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Risk of mortality and complications in patients with schizophrenia and diabetes mellitus: population-based cohort study

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Background

Schizophrenia patients have markedly elevated prevalence of diabetes compared with the general population. However, risk of mortality and diabetes-related complications among schizophrenia patients with co-occurring diabetes is understudied.

Aims

We investigated whether schizophrenia increased the risk of overall mortality, complications and post-complication mortality in people with diabetes.

Method

This population-based, propensity-score matched (1:10) cohort study identified 6991 patients with incident diabetes and pre-existing schizophrenia and 68 682 patients with incident diabetes only between 2001 and 2016 in Hong Kong using a medical record database of public healthcare services. Association between schizophrenia and all-cause mortality was examined with a Cox proportional hazards model. Effect of schizophrenia on first-year complication occurrence following diabetes diagnosis and post-complication mortality rates were evaluated.

Results

Schizophrenia was associated with increased all-cause mortality (adjusted hazards ratio [aHR] 1.11, 95% CI 1.05–1.18), particularly among men and older age groups. Schizophrenia patients with diabetes had higher metabolic complication rate (aHR 1.99, 95% CI 1.63–2.42), lower microvascular complication rate (aHR 0.75, 95% CI 0.65–0.86) and comparable macrovascular complication rate (aHR 0.93, 95% CI 0.85–1.03), relative to patients with diabetes only. Among patients with diabetes complications, schizophrenia was associated with elevated all-cause mortality after macrovascular (aHR 1.19, 95% CI 1.04–1.37) and microvascular (aHR 1.33, 95% CI 1.08–1.64) complications. Gender-stratified analyses revealed that a significant effect of schizophrenia on heightened post-complication mortality was observed in men only.

Conclusions

Schizophrenia patients with co-occurring diabetes are at increased risk of excess mortality, including post-complication mortality. Further research identifying effective interventions is warranted to optimise diabetes-related outcomes in this vulnerable population.

Keywords

Schizophrenia; diabetes mellitus; mortality; diabetes complications; population-based study.

Schizophrenia is a severe mental disorder affecting approximately 0.5–1% of the general population.[1] People with schizophrenia have markedly increased risk of premature mortality, with 15–20 years of reduction in life expectancy,[2,3] and the excess death is mainly attributable to physical diseases.[2] It is well recognised that diabetes mellitus and its complications have contributed substantially to the worldwide burden of mortality and disability.[4] Diabetes is a major risk factor for cardiovascular disease,[5] which is the leading cause of death in schizophrenia.[2] In fact, substantial evidence has shown that prevalence of diabetes is two to three times higher in people with schizophrenia than in the general population.[6] A multitude of factors may underlie the association between schizophrenia and increased risk for diabetes, including unhealthy lifestyle such as smoking, poor diet and physical inactivity; antipsychotic-induced metabolic side-effects; altered immune-inflammatory responses and shared genetic vulnerability.

There is limited research examining mortality risk in patients with schizophrenia with co-occurring diabetes. Accumulating data have revealed increased mortality rates among patients with schizophrenia and diabetes compared with those with diabetes only.[7–12] However, many previous studies are hampered by several important methodological limitations, including small sample size;[7–9,13] recruitment of prevalent diabetes cohorts without controlling for illness duration;[7,9,13] non-adjustment for confounding effect of baseline medical comorbidity;[7,10,12,13] focus on broadly defined category of severe mental disorders without diagnostic breakdown into schizophrenia for analysis;[10,13] and inclusion of patients with schizophrenia with history of psychiatric in-patient treatment only, which may result in potential bias towards those with greater illness severity.[8,11] Even fewer studies have assessed occurrence of diabetes complications among patients with schizophrenia with diabetes. Mixed findings were observed, with patients having schizophrenia and diabetes being found to display higher,[11,13] lower[12] or comparable[9,11,12] complication rates relative to those with diabetes alone. Until now, only one study has evaluated mortality after diabetes complications in a schizophrenia sample.[12] Whether schizophrenia is associated with elevated risks for excess mortality and complications in people with diabetes remains to be clarified.

Aims of study

To this end, we conducted a population-based cohort study with an aim to examine all-cause mortality in patients with pre-existing schizophrenia and newly diagnosed diabetes, compared with patients with incident diabetes only, with up to 16 years of follow-up. In addition, we specifically investigated occurrence of diabetes complications within the first year of diagnosis of diabetes as an indicator of disease severity shortly after presentation, and all-cause mortality after diabetes complications. We used clinical data retrieved from a territory-wide medical record database of public healthcare services in Hong Kong. Propensity score matching was

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applied to match patients with co-occurring schizophrenia and diabetes with those having diabetes only, to optimise control for potential confounding of baseline covariates, taking into consideration the effect of pre-existing medical comorbidity.

Method

Study design and data source

This was a population-based cohort study comparing the risks of all-cause mortality and diabetes complications in patients with incident diabetes with versus without pre-existing schizophrenia in Hong Kong. We obtained study data from the Clinical Data Analysis and Reporting System (CDARS),[14] a territory-wide electronic health record database developed by the Hospital Authority. The Hospital Authority is a statutory body that manages all public hospitals, specialist and general out-patient clinics in Hong Kong, and provides government-subsidised universal health coverage to all Hong Kong residents (approximately 7.5 million), including at least 90% of patients with diabetes in Hong Kong.[15] The CDARS has been described in detail elsewhere.[14] Briefly, CDARS is an integrated electronic record system capturing patients' longitudinal clinical data across all Hospital Authority facilities since 1995, via its access to the computerised clinical management system, which contains clinical information about demographics, diagnoses, prescriptions, hospital admissions, out-patient attendances and visits to emergency departments. These clinical data are entered into the system by treating clinicians and other healthcare staff. Patients' mortality data can be retrieved from CDARS through its internal linkage to regional deaths registry from the Immigration Department. Each patient is assigned a unique, anonymised identifier by CDARS, to facilitate linking to all medical records and to protect patient privacy. Clinical database extracted from CDARS has previously been used to generate high-quality population-based studies on various physical and psychiatric conditions, including diabetes and schizophrenia.[16,17]

Study population

All individuals aged ≥18 years, who were diagnosed with an incident diabetes managed by public healthcare services in Hong Kong between 1 January 2001 and 31 December 2016, were identified as a study cohort. Ascertainment of diabetes was defined by fulfilling any one of the following criteria: (a) first-recorded diagnosis of diabetes (type 1 or type 2) by the ICD-9-CM[18] (codes 250, 357.2, 366.41 and 362.01–362.07) for in-patient admission or specialist out-patient attendance, or by the International Classification of Primary Care, Second Edition[19] (code T90) for general out-patient attendance; and (b) dispensation of antihyperglycaemic medication (including sulfonylureas, insulins, metformin, thiazolidinediones, α-glucosidase inhibitors, meglitinides, incretin mimetics/glucagon-like peptide-1 analogues and dipeptidyl peptidase inhibitors). Onset of diagnosis (i.e. date of ascertainment of incident diabetes) was assigned as the earliest date that a patient met the defining criteria. We then derived a group of patients who were diagnosed with schizophrenia or schizoaffective disorder (henceforth termed as schizophrenia) by the ICD-10 (codes F20 and F25) for psychiatric in-patient admission or out-patient attendance preceding ascertainment of first diagnosis of diabetes from the incident diabetes cohort.[20] Patients with past record of diabetes diagnosis or prescription of any antihyperglycaemic medications before diagnostic assignment of schizophrenia were excluded. To evaluate the influence of schizophrenia on mortality and occurrence of diabetes complications, the remaining patients in the diabetes cohort served as a comparison group for analyses. Patients with other non-affective psychoses, mania or bipolar disorder (ICD-10 codes F22, F23, F28, F29, F30 and F31) recorded as the principal psychiatric diagnosis were excluded from the comparison group. The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 16-470). The study data were anonymised and individual patient records were completely unidentifiable during the analysis. Because our study was based on a medical record database, the requirement for informed consent was waived.

Propensity score matching and covariates

Propensity score matching was performed to minimise differences in baseline characteristics between patients with diabetes in schizophrenia and comparison groups, so as to generate a matched cohort with well-balanced covariates. Propensity score was the conditional probability of being assigned to schizophrenia group as opposed to the comparison group, estimated using logistic regression model with the given covariates.[21] Taking into consideration the availability of clinical information that were adequately recorded in, and could be reliably retrieved from, the database, an array of candidate covariates were selected *a priori* and included in the propensity model: demographics (age at incident diabetes, gender); calendar-year period (5-year interval) of ascertainment for incident diabetes; catchment area where patients received medical services for diabetes (for geographic and hospital-based variation); and physical comorbidities as measured by Charlson comorbidity index,[22] hypertension and dyslipidaemia, and alcohol and substance use disorders. We employed a nearest-neighbour matching algorithm, and matched patients with schizophrenia to patients in the comparison group in a 1:10 ratio without replacement, with a calliper of 0.15 of the s.d. of the logit of propensity score. Our 1:10 matched cohort design enabled the original sample of the comparison group to be more fully utilised for data analyses, given its large sample size (n = 589 655). Unmatched patients were excluded from the analysis. We assessed between-group balance of covariates by computing standardised differences (<10% indicating good balance of covariates) for all covariates included in the propensity score model, and examining reduction in pseudo R^2 (value close to zero indicating good balance of covariates) in the logistic regression model[23] for the schizophrenia group, before and after matching. Standardised differences were <10% for all covariates (Supplementary Fig. 1 available at https://doi.org/10.1192/bjp.2020.248) and pseudo R^2 decreased from 0.054 to 0.003 after matching, indicating that a balance of covariates was achieved. Physical diseases and alcohol/substance use disorders were identified by ICD-9-CM and ICD-10 codes, respectively (Supplementary Table 1).

Outcomes

The primary outcome was all-cause mortality after ascertainment of incident diabetes. Two sets of secondary outcomes were also investigated. First, we assessed occurrence of diabetes complications within 1 year of incident diabetes, as a proxy measure for severity of diabetes, with the presence of complications indicative of more advanced disease stage shortly after presentation. Complications were classified and quantified by the adapted Diabetes Complications Severity Index (DCSI), which is a validated measure in predicting mortality, hospital admissions and healthcare utilisation among patients with diabetes.[24] Briefly, the DCSI is a scoring scheme comprising seven categories of complications, including cardiovascular disease, cerebrovascular disease, peripheral vascular disease, nephropathy, neuropathy, retinopathy and metabolic complications. In addition to specific DCSI-derived categories, diabetes complications were classified as macrovascular (including cardiovascular, cerebrovascular and peripheral vascular diseases) or microvascular (including retinopathy, nephropathy

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Table 1 Characteristics of patients with diabetes with or without schizophrenia

Characteristics[a]	Before matching			After matching		
	Schizophrenia[b] (*n* = 7001)	Comparison group (*n* = 589 655)	*P*-value	Schizophrenia[b] (*n* = 6991)	Comparison group (*n* = 68 682)	*P*-value
Age, years	54.0 (12.7)	62.4 (13.4)	<0.001	54.4 (12.9)	54.0 (12.7)	0.018
Male gender	3101 (44.3)	303 397 (51.5)	<0.001	3096 (44.2)	30 178 (43.9)	0.578
Calendar-year period			<0.001			0.824
2001–2005	1385 (19.8)	175 336 (29.7)		1381 (19.8)	13 437 (19.6)	
2006–2010	2347 (33.5)	183 821 (31.2)		2345 (33.5)	22 905 (33.4)	
2011–2016	3269 (46.7)	230 498 (39.1)		3265 (46.7)	32 340 (47.1)	
Medical comorbidity						
Hypertension	1991 (28.4)	207 977 (35.3)	<0.001	1990 (28.5)	19 867 (28.9)	0.418
Dyslipidaemia	1264 (18.1)	104 309 (17.7)	0.427	1264 (18.1)	12 624 (18.4)	0.537
Charlson comorbidity index[c]	2.4 (1.6)	3.2 (1.8)	<0.001	2.40 (1.5)	2.38 (1.6)	0.447
Alcohol use disorder	85 (1.2)	848 (0.10)	<0.001	85 (1.2)	517 (0.8)	<0.001
Substance use disorder	172 (2.5)	1023 (0.20)	<0.001	172 (2.5)	697 (1.0)	<0.001
Catchment areas of public healthcare service[d]			<0.001			0.993
Hong Kong East Cluster	528 (7.6)	29 946 (9.17)		528 (7.6)	5156 (7.5)	
Hong Kong West Cluster	462 (6.6)	19 940 (6.11)		462 (6.6)	4571 (6.7)	
Kowloon Central Cluster	1055 (15.1)	56 318 (17.25)		1055 (15.1)	10 356 (15.1)	
Kowloon East Cluster	1064 (15.2)	52 699 (16.14)		1064 (15.2)	10 622 (15.5)	
Kowloon West Cluster	1453 (20.8	64 594 (19.79)		1453 (20.8)	14 142 (20.6)	
New Territories East Cluster	1064 (15.2)	54 465 (16.69)		1064 (15.2)	10 590 (15.4)	
New Territories West Cluster	1365 (19.5)	48 458 (14.85)		1365 (19.5)	13 245 (19.3)	

Data are presented in number and percentage for all variables, with the exception of age and Charlson comorbidity index, which are presented in mean (s.d.).
a. Potential group differences were examined with independent-samples *t*-tests and chi-square tests for continuous and categorical variables, respectively.
b. Before matching, a schizophrenia group included 6680 patients diagnosed with schizophrenia and 321 patients diagnosed with schizoaffective disorder; after matching, a schizophrenia group included 6670 patients diagnosed with schizophrenia and 321 patients diagnosed with schizoaffective disorder.
c. Age-adjusted adapted Charlson comorbidity index was computed. As diabetes was the disease of interest for study participant identification, it was thus excluded from the score calculation.
d. In Hong Kong, the Hospital Authority manages public healthcare service delivery (in-patient and specialist/general out-patient services), which is organised into seven clusters based on geographical locations (i.e. catchment areas).

and neuropathy), for analyses. Second, we examined all-cause mortality rates among patients diagnosed with macrovascular and microvascular complications within 1 year of incident diabetes. Diabetes complications were identified by ICD-9-CM codes (Supplementary Table 1) from both in-patient and out-patient records. Study cohort was followed from the date of ascertainment of incident diabetes until the date of death or until 31 December 2016, whichever came first.

Statistical analyses

The analyses of mortality and diabetes complications were based on the propensity score-matched sample. Demographic and baseline characteristics between matched schizophrenia and comparison groups were compared with chi-square and independent-samples *t*-tests for categorical and continuous variables, respectively. Incidence rates for all-cause mortality of the overall sample, as well as among subsamples of patients diagnosed with macrovascular and microvascular complications within 1 year after incident diabetes (i.e. post-macrovascular and post-microvascular complication all-cause mortality rates), were estimated by an exact 95% confidence interval based on a Poisson distribution. Survival rates were estimated with the Kaplan–Meier method, and compared between two groups by log-rank test. Cox proportional hazards regression models were applied to examine the effect of schizophrenia on mortality rates (with hazards ratios and 95% confidence intervals calculated), adjusting for covariates that were significantly different between two groups. The proportional hazards assumption was assessed according to scaled Schoenfeld residuals, and was fulfilled for each of the models. A series of multivariate logistic regression analyses (with odds ratios and 95% confidence intervals calculated), adjusting for covariates that were significantly different between groups, were performed to investigate the associations between schizophrenia and occurrence of diabetes complications (relative to the comparison group). Furthermore, two sets of additional analyses were conducted. First, we stratified the analyses on mortality and complications by age (<50 years, 50–69 years and ≥70 years). Second, the analyses were repeated for men and women separately, to assess gender specificity of the associations between schizophrenia and study outcomes. All statistical analyses were performed with SPSS version 25 for Windows, and $P < 0.05$ was considered statistically significant.

Results

Characteristics of the study sample

A total of 596 656 individuals with incident diabetes, including 7001 patients with schizophrenia, were identified as the original cohort. After matching, the schizophrenia group comprised 6991 patients (3096 men and 3895 women; mean age 54.4 ± 12.9 years), and the comparison group comprised 68 682 patients (30 178 men and 38 504 women; mean age 54.0 ± 12.7 years). The mean duration of follow-up for the matched sample was 6.2 years (s.d. 4.3). Demographic and baseline characteristics of the schizophrenia and comparison groups before and after matching are summarised in Table 1. There were significant differences between two groups of the matched sample in age, as well as the prevalence of alcohol and substance use disorders (higher rates in schizophrenia group), which were adjusted as covariates in subsequent analyses for mortality and complication outcomes.

Mortality of the overall diabetes sample

As shown in Table 2, the incidence rates per 1000 person-years were 30.4 (95% CI 28.7–32.1) and 18.0 (95% CI 17.6–18.4) for all-cause mortality in the schizophrenia and comparison groups, respectively. The Kaplan–Meier survival curves showed increased mortality rate in patients with schizophrenia relative to those in the comparison group ($P = 0.002$ by log-rank test) (Fig. 1(a)). Cox proportional hazards regression analysis also indicated significant association

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Table 2 Hazard ratios for mortality in patients with diabetes with or without schizophrenia

	Schizophrenia			Comparison group				
	n[a]	Death/ person-years	Incidence per 1000 person-years (95% CI)	*n*[a]	Death/person-years	Incidence per 1000 person-years (95% CI)	Adjusted hazard ratio (95% CI)	*P*-value
Total[b]								
Overall mortality	6991	1225/40 362	30.4 (28.7–32.1)	68 682	7702/427 000	18.0 (17.6–18.4)	1.11 (1.05–1.18)	0.001
Post-macrovascular complication death[c]	468	236/1955	120.7 (107.1–136.1)	4982	1827/24 545	74.4 (71.2–77.8)	1.19 (1.04–1.37)	0.001
Post-microvascular complication death[d]	214	97/788	123.0 (102.1–148.3)	2791	838/13 085	64.0 (60.0–68.4)	1.33 (1.08–1.64)	0.008
Age subgroups (overall mortality)								
<50 years	2573	224/16 417	13.6 (12.0–15.5)	24 012	1106/158 402	7.0 (6.6–7.4)	1.03 (0.89–1.19)	0.679
50–69 years	3564	570/20 205	28.2 (26.0–30.6)	35 913	3314/220 206	15.1 (14.6–15.6)	1.05 (0.96–1.14)	0.315
≥70 years	854	431/3740	115.2 (105.4–125.9)	8758	3282/48 392	67.8 (65.5–70.1)	1.33 (1.20–1.47)	<0.001
Men[e]								
Overall mortality	3096	653/17 234	37.9 (35.1–40.9)	30 178	3854/180 827	21.3 (20.7–22.0)	1.17 (1.07–1.27)	<0.001
Post-macrovascular complication death[c]	235	132/860	153.5 (131.2–179.6)	2882	916/14 145	64.8 (60.8–68.9)	1.25 (1.04–1.50)	0.017
Post-microvascular complication death[d]	119	48/425	112.8 (86.4–147.3)	1477	423/6761	62.6 (57.1–68.6)	1.35 (1.00–1.82)	0.051
Age subgroups (overall mortality)								
<50 years	1233	127/7683	16.5 (13.9–19.6)	11 253	660/72 657	9.1 (8.4–9.8)	1.13 (0.93–1.36)	0.223
50–69 years	1533	328/8241	39.8 (35.8–44.3)	15 719	1897/92 285	20.6 (19.7–21.5)	1.13 (1.00–1.27)	0.046
≥70 years	330	198/1310	151.1 (132.9–171.8)	3206	1297/15 885	81.7 (77.5–86.0)	1.35 (1.16–1.57)	<0.001
Women[f]								
Overall mortality	3895	572/23 128	24.7 (22.8–26.8)	38 504	3848/246 173	15.6 (15.2–16.1)	1.01 (0.93–1.11)	0.767
Post-macrovascular complication death[c]	233	104/1095	95.0 (79.1–114.0)	2100	911/10400	87.6 (82.3–93.2)	1.07 (0.88–1.32)	0.496
Post-microvascular complication death[d]	95	49/363	135.0 (104.1–175.2)	1314	415/6324	65.6 (59.8–72.0)	1.26 (0.94–1.70)	0.126
Age subgroups (overall mortality)								
<50 years	1340	97/8734	11.1 (9.1–13.5)	12 759	446/85 744	5.2 (4.7–5.7)	0.92 (0.74–1.15)	0.454
50–69 years	2031	242/11 964	20.2 (17.9–22.9)	20 194	1417/127 921	11.1 (10.5–11.7)	0.96 (0.83–1.10)	0.512
≥70 years	524	233/2430	95.9 (84.9–108.4)	5551	1985/32 508	61.1 (58.5–63.7)	1.16 (1.01–1.33)	0.032

Hazard ratios for all-cause mortality were obtained by Cox proportional regression analyses.
a. Number of patients included in the respective mortality analysis.
b. Adjusted for age and alcohol and substance use disorders.
c. Patients with medical conditions corresponding to macrovascular complications before study entry (first-recorded diabetes) were excluded from analysis.
d. Patients with medical conditions corresponding to microvascular complications before study entry (first-recorded diabetes) were excluded from analysis.
e. Adjusted for age and alcohol and substance use disorders.
f. Adjusted for hypertension and alcohol and substance use disorders.

between schizophrenia and heightened mortality risk, with an adjusted hazard ratio of 1.11 (95% CI 1.05–1.18). Stratified analyses further revealed that elevated mortality rates in the schizophrenia group were particularly noted among men in the older age groups (men overall: adjusted hazard ratio 1.17, 95% CI 1.07–1.27; men aged 50–69 years: adjusted hazard ratio 1.13, 95% CI 1.00–1.27; men aged ≥70 years: adjusted hazard ratio 1.35, 95% CI 1.16–1.57). For women with schizophrenia, increased mortality rate was only observed among those aged ≥70 years (women overall: adjusted hazard ratio 1.01, 95% CI 0.93–1.11; women aged ≥70 years: adjusted hazard ratio 1.16, 95% CI 1.01–1.33) (Table 2).

Diabetes complications

Table 3 presents diabetes complication rates within 1 year after diagnosis of incident diabetes. Patients with schizophrenia had significantly lower likelihood of experiencing any microvascular complications (adjusted odds ratio 0.75, 95% CI 0.65–0.86) and several specific complications, including cardiovascular disease (adjusted odds ratio 0.79, 95% CI 0.68–0.90), retinopathy (adjusted odds ratio 0.48, 95% CI 0.37–0.64) and nephropathy (adjusted odds ratio 0.76, 95% CI 0.61–0.94), but higher likelihood of increased metabolic complication rate (adjusted odds ratio 1.99, 95% CI 1.63–2.42), compared with patients in the comparison group. There were no significant group differences regarding the number of diabetes complications. Similar patterns of diabetes complication rates as those observed in the overall sample were found in both men and women, except that there was a significantly higher cerebrovascular complication rate among female patients in the schizophrenia group compared with the comparison group (Supplementary Table 2). In contrast, stratified analyses revealed differential associations between schizophrenia and complication risks by age, with lower rates of specific macrovascular and microvascular complications being observed among patients with schizophrenia in <50 years and 50–69 years (but not ≥70 years) age groups, relative to those in the comparison group (Supplementary Table 3).

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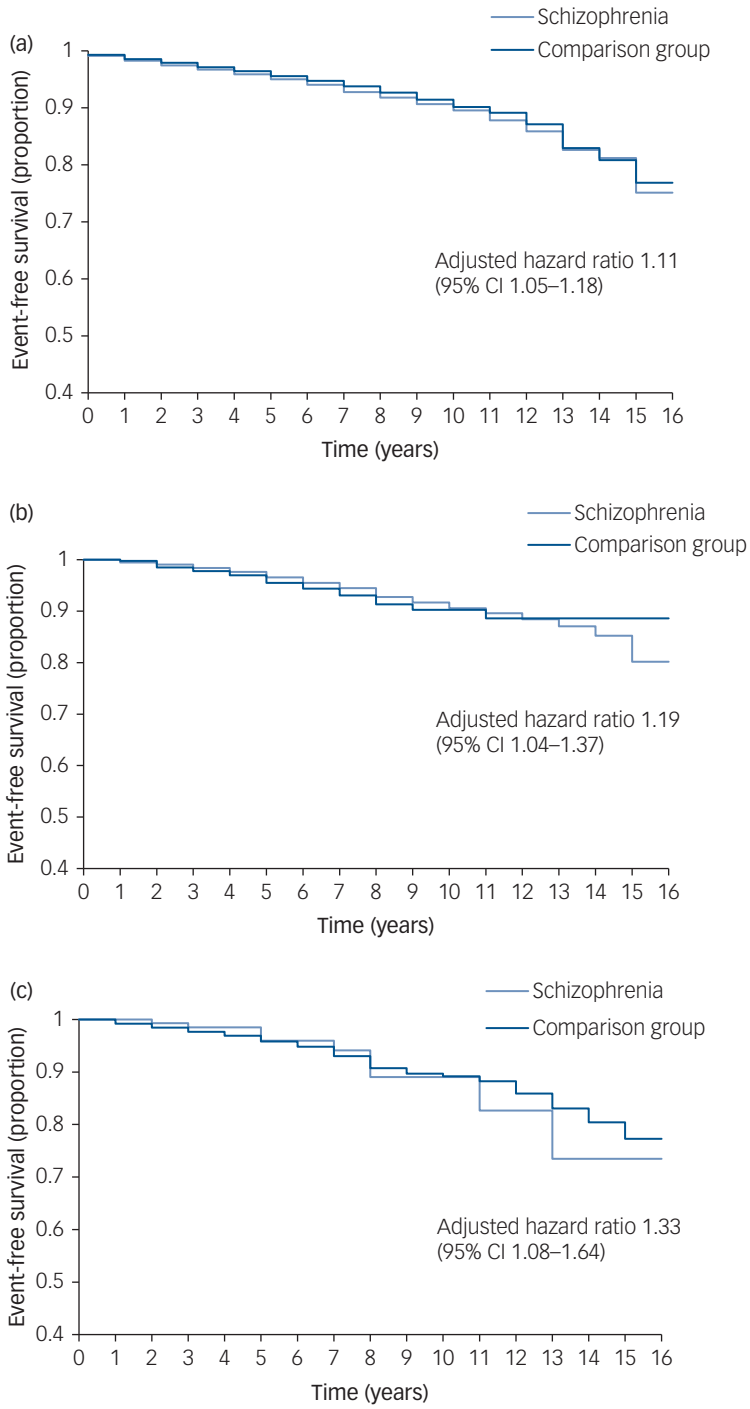

Fig. 1 Kaplan–Meier survival estimates for (a) overall all-cause mortality, (b) all-cause mortality after macrovascular complications and (c) all-cause mortality after microvascular complications for patients with diabetes with or without schizophrenia.

Mortality after diabetes complication diagnoses

The incidence rates per 1000 person-years were 120.7 (95% CI 107.1–136.1) and 123.0 (95% CI 102.1–148.3) for all-cause mortality in the schizophrenia group, after occurrence of macrovascular and microvascular complications, respectively (Table 2). In the comparison group, the incidence rates were 74.4 (95% CI 71.2–77.8) and 64.0 (95% CI 60.0–68.4) per 1000 person-years for post-macrovascular and post-microvascular complication all-cause mortality, respectively. The Kaplan–Meier survival analyses demonstrated significantly higher mortality risks after both macrovascular ($P = 0.006$ by log-rank test) and microvascular ($P = 0.003$ by log-rank test) complications in the schizophrenia group compared with the comparison group (Fig. 1(b) and 1(c)). Adjusted hazard ratios of patients with schizophrenia were 1.19 (95% CI 1.04–1.37) for post-macrovascular complication mortality and 1.33 (95% CI 1.08–1.64) for post-microvascular complication mortality, indicating significant associations between schizophrenia and elevated mortality risks subsequent to diabetes complications. Gender-stratified analyses further showed that men, but not women with schizophrenia had increased post-complication

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Table 3 Diabetes complications in patients with or without schizophrenia

Complications[a]	Schizophrenia[b]	Comparison group[c]	Adjusted odds ratio (95% CI)[d]	*P*-value
Macrovascular complications	468 (6.7)	4982 (7.3)	0.93 (0.85–1.03)	0.176
Cardiovascular disease	231 (3.4)	2917 (4.3)	0.79 (0.68–0.90)	0.001
Cerebrovascular disease	103 (1.5)	883 (1.3)	1.21 (0.98–1.49)	0.073
Peripheral vascular disease	38 (0.5)	358 (0.5)	1.05 (0.75–1.47)	0.773
Microvascular complications	214 (3.1)	2791 (4.1)	0.75 (0.65–0.86)	<0.001
Retinopathy	54 (0.8)	1101 (1.6)	0.48 (0.37–0.64)	<0.001
Nephropathy	91 (1.3)	1177 (1.7)	0.76 (0.61–0.94)	0.013
Neuropathy	39 (0.6)	465 (0.7)	0.81 (0.59–1.13)	0.217
Metabolic complications	120 (1.7)	584 (0.9)	1.99 (1.63–2.42)	<0.001
DCSI complication count ≥2[e]	72 (1.1)	878 (1.3)	0.82 (0.64–1.04)	0.103

Patients with medical conditions corresponding to the complication(s) of interest before study entry were excluded from analysis. DCSI, Diabetes Complications Severity Index.
a. Diabetes complications are ascertained according to the diagnoses included for calculating DCSI complication count.
b. A total of 6691 patients in the schizophrenia group were included in analyses except for cardiovascular disease ($n = 6912$), cerebrovascular disease ($n = 6935$), peripheral vascular disease ($n = 6987$), nephropathy ($n = 6942$) and DCSI complication count ($n = 6816$).
c. A total of 68 682 patients in the comparison group were included in analyses, except for cardiovascular disease ($n = 67\,933$), cerebrovascular disease ($n = 8272$), peripheral vascular disease ($n = 68\,641$), nephropathy ($n = 68\,267$) and DCSI complication count ($n = 67\,168$).
d. Adjusted for age and alcohol and substance use disorders.
e. DCSI complication count is a count of any complication in the seven categories (retinopathy, nephropathy, neuropathy, cardiovascular disease, cerebrovascular disease, peripheral vascular diseases and metabolic complications) and ranges from zero to seven.

mortality. In particular, men with schizophrenia exhibited heightened mortality rate after macrovascular complications (adjusted hazard ratio 1.25, 95% CI 1.04–1.50), and higher post-microvascular complication mortality, albeit approaching significance ($P = 0.051$) (Table 2).

Discussion

In this territory-wide population-based study of patients with newly diagnosed diabetes, we observed a significant, albeit small, association between schizophrenia and elevated all-cause mortality rate. Additional analyses further found that the effect of schizophrenia on increased mortality was more prominent in men and older age groups. Our results generally concur with the literature, which indicates increased mortality risk conferred by schizophrenia among patients with diabetes,[7–12] but is contrary to one prior report showing comparable mortality rates between patients with diabetes with and without severe mental disorders (including schizophrenia) over a 7-year follow-up period.[13] Of note, most previous studies demonstrated relatively higher mortality risk, with approximately two- to three-fold increase in excess death among patients with diabetes and schizophrenia compared with those with diabetes alone.[8,10–12] Such discrepancy might partly be attributable to methodological differences across studies. In particular, the majority of earlier studies did not control for confounding effect of pre-existing physical comorbidity and alcohol or substance use disorder (more frequently co-occurring with schizophrenia) on mortality risk,[7,10,12,13] and some investigated prevalent (rather than incident) diabetes cohort,[7,9,13] or included patients with schizophrenia with history of psychiatric hospital admissions only (excluding patients treated only in out-patient settings).[8,11] These methodological constraints might lead to potential bias in overestimating the mortality risk associated with schizophrenia among patients with diabetes.

Few studies have investigated occurrence of diabetes complications among patients with coexisting schizophrenia, particularly based on incident diabetes cohorts,[8,11,12] and inconsistent findings were noted. Wu et al found that schizophrenia was associated with an increased risk for macrovascular (but not microvascular) complications among patients with incident diabetes,[11] whereas a recent Danish nationwide study showed that individuals with schizophrenia and incident diabetes had lower (microvascular) or similar (macrovascular) complication rates compared with those with diabetes only.[12] In the current study, we specifically examined the first-year, rather than long-term, occurrence of complications after diagnosis of incident diabetes. Our findings that schizophrenia was associated with increased risk of acute metabolic complications largely agree with a previous study reporting significantly a higher rate of hospital visits for hyper- or hypoglycaemia in patients with schizophrenia and newly diagnosed diabetes than those with diabetes alone.[8] Conversely, our results revealed that overall, patients with schizophrenia exhibited lower microvascular and comparable macrovascular complication rates relative to patients with diabetes without schizophrenia. Importantly, the association between reduced complication rates and schizophrenia was most marked in the youngest age group (and was no longer observed in patients ≥70 years). As development of macrovascular and microvascular complications takes place gradually over time, occurrence of these complications within the first year of incident diabetes primarily indicates more advanced disease stage upon (or shortly after) presentation. In fact, it might be possible that the complication rates in the schizophrenia group was underestimated, as there is some evidence suggesting that the prevalence of undiagnosed diabetes is higher among patients with schizophrenia, particularly in the younger age group, than in the general population.[25] Given that our diabetes cohort was identified with recorded diagnosis and/or prescription of antihyperglycaemic medications, we were not able to include patients without recognised diabetes diagnosis, thereby precluding us from estimating the degree of underdiagnosis of diabetes among patients with schizophrenia. Alternatively, it could be that patients with pre-existing schizophrenia diagnosis were receiving medical surveillance via specialist psychiatric services, which offered regular monitoring of glycaemic and metabolic parameters.[12] This may therefore increase the likelihood of earlier diagnosis of diabetes, with consequent decreased occurrence of complications upon presentation for diabetes treatment, especially among younger patients. As existing data is limited in this respect, further research is warranted to clarify the association between schizophrenia and occurrence of complications in the early course of treatment for diabetes.

Thus far, there is only one published report (the Danish nationwide study) examining post-complication mortality among patients with schizophrenia and co-occurring diabetes, and this report demonstrated that schizophrenia was associated with elevated mortality rates subsequent to diabetes complications.[12] Similarly, we found that patients with schizophrenia and diabetes had significantly higher all-cause mortality rates after both macrovascular

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and microvascular complications diagnosed during the first year of incident diabetes, compared with those with diabetes alone. Our additional analyses further suggested differential effect of schizophrenia on post-complication mortality between men and women, with increased mortality risk being observed only in men. This is contrary to the findings of the Danish study, which revealed significant association between schizophrenia and raised post-complication mortality rate in both men and women.[12] It should, however, be noted that our results may not be directly comparable with those of the Danish study in this respect, because of the difference in the time period used to capture complication occurrence after diabetes diagnosis.

It is acknowledged that the association between schizophrenia and excess mortality among patients with coexisting diabetes is likely multifactorial, encompassing patient, physician and system factors. Many, although not all,[11] studies have shown that patients with schizophrenia are less likely to receive equitable diabetes care, including education about diabetes; guideline-recommended evaluations such as measurement of haemoglobin A_{1c} and lipid profile, screening for nephropathy and eye and foot examination; and optimal treatment with antihyperglycaemic medications.[26,27] Evidence also indicates lower receipt of cardioprotective medications among patients with schizophrenia for reduction of diabetes-related cardiovascular morbidity.[28] Symptoms of schizophrenia, such as cognitive dysfunction and diminished motivation, may impair patients' ability for proper diabetes self-management, resulting in poorer treatment outcomes. Alternatively, raised mortality in patients with diabetes with schizophrenia could be attributable to lifestyle behaviours, including physical inactivity, unhealthy diet and smoking. Future investigation is required to systematically delineate the impact of these potentially modifiable lifestyle factors on diabetes-related outcomes in patients with schizophrenia.

Several limitations of this study should be noted. First, our retrieved data did not contain information to distinguish between type 1 and type 2 diabetes, which are associated with differential outcomes in terms of premature mortality and complication rates. Nonetheless, as our analysis only included participants aged ≥18 years with newly diagnosed diabetes during the study period (with >85% of patients in schizophrenia and comparison groups diagnosed with incident diabetes at ≥40 years old), and evidence indicates that type 1 diabetes is mainly diagnosed during childhood and adolescence, our cohort should comprise mostly patients with type 2 diabetes. Second, lifestyle variables, such as physical activity levels, dietary patterns and smoking, were insufficiently recorded in the database, and were therefore not included in the analysis. Third, we did not have prescription data on antipsychotic medications, which are associated with increased risk of diabetes. Fourth, patients' adherence to prescribed antihyperglycaemic medications could not be assessed in this study. Fifth, we did not have information about the specific causes of death and were not able to examine diabetes-related mortality. Sixth, data regarding the rates of receipt for guideline-concordant assessments (such as haemoglobin A_{1c} and lipid profile tests, retinal examination etc.) were not available, hence the relationship between quality of diabetes care and schizophrenia could not be evaluated. Seventh, although propensity score matching was used to balance baseline covariates between the schizophrenia and comparison groups, our findings might still be influenced by residual confounding because of differences in unmeasured variables. Lastly, CDARS-derived diagnosis of schizophrenia has not been systematically validated. Although evidence has shown that clinical diagnosis of schizophrenia routinely collected in a health record database is generally reliable for research (yielding high concordance rate with research diagnosis), future studies evaluating the validity of CDARS-derived diagnoses for schizophrenia and other psychoses are needed, to facilitate estimation of diagnostic accuracy and the potential effect of misdiagnosis bias on outcome analyses.

In conclusion, in a large population-based cohort of patients with incident diabetes, our study indicates that schizophrenia is associated with elevated mortality risk. Patients with pre-existing schizophrenia generally present lower or similar rates of macrovascular and microvascular complications in the first year of diabetes diagnosis compared with those with diabetes alone, but exhibit increased risk of post-complication mortality. Our findings thus confirm the presence of physical health disparities, and highlight an unmet treatment need for diabetes in patients with schizophrenia. More research is needed to better understand the adverse effect of, and interactions among, various factors contributing to excess mortality among this vulnerable group of patients with schizophrenia with co-occurring diabetes. Future studies should also focus on effective interventions, in particular lifestyle modification, to improve long-term diabetes-related outcomes.

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Supplementary material

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Data availability

The data that support the findings of this study are available from the corresponding author, W.C.C., upon reasonable request.

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Author contributions

W.C.C. and C.S.M.W. conceptualised and designed the study. W.C.C. contributed to the acquisition of data, oversaw the data analysis and interpreted the results. J.K.N.C. and C.S.M.W. contributed to the data analysis and interpretation of the results. J.K.N.C. and W.C.C. wrote the manuscript. C.S.M.W. contributed substantially to the revision of manuscript drafts. P.C.F.O. and E.Y.H.C. participated in the interpretation of the results. All authors reviewed and approved the final manuscript.

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Declaration of interest

None.

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