, Supervision, Validation, Writing - review & editing. **Yeates Conwell:** Methodology, Supervision, Validation, Writing - review & editing. **Kjeld Andersen:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Supervision, Validation, Writing - review & editing.

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