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ORIGINAL ARTICLE

Long-term mortality of persons with severe mental illness and diabetes: a population-based cohort study in Denmark

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Background. Persons with severe mental illness (SMI) have excess mortality, which may partly be explained by their high prevalence of diabetes.

Method. We compared the overall and cause-specific mortality in persons with SMI and diabetes with that of the general Danish population between 1997 and 2009 by linking data from Danish national registries.

Results. The cohort counted 4734703 persons, and during follow-up 651080 persons died of whom 1083 persons had SMI and diabetes. Compared with the background population, the overall mortality rate ratios (MRRs) for persons with SMI and diabetes were 4.14 [95% confidence interval (CI) 3.81–4.51] for men and 3.13 (95% CI 2.88–3.40) for women. The cause-specific MRRs for persons with SMI and diabetes were lowest for malignant neoplasms (women: MRR=1.98, 95% CI 1.64–2.39; men: MRR=2.08, 95% CI 1.69–2.56) and highest for unnatural causes of death (women: MRR=12.31, 95% CI 6.80–22.28; men: MRR=7.89, 95% CI 5.51–11.29). The cumulative risks of death within 7 years of diabetes diagnosis for persons with SMI and diabetes were 15.0% (95% CI 12.4–17.6%) for those younger than 50 years, 30.7% (95% CI 27.8–33.4%) for those aged 50–69 years, and 63.8% (95% CI 58.9–68.2%) for those aged 70 years or older. Among persons suffering from both diseases, 33.4% of natural deaths were attributed to diabetes and 14% of natural deaths were attributed to the interaction between diabetes and SMI.

Conclusions. Long-term mortality is high for persons with SMI and diabetes. This calls for effective intervention from a coordinated and collaborating healthcare system.

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Key words: Bipolar affective disorder, diabetes mellitus, mortality, schizophrenia, severe mental illness.

Introduction

Managing patients with mental and physical multimorbidity is a major challenge for modern healthcare systems, and these patients often have poor outcomes (Mercer *et al.* 2012; Smith *et al.* 2012). Persons with schizophrenia and bipolar affective disorder have, for example, a two- to three-fold increased risk of premature death (Laursen *et al.* 2007; Osborn *et al.* 2007; Hoang *et al.* 2011; Wahlbeck *et al.* 2011), which corresponds to a life expectancy gap of 15–20 years compared with the background population (Wahlbeck *et al.* 2011). Their cause-specific mortality rate ratios (MRRs) are high for almost all causes (Laursen *et al.* 2007; Osborn *et al.* 2007; Wahlbeck *et al.* 2011), especially for suicide (Laursen *et al.* 2007; Nordentoft *et al.* 2011), but most of the excess mortality is explained by physical disorders (Laursen *et al.* 2007; Hoang *et al.* 2011). The underlying causal mechanisms for this excess mortality among persons with severe mental illness are not completely understood, but may be associated with suboptimal treatment of somatic diseases (Frayne *et al.* 2005; Hippisley-Cox *et al.* 2007), co-morbidity (Fleischhacker *et al.* 2008; Laursen *et al.* 2011), metabolic disorders induced by antipsychotic medication (weight gain, dyslipidaemia, diabetes and the metabolic syndrome) (American Diabetes Association *et al.* 2004) and unhealthy life-style (sedentary life-style, smoking, obesity and unhealthy diet) (Brown *et al.* 1999; Vinogradova *et al.* 2010).

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Although 10–20% of persons with severe mental illness have type 2 diabetes (Dixon *et al.* 2000; Galletly *et al.* 2012; Manu *et al.* 2012), little is known about the long-term mortality of persons with severe mental illness and diabetes. Diabetes is associated with an increased risk of early death (Carstensen *et al.* 2008; Seshasai *et al.* 2011), and this association may be even stronger in persons with severe mental illness who tend to be less likely to meet diabetes performance measures (Frayne *et al.* 2005). Two studies have found a higher mortality among persons with severe mental illness and diabetes than among those suffering from diabetes only (Vinogradova *et al.* 2010) or severe mental illness only (Jackson *et al.* 2007). However, one study showed no difference in mortality for persons with severe mental illness and diabetes as compared with those suffering from diabetes only (Brown *et al.* 2010). No studies have compared these patients' mortality rates with those of the background population or assessed their cause-specific mortality.

The aim of the present study was to study the overall and cause-specific mortality for all persons with severe mental illness with co-occurring incident diabetes in a large population-based cohort with up to 13 years of follow-up.

Method

Study population

A population-based cohort study was conducted by using information from nationwide registries, including the Danish Civil Registration System (CRS) (Pedersen *et al.* 2006), the Danish Psychiatric Central Register (Mors *et al.* 2011), the Danish National Diabetes Register (Carstensen *et al.* 2008) and the Danish Causes of Death Register (Helweg-Larsen, 2011). In these registries, information on Danish citizens is universally stored with reference to a unique 10-digit CRS number assigned to all Danish residents at birth. This enables accurate linkage of information on a personal level (Pedersen *et al.* 2006). We included all persons who were born in Denmark and alive on 1 January 1997.

Procedures

Information on date of birth, date of death or date of emigration, and total number of deaths was obtained from the Danish CRS (Pedersen *et al.* 2006). Information on diabetes was obtained from the Danish National Diabetes Register (Carstensen *et al.* 2008), which was established by the Danish National Board of Health in order to provide information on diabetes for persons treated in primary as well as in secondary care. This register was established by linking information from the following registers: the Danish National Hospital Register (Andersen *et al.* 1999), the Danish National Health Insurance Service Register (Olivarius *et al.* 1997) and the Danish Register of Medicinal Product Statistics (Kildemoes *et al.* 2011). The Danish National Diabetes Register does not contain information on values for measured blood glucose, and therefore the identification of persons with diabetes relies on a validated algorithm. Individuals were classified as having diabetes on the day where at least one of the following six criteria was met:

(1) A diagnosis of diabetes made at any Danish hospital in conformity with the Danish version of the 8th and the 10th revision of the International Classification of Diseases (ICD-8 and ICD-10) as registered in the Danish National Hospital Register. The ICD-8 (249, 250) was used until January 1994 and was thereafter replaced by the ICD-10 (E10–E14, H36.0, O24, excluding O24.4).
(2) A referral to chiropody of diabetic patients as registered in the Danish National Health Insurance Service Register.
(3) Five blood glucose measurements within 1 year as registered in the Danish National Health Insurance Service Register.
(4) Two blood glucose measurements per year for five consecutive years as registered in the Danish National Health Insurance Service Register.
(5) Two redemptions of oral glucose-lowering drugs within 6 months as registered in the Danish Register of Medicinal Product Statistics (except for women aged 20–39 years prescribed metformin alone, since this is also used as medication for polycystic ovarian syndrome).
(6) Two redemptions of prescribed insulin as registered in the Danish Register of Medicinal Product Statistics.

The Danish National Diabetes Register has been registering persons with diabetes since 1990. We identified persons in Denmark registered with a diagnosis of diabetes in the Danish National Diabetes Register after 1 January 1997. The proportion of identified persons with diabetes according to the criteria in the algorithm was distributed as follows: diagnosis, 27.9%; chiropody, 7.1%; five blood glucose in 1 year, 40.3%; two blood glucose in 5 years, 0.1%; oral glucose-lowering drugs, 23.9%; and insulin, 0.6%. Individuals registered from 1990 to 1997 were excluded on account of inadequate register validity in the Registry's first years of operation (Carstensen *et al.* 2008).

Information on psychiatric disorders was obtained from the Danish Psychiatric Central Register (Mors *et al.* 2011), which contains information on all admissions to psychiatric hospitals in Denmark since 1969,

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and on all out-patient contacts since 1995. Before 1 January 1994, diagnoses were classified according to the Danish version of ICD-8 and from 1 January 1994 according to the ICD-10. All psychiatric admissions in Denmark with a diagnosis of severe mental illness comprising schizophrenia [ICD-8: 295 (excluding 295.79), and ICD-10: F20], schizo-affective disorders (ICD-8: 295.79, 296.89, and ICD-10: F25) and bipolar affective disorders (ICD-8: 296.19, 296.39, and ICD-10: F30, F31) diagnosed after 1 January 1969 were identified at the start of follow-up.

Information on causes of death was obtained from the Danish Causes of Death Register (Helweg-Larsen, 2011), which contains information on all deaths of Danish citizens and residents, place of death, and cause of death between 1970 and 2009. Causes of death were classified into 10 categories. Unnatural causes comprised suicide (ICD-10: X60–X84, Y87.0) and accidents (ICD-10: V01–X59, Y10–Y86, Y87.2, Y88–Y89). Natural causes comprised old age and apoplexy (ICD-10: I60–I72, R54, F03.9), malignant neoplasms (ICD-10: C00–D09), myocardial infarction (MI) (ICD-10: I21), cardiac death, non-MI [ICD-10: I00–I25 (excluding I21), I27 and I30–I52], respiratory diseases (ICD-10: J00–J99), endocrine and metabolic conditions (ICD-10: E00–E07, E10–E90), infectious diseases (A00–A09, A15–A99, B00–B99) and a combined group of the remaining causes of death, also including homicide (ICD-10: X85–Y09, Y87.1).

Statistical analysis

Follow-up started on 1 January 1997 and ended on 31 December 2009, the day of emigration or the day of death, whichever came first. MRRs were calculated for overall mortality, for mortality due to natural and unnatural causes, and for cause-specific mortality for persons with severe mental illness and diabetes, persons suffering from diabetes only, and persons suffering from severe mental illness only as compared with persons without either of these diseases. We evaluated whether the overall MRRs varied between the three subgroups of diseases (diabetes only, severe mental illness only or both diseases) by testing for statistical interaction on a multiplicative scale and on an additive scale. The latter was tested using the method described by Andersson *et al.* (2005) for calculation of the synergy index for the possible synergistic action between severe mental illness and diabetes.

Further, we calculated the attributable proportion (AP) due to interaction as a measure of the excess MRR for persons with both diseases not explained by the independent effects of severe mental illness or diabetes. We used adjusted MRRs for these analyses. The AP due to interaction was calculated by subtracting the difference in MRRs between persons with diabetes and persons in the background population without diabetes from the difference in MRRs between persons with severe mental illness and diabetes (smi+dm) and persons with severe mental illness without diabetes (smi) and dividing this result by the MRR for persons with both diseases [e.g. $AP_{interaction} = ([MRR_{smi+dm} - MRR_{smi}] - [MRR_{dm} - MRR_{background}])/MRR_{smi+dm}$] (Andersson *et al.* 2005). The AP due to diabetes among persons suffering from both diseases was calculated using the formula: $AP_{diabetes} = [(MRR_{smi+dm} - MRR_{smi})/MRR_{smi+dm}]$ (Uter & Pfahlberg, 1999). This proportion estimated the proportion of deaths that would not have occurred if persons with severe mental illness and diabetes had had the same mortality as persons with severe mental illness alone, and thus the number of hypothetically preventable deaths due to diabetes among persons with both diseases were calculated using the formula: $n \times AP_{diabetes}$.

Survival was analysed with time since diabetes diagnosis as a time scale, and cumulative mortality proportions (CMPs) were estimated by Kaplan–Meier curves for overall mortality. CMPs due to natural causes were estimated by the Aalen–Johansen estimator, taking into account the competing risk from unnatural causes of death. The risk of dying during this period was estimated for persons suffering from severe mental illness and diabetes and for persons suffering from diabetes only.

Data were analysed by using the log-linear Poisson regression, with the logarithm to the person years as an offset variable in SAS GENMOD (SAS Institute Inc., USA) using version 9.2 procedures. The psychiatric diagnoses schizophrenia, schizo-affective disorders and bipolar affective disorders were evaluated combined. MRRs were adjusted for age and calendar period and stratified by age and gender for overall mortality. MRRs were adjusted for age and calendar period and stratified by gender for natural, unnatural, and cause-specific deaths. Age, calendar year, diagnosis of severe mental illness and diagnosis of diabetes were treated as time-dependent variables, whereas the rest were treated as time-independent variables. Tests for differences, 95% confidence intervals (CIs) and p values were based on likelihood ratio tests.

Results

The cohort comprised 4734703 persons, of whom 651080 died during the study period. A total of 37389 persons had severe mental illness (9540 deaths), 248176 had incident diabetes (56858 deaths), and 4284 persons had severe mental illness and diabetes (1083 deaths) (Table 1).

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Table 1. *Number of deaths according to background variables for a population-based cohort in Denmark, 1997–2009 (n=4 734 703)*[a]

	Deaths, *n*	Person years at risk
Age		
<50 years	35 226	29 576 117
50–69 years	147 007	15 361 302
⩾70 years	468 847	6 833 200
Gender		
Women	332 055	26 302 367
Men	319 025	25 468 252
Calendar period		
1997–1999	151 497	11 919 077
2000–2003	202 973	15 872 423
2004–2007	197 826	15 946 015
2008–2009	98 784	8 033 103
Diseases		
Severe mental illness	9540	341 212
Diabetes	56 858	1 213 364
Severe mental illness and diabetes	1083	19 403
None	583 599	50 196 640

[a] Persons with severe mental illnesses comprised persons with schizophrenia, schizo-affective disorders and bipolar affective disorders. Information on severe mental illness since 1969 was obtained from the Danish Psychiatric Central Register. Information on diabetes since 1997 was obtained from the Danish National Diabetes Register.

Overall mortality

Overall, MRRs were higher for persons with severe mental illness and diabetes (men: 4.14, 95% CI 3.81–4.51; women: 3.13, 95% CI 2.88–3.40) as compared with those suffering from diabetes only (men: 1.75, 95% CI 1.72–1.77; women: 1.56, 95% CI 1.54–1.58) and those suffering from severe mental illness only (men: 3.06, 95% CI 2.97–3.15; women: 2.26, 95% CI 2.20–2.32) (Table 2). The interaction was lower than would be expected on a multiplicative scale (men: $p<0.0001$; women: $p=0.0089$) and higher than would be expected on an additive scale (synergy index for men: 1.12, 95% CI 1.00–1.26; and for women: 1.17, 95% CI 1.03–1.33).

The corresponding MRRs for natural deaths were 3.92 (95% CI 3.59–4.29) for men and 3.11 (95% CI 2.86–3.39) for women among persons with severe mental illness and diabetes. The MRRs rose by decreasing age; for example, persons younger than 50 years with severe mental illness and diabetes had a 12- to 14-fold higher risk of death than the background population (Table 2).

The AP due to interaction between severe mental illness and diabetes was estimated to be 14.3% [i.e. ([3.92–2.62] – [1.74–1])/3.92] (95% CI 6.3–22.2%) and 14.8% (95% CI 7.3–22.4%) for natural deaths among men and women, respectively (Table 3).

The AP of natural deaths due to diabetes among persons with severe mental illness and diabetes was calculated to be 33.2% [i.e. (3.92–2.62)/3.92] and 33.4% for men and women, respectively. Consequently, the number of natural deaths that would not have occurred if persons with severe mental illness and diabetes had had the same mortality as persons with severe mental illness alone was 162 and 176 among men and women, respectively, or in total 338 out of 1013 natural deaths (33.4%) was attributed to diabetes (Table 3).

The absolute risk of dying within 7 years of the diabetes diagnosis (the CMP) for persons with severe mental illness and diabetes was 15.0% (95% CI 12.4–17.6%) for those younger than 50 years, 30.7% (95% CI 27.8–33.4%) for those aged 50–69 years, and 63.8% (95% CI 58.9–68.2%) for those aged 70 years or older. The corresponding CMPs for persons with diabetes, but no history of severe mental illness, were 5.2% (95% CI 4.9–5.4%), 17.7% (95% CI 17.5–17.9%) and 53.6% (95% CI 53.2–54.0%) (Fig. 1*a*).

For natural causes only, the corresponding CMPs within 7 years after the diabetes diagnosis were slightly lower (Fig. 1*b*).

Cause-specific death

The MRRs for all causes of death were higher for persons with diabetes, severe mental illness, and severe mental illness and diabetes than for the background population, although the association did not reach statistical significance for suicide among women with diabetes only (Fig. 2*b*). The cause-specific MRRs tended to be highest for persons with severe mental illness and diabetes for natural deaths; and the cause-specific MRRs tended to be highest for persons with severe mental illness only for unnatural deaths, although not always statistically significant. For persons with both diseases, the cause-specific MRRs were lowest for malignant neoplasms (women: MRR=1.98, 95% CI 1.64–2.39; men: MRR=2.08, 95% CI 1.69–2.56) and highest for suicide among women (MRR=12.31, 95% CI 6.80–22.28) and accidents among men (MRR=7.89, 95% CI 5.51–11.29).

Discussion

This large population-based cohort study showed that persons with severe mental illness and diabetes had a three- to four-fold higher risk of death than the general population, and also indicated that the MRRs increased with decreasing age. Persons suffering from

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Table 2. *Mortality rate ratios for persons with diabetes, severe mental illness and severe mental illness and diabetes as compared with the background population in Denmark 1997–2009*

	Diabetes	Severe mental illness	Severe mental illness and diabetes
Women			
Overall mortality	1.56 (1.54–1.58)	2.26 (2.20–2.32)	3.13 (2.88–3.40)
Type of death			
Natural deaths	1.58 (1.56–1.60)	2.07 (2.01–2.13)	3.11 (2.86–3.39)
Unnatural deaths	1.18 (1.09–1.28)	7.18 (6.60–7.81)	4.43 (2.97–6.61)
Age			
<50 years	4.28 (3.89–4.70)	6.25 (5.70–6.85)	13.99 (10.22–19.16)
50–69 years	2.28 (2.21–2.35)	3.27 (3.12–3.44)	4.85 (4.22–5.58)
⩾70 years	1.43 (1.41–1.45)	1.76 (1.69–1.82)	2.37 (2.13–2.65)
Men			
Overall mortality	1.75 (1.72–1.77)	3.06 (2.97–3.15)	4.14 (3.81–4.51)
Type of death			
Natural deaths	1.74 (1.72–1.76)	2.62 (2.54–2.71)	3.92 (3.59–4.29)
Unnatural deaths	1.31 (1.22–1.41)	8.75 (8.19–9.34)	7.81 (5.85–10.44)
Age			
<50 years	4.43 (4.14–4.75)	7.09 (6.70–7.51)	12.58 (10.00–15.83)
50–69 years	2.27 (2.22–2.32)	3.40 (3.26–3.56)	5.43 (4.82–6.11)
⩾70 years	1.54 (1.52–1.56)	1.89 (1.79–1.99)	2.57 (2.23–2.97)

Data are given as mortality rate ratio (95% confidence interval).

Table 3. *Mortality rates, mortality rate ratios and number of deaths evaluated for natural deaths among persons with severe mental illness and diabetes*

	Deaths, *n*	Person-years	Mortality rate per 1000 person-years (95% CI)	Mortality rate ratio (95% CI)
Men				
None of the diseases	265 883	24 658 961	10.78 (10.74–10.82)	1 (reference)
Diabetes	29 783	628 109	47.42 (46.88–47.96)	1.74 (1.72–1.76)
Severe mental illness	3704	172 074	21.53 (20.84–22.23)	2.62 (2.54–2.71)
Both diseases	487	9108	53.47 (48.93–58.44)	3.92 (3.59–4.29)
Women				
None of the diseases	288 474	25 537 679	11.30 (11.25–11.34)	1 (reference)
Diabetes	25 641	585 255	43.81 (43.28–44.35)	1.58 (1.56–1.60)
Severe mental illness	4317	169 138	25.52 (24.77–26.30)	2.07 (2.01–2.13)
Both diseases	526	10 295	51.09 (46.91–55.65)	3.11 (2.86–3.39)

CI, confidence interval.

both severe mental illness and diabetes tended to have higher mortality than would be expected when adding the independent risk of death associated with each of the two diseases, but a lower mortality than would be expected if the risks were multiplied. Not all authors agree upon using the synergy index as an indication of biological interaction (Greenland, 1993; Zammit *et al.* 2010), as it rests upon the assumption that there is no residual confounding from unmeasured or unknown risk factors (Greenland, 1993). Thus the results regarding synergistic action should be interpreted cautiously.

We estimated that 338 natural deaths among persons with both diseases were attributed to diabetes and would not have occurred if these persons had had the same mortality as persons with severe mental illness only. Further, we estimated that the interaction between diabetes and severe mental illness may

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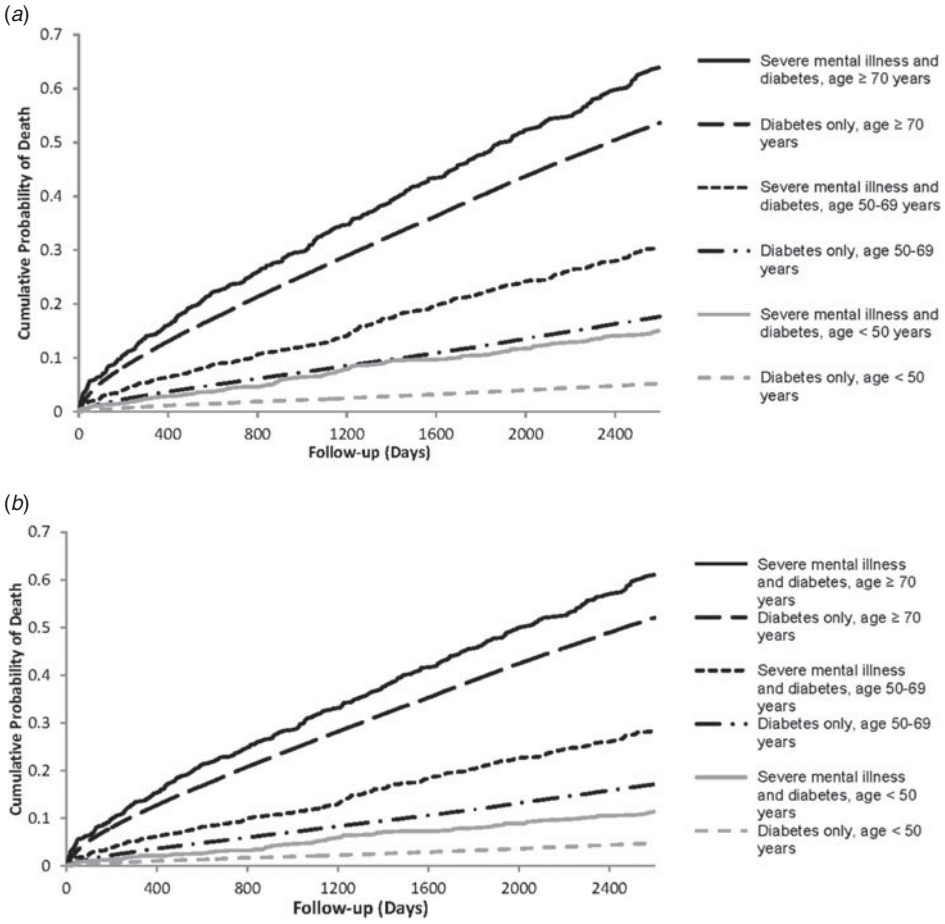

Fig. 1. Age-stratified cumulative mortality curves for persons suffering from diabetes. (*a*) Estimated cumulative mortality curves for overall mortality by the Kaplan–Meier estimator for up to 7 years (2600 days) after onset of diabetes plotted by applying hazard ratios for death from any cause (specific for age at risk) from the present analyses. (*b*) Estimated cumulative mortality curves for mortality due to natural causes by the Aalen–Johansen estimator for up to 7 years after onset of diabetes plotted by applying hazard ratios for death from natural causes (specific for age at risk) from the present analyses, taking into account competing risk from unnatural causes.

account for 14% of the natural deaths among persons with both diseases.

The cumulative risks of death within 7 years of diabetes diagnosis for persons with severe mental illness and diabetes ranged from 15.0% for those younger than 50 years to 63.8% for those aged 70 years or older. The cause-specific MRRs tended to be highest for persons with severe mental illness and diabetes for natural deaths; and the cause-specific MRRs tended to be highest for persons with severe mental illness only for unnatural deaths. For persons with both diseases, the cause-specific MRRs were lowest for malignant neoplasms and highest for suicide and accidents.

Our study has several strengths that count a large, nationwide and population-based cohort which could be followed for up to 13 years virtually without loss to follow-up. Bias due to selection of study participants, loss to follow-up and non-response therefore cannot explain our findings. Information on mortality, psychiatric hospital contacts and diabetes diagnoses enjoyed high validity and completeness, which minimizes any potential information bias. The schizophrenia diagnosis in the Danish Psychiatric Central Register has been shown to have a sensitivity of 93% and a positive predictive value of 87% (Jakobsen *et al.* 2005), and the diabetes diagnosis in the Danish National Diabetes Register has been shown to have a sensitivity of 86% and a positive predictive value of 90% (Carstensen *et al.* 2008). The validity and completeness of registration of death in the Danish CRS is considered to be close to 100% (Pedersen *et al.* 2006), which makes our estimates of overall mortality very accurate. However, the quality of the cause of death registration on death certificates is known to vary (Helweg-Larsen, 2011), which makes the cause-specific mortality prone to bias if the quality of the

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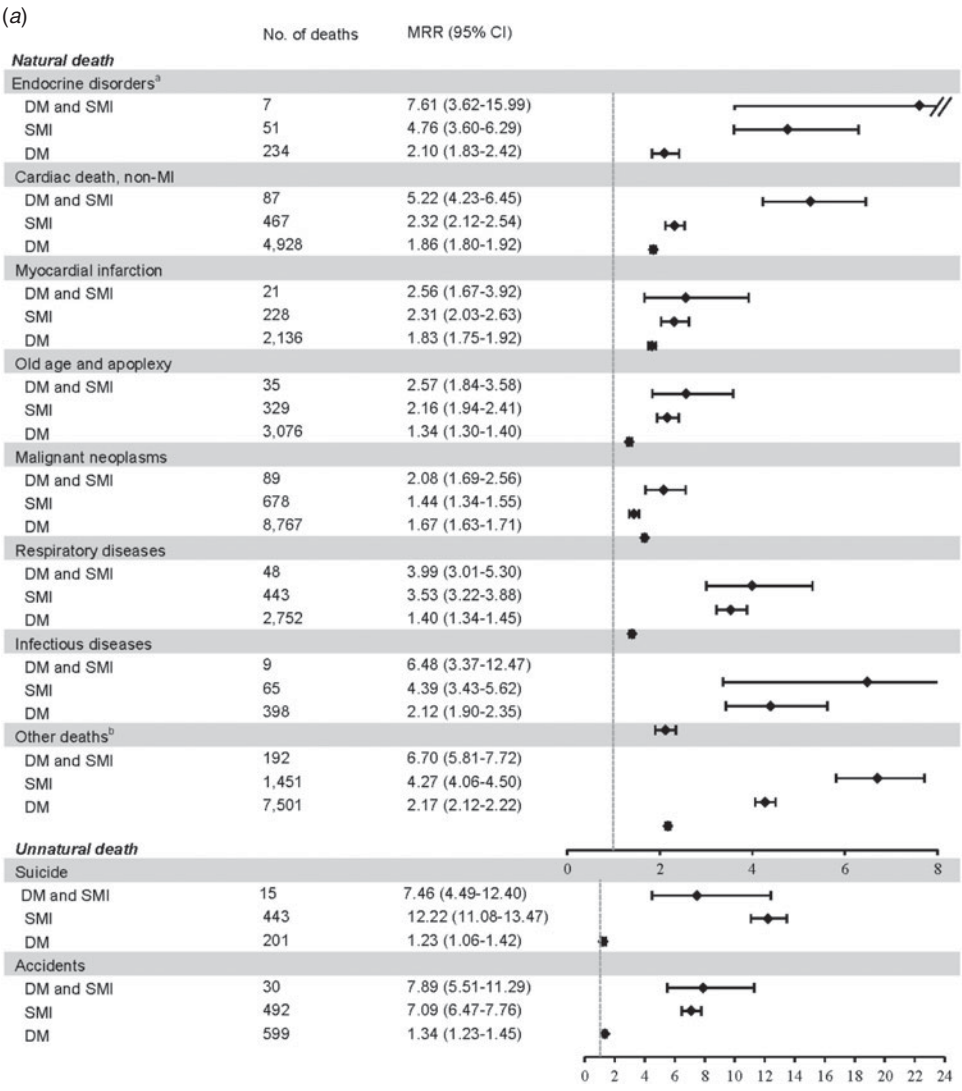

Fig. 2. For legend see next page.

diagnoses for causes of death depended on the type of underlying disease.

However, our study also has some limitations. It has been estimated that at least one-third of all persons with diabetes in the general population may go undiagnosed (American Diabetes Association, 2009), and the proportion of undiagnosed diabetes may be even higher among persons with severe mental illness. This will tend to equalize the difference between the MRRs for persons with severe mental illness and diabetes and persons suffering from severe mental illness only. This potential bias is, however, difficult to avoid because testing all participants for diabetes is not feasible in a cohort with a sufficient sample size to answer the research question raised in the present paper. In order to include only persons with newly diagnosed diabetes, we excluded persons that were registered in the Danish National Diabetes Register between 1990 and 1997, as they may be prevalent cases (Carstensen *et al.* 2008). A few prevalent cases of diabetes may have been included if they were diagnosed before 1990, but did not receive any diabetes care between 1990 and 1997.

Our study was limited by a lack of important clinical information. We did not have sufficient information to evaluate how the severity of the diabetes or the severe mental illness affected the long-term outcome. In addition, we had no information on the metabolic syndrome. It has been shown that approximately 40% of persons with severe mental illness meet the criteria for the metabolic syndrome (McEvoy *et al.* 2005; Vancampfort *et al.* 2013), which is the case for only approximately 20% of the background population (Ford *et al.* 2002). The metabolic syndrome is strongly associated with the risk of cardiovascular disease (Alexander *et al.* 2003), which may explain at least

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(*b*)

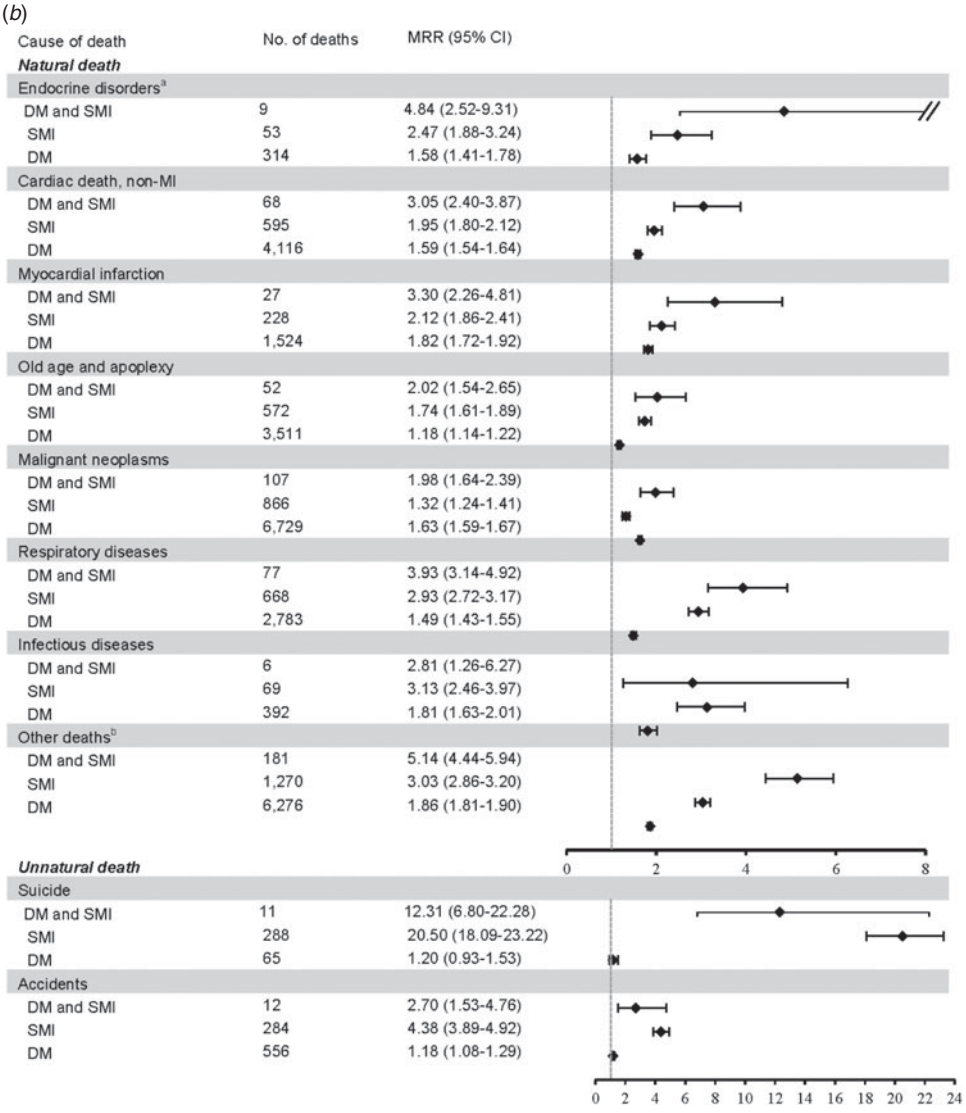

Fig. 2. Mortality rate ratios (MRRs) for cause-specific death among persons with a history of severe mental illness (SMI) and diabetes (DM), diabetes, or severe mental illness compared with persons without such a history, stratified by gender: (*a*) men; (*b*) women. [a] As Seshasai *et al.* (2011), we did not include death from diabetes in the endocrine category. [b] Other deaths = the remaining causes of death, including homicide. CI, Confidence interval; MI, myocardial infarction.

part of the high mortality among persons with severe mental illness alone. We had no information on potentially confounding factors such as socio-economic factors, general health status, life-style factors, medications and healthcare utilization and therefore cannot exclude residual confounding. However, some of these factors may be intermediate variables and should not be adjusted for, as they may be important steps on the causal pathway between severe mental illness, diabetes and mortality.

To our knowledge, the present study is the first to compare the overall mortality of persons with severe mental illness and diabetes with that of the background population and to estimate cause-specific MRRs. A British register-based study showed that 96 out of 416 (23.1%) persons with severe mental illness and diabetes died during 5 years of follow-up compared with 8603 out of 43 589 (19.7%) persons with diabetes only (Vinogradova *et al.* 2010). An American study found that 41% of 41 persons with severe mental illness and diabetes died during a 12-year follow-up period compared with 10% of 156 persons with severe mental illness alone (Jackson *et al.* 2007). In contrast, an American study found no difference in the CMPs between persons with severe mental illness and diabetes (n=201) and persons with diabetes only (n=99) during 7 years of follow-up (20.9% *v.* 21.2%) (Brown *et al.* 2010). However, the authors emphasized that

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the lack of association could be due to confounding by factors not accounted for, such as younger age and better control of blood glucose in the group where those investigated had both diseases (Brown *et al.* 2010).

The underlying mechanism of the excess mortality for persons with both severe mental illness and diabetes is unclear, but it may have several explanations. The treatment of somatic diseases among persons with severe mental illness is known to be suboptimal (Frayne *et al.* 2005; Hippisley-Cox *et al.* 2007). At the healthcare-system level, the explanations for suboptimal care management of diabetes may partly be rooted in time constraints that arise because of competing conditions (Frayne *et al.* 2005). At the patient level, diabetes care for persons with severe mental illness may be adversely affected due to communication and adherence difficulties (Frayne *et al.* 2005). Furthermore, patients with schizophrenia are known to have cognitive and social dysfunctions that could hamper self-care and diabetes medication compliance (Dixon *et al.* 2000). Finally, severe mental illness is known to be associated with substance abuse disorders (Nordentoft *et al.* 2011; Prisciandaro *et al.* 2011), and it has been shown that substance abuse disorders have a significant impact on the mortality of individuals with diabetes, which may stem from their inadequate diabetes care adherence (Prisciandaro *et al.* 2011). The use of antipsychotic medication has been associated with excess mortality among persons with severe mental illness in some (Saha *et al.* 2007; Ray *et al.* 2009), but not in all studies (Tiihonen *et al.* 2009). However, little is known about the significance of antipsychotic medication for the prognosis of persons with severe mental illness and diabetes. We found that the MRRs of non-MI cardiac death were particularly high among persons with severe mental illness and diabetes. We do not know of any biological explanation for this association, but antipsychotic medication has been associated with sudden cardiac death (Ray *et al.* 2009), and future studies should evaluate whether this association is particularly strong among persons with diabetes. Furthermore, although both severe mental illness and diabetes are associated with increased risk of suicide in ours as well as in other studies (Laursen *et al.* 2007; Nordentoft *et al.* 2011; Seshasai *et al.* 2011), persons with both diseases tended to have a lower risk of suicide than persons suffering from severe mental illness only. This may be explained by the fact that the risk of suicide for persons with severe mental illness is highest within the first years after diagnosis (Nordentoft *et al.* 2011), which often lies several years prior to a possible diabetes diagnosis (Carstensen *et al.* 2008; Laursen *et al.* 2009). Thus, persons with severe mental illness who survived until they had their diabetes diagnosed may be a selected subgroup with a lower risk of suicide.

Conclusions

In conclusion, persons with severe mental illness and diabetes have high mortality due to severe mental illness, diabetes and the interaction between the two diseases. An interaction between diabetes and severe mental illness increased the mortality beyond that explained by severe mental illness and diabetes acting independently. These findings call for effective intervention from a coordinated and collaborating healthcare system in order to reduce the inequality in outcome. A better understanding of why persons with severe mental illness and diabetes have a high mortality is needed in order to develop effective interventions that can improve care.

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Declaration of Interest

None.

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