

Severe Mental Illness and Type 2 Diabetes Outcomes and Complications: A Nationwide Cohort Study

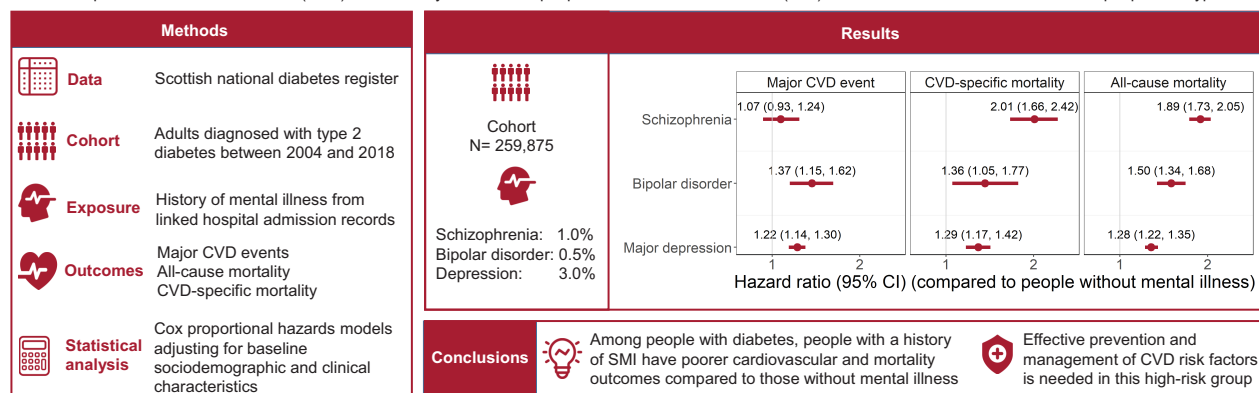
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Aim: To compare cardiovascular disease (CVD) and mortality outcomes in people with severe mental illness (SMI) versus no mental illness in a cohort of people with type 2 diabetes



ARTICLE HIGHLIGHTS

- We aimed to compare cardiovascular and mortality outcomes in people with severe mental illness versus no mental illness in a national cohort study of people in Scotland with type 2 diabetes.
- After adjusting for sociodemographic characteristics, the risk of major cardiovascular disease events, cardiovascular disease-specific mortality, and all-cause mortality was higher in people with schizophrenia, bipolar disorder, and major depression compared with people without a history of mental illness.
- Effective prevention and management of cardiovascular risk factors is needed in people with severe mental illness and type 2 diabetes.



Severe Mental Illness and Type 2 Diabetes Outcomes and Complications: A Nationwide Cohort Study

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Scottish Diabetes Research Network
Epidemiology Group

OBJECTIVE

To compare cardiovascular and mortality outcomes in people with severe mental illness (SMI) versus no mental illness in a national cohort study of people with type 2 diabetes.

RESEARCH DESIGN AND METHODS

We included adults diagnosed with type 2 diabetes between 2004 and 2018 from the national Scottish diabetes register, ascertaining history of mental illness from linked psychiatric and general hospital admission records. We identified major cardiovascular disease (CVD) events, all-cause mortality, and CVD-specific mortality through record linkage. Using Cox regression, we estimated hazard ratios (HRs) for associations between SMI and outcomes, adjusting for baseline socio-demographic and clinical characteristics, including history of CVD, comorbidity, hypertension, high cholesterol, HbA_{1c}, BMI, alcohol use disorder, and smoking.

RESULTS

Among 259,875 people with type 2 diabetes, 1.0%, 0.5%, and 3.0% had schizophrenia, bipolar disorder, and major depression, respectively. After adjusting for sociodemographic characteristics, the risk of major CVD events was higher in people with schizophrenia (HR 1.22, 95% CI 1.06–1.41), bipolar disorder (HR 1.58, 95% CI 1.33–1.87), and major depression (HR 1.59, 95% CI 1.49–1.70) compared with people without a history of mental illness. SMI was also associated with an approximately twofold increased risk of CVD-specific and all-cause mortality. All associations attenuated following further adjustment for clinical characteristics.

CONCLUSIONS

Among people with diabetes, people with a history of SMI have poorer cardiovascular and mortality outcomes compared with those without mental illness. While the underlying mechanisms are further investigated, effective prevention and management of cardiovascular risk factors is needed in this high-risk group.

People with severe mental illness (SMI), including schizophrenia, bipolar disorder, and major depression, have 10–20 years shorter life expectancy than the general population (1). This premature mortality is largely due to a higher burden of physical disease, particularly cardiovascular disease (CVD) (2,3), for which diabetes is a major risk factor (4). SMI is associated with a two- to threefold increased risk of

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type 2 diabetes (5–8), a health gap that may be widening (6). Multiple factors play a role in this increased risk, including lifestyle factors, psychotropic medication adverse effects, and genetic factors, all of which may in turn adversely affect diabetes progression and risk of complications (9). Although depression in people with diabetes has been shown to be associated with increased risks of CVD and cardiac death (10), other complications (11), and all-cause mortality (12,13), few studies have focused on severe depression. Schizophrenia and, to a greater extent, bipolar disorder are similarly understudied (14–21).

In the handful of existing studies, SMI is reasonably and consistently associated with an increased risk of mortality in people with diabetes (14,19–26), but the association with CVD mortality has rarely been reported (21,25), although it is often included within a composite of macrovascular outcomes. Findings on associations between SMI and macrovascular and microvascular complications of diabetes are inconsistent. Some studies report that SMI is associated with a higher risk of cardiovascular outcomes (17,20,25,27,28), whereas others report a similar or lower risk in those with versus without SMI (14,16,18,23,25). A similarly mixed picture has emerged for microvascular complications (14,17,18,20,24). However, shortcomings of existing studies include small study populations (19,28), selection bias (23), lack of adjustment for diabetes duration (16,22), definition of major depression (27), and short follow-up (14,16). Studies have also frequently included composite outcomes (e.g., combining all circulatory disease outcomes within a broad macrovascular outcome), which may have masked differing associations with individual diabetes complications.

In this study we sought to address some of these limitations and gaps through interrogation of a large nationally representative diabetes cohort with sufficient power and follow-up time to reliably estimate associations between SMI and individual outcomes. Our aim was to determine the independent effects of schizophrenia, bipolar disorder, and major depression on the risk of major CVD events, CVD-specific mortality, and all-cause mortality among people with type 2 diabetes.

RESEARCH DESIGN AND METHODS

This report is written in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Reporting of Studies Conducted using Observational Routinely-collected Data (RECORD) statements.

Data Sources

This study uses data from the Scottish Diabetes Research Network National Diabetes Dataset (SDRN-NDS) (29). This data set is estimated to include 99% of people diagnosed with diabetes in Scotland (29). It is a broad data set including information on, but not limited to, type of diabetes, sociodemographic characteristics, routine diabetes care, including retinopathy screening, and linked acute and psychiatric hospital records and death records (29).

Study Population

We included adults diagnosed with type 2 diabetes in Scotland between 2004 and 2018, who were aged ≥ 18 years before the end of the follow-up period (30 April 2019) and whose data could be linked to Scottish hospital and death records (Fig. 1).

SMI

We determined history of a mental illness from acute and psychiatric hospital inpatient admission records. We used *International Classification of Diseases* 9th Revision (ICD-9) codes for morbidity

records before 1996 and ICD-10 codes for morbidity records from 1996 onward. We identified mental illnesses from primary and secondary diagnosis fields of admissions that occurred after the individual's 18th birthday and before their diabetes diagnosis (Supplementary Table 1). We categorized people into mutually exclusive SMI groups, using a severity hierarchy when more than one diagnosis was recorded: schizophrenia was considered the most severe disorder, followed by bipolar disorder and finally, major depression.

Outcomes

Primary outcomes were major CVD event (stroke or myocardial infarction [MI]), in the whole cohort and in the subgroup of people without a history of a major CVD event, CVD-specific mortality (comprising ischemic heart disease and cerebrovascular disease), and all-cause mortality. Secondary outcomes were retinopathy, renal replacement therapy, and lower-limb amputation. We ascertained major CVD events from acute hospital and death records using ICD-10 codes for stroke (I60, I61, I63, I64) and MI (I21, I22) (ICD-10 codes have been used for death records in Scotland from 2000). We identified mortality from death records, using ICD-10 codes to define CVD-specific mortality from the primary cause of death (Supplementary Table 2). For retinopathy, we used data from the Scottish diabetic eye screening program to identify people whose screening result indicated referral to an eye clinic for assessment of suspected retinopathy

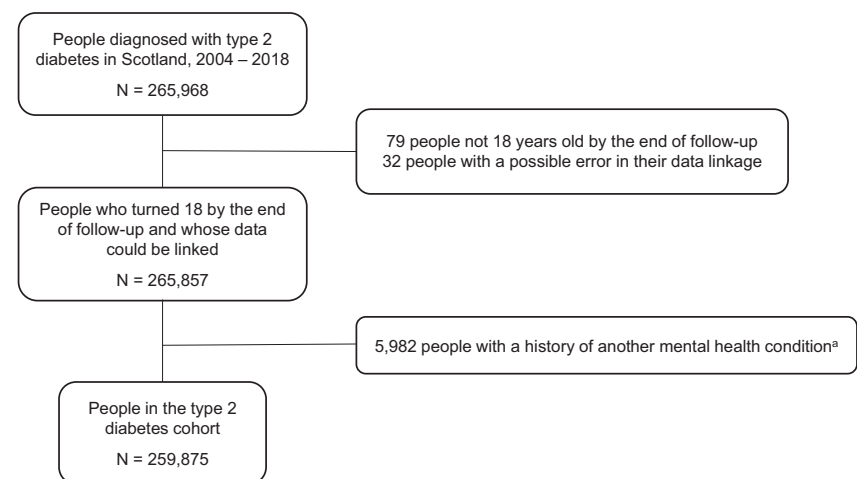


Figure 1—Flow diagram describing the selection of the study population. ^aIncluding other psychoses, other mood disorders, disorders of adult personality and behavior, eating disorders, neuroses, dissociative and somatoform disorders, behavioral and emotional disorders with onset in childhood and adolescence, nonorganic sleep disorders, disorders of psychosocial development, and unspecified mental disorders.

or maculopathy. Data from the screening program are available for all health boards in Scotland from 2009; hence, we restricted our analysis of retinopathy to people diagnosed with type 2 diabetes from 2009 onward. Receipt of renal replacement therapy was ascertained from linkage to the Scottish Renal Registry. Lower-limb amputations were identified from hospital records using the Office of Population Censuses and Surveys' Classification of Surgical Operations and Procedures, 4th revision (OPCS-4) codes for amputation of the leg, foot, or toe (X09, X10, X11).

Sociodemographic and Clinical Characteristics

We ascertained sex, age at type 2 diabetes diagnosis, year of type 2 diabetes diagnosis, area-based deprivation, ethnicity, and National Health Service (NHS) Health Board from the SDRN-NDS. Area-based deprivation was measured by the Scottish Index of Multiple Deprivation (SIMD) 2016 (30). The SIMD 2016 is derived by dividing Scotland into almost 7,000 small areas and using census data to measure deprivation within each area based on 38 indicators across the domains of income, employment, education, health, access to services, crime, and housing. The deprivation measure was then divided into quintiles based on the entire Scottish population. Ethnicity was categorized as White; Asian, Asian Scottish, or Asian British; mixed or multiple ethnic groups; or other. NHS Scotland comprises 14 regional health boards.

We used ICD-9 and ICD-10 codes (Supplementary Table 3) to ascertain a history of CVD, history of alcohol use disorder, and comorbidity from acute hospital records using a 10-year look-back period from the date of diabetes diagnosis. We measured comorbidity using a modified version of the Charlson Index, excluding diabetes and CVD events (Supplementary Text 1). We ascertained hypertension, high cholesterol, HbA_{1c}, and BMI from the SDRN-NDS using records from within 180 days of the type 2 diabetes diagnosis date (see Supplementary Text 2). We identified hypertension using a combination of systolic and diastolic blood pressure measurements and prescriptions for hypertension treatment to ascertain whether the person had either previous or current hypertension. Likewise, we identified high cholesterol using a combination of total cholesterol measurements and prescriptions for

lipid-lowering medication to ascertain whether the person had either previous or current high cholesterol. We categorized BMI using cutoffs of 25, 30, 35, and 40 kg/m². We defined smoking status from the SDRN-NDS using the record closest to the type 2 diabetes diagnosis date.

Statistical Analysis

We compared outcomes in people with a history of schizophrenia, bipolar disorder, or major depression versus those with no prior hospital record for any mental illness. For the primary outcomes, we used Cox regression models to evaluate time from the date of diabetes diagnosis to the event, censoring at the end of the study period. For CVD events and CVD-specific mortality, we accounted for death from other causes as a competing risk, censoring at the date of death where this occurred before the end of the study period. For each primary outcome, we fitted two models. The first adjusted only for sociodemographic confounders of SMI and diabetes outcomes: sex, age at type 2 diabetes diagnosis, calendar year of type 2 diagnosis, deprivation, ethnicity, and health board. The second adjusted for these confounders plus baseline values of potential mediators, including history of CVD, comorbidity, hypertension, high cholesterol, HbA_{1c}, BMI, alcohol use disorder, and smoking. The purpose of the second model was to examine whether clinical and lifestyle factors may help to explain any association between SMI and the outcomes. Age at diagnosis, year of diagnosis, and log HbA_{1c} were included in the models as continuous variables with both linear and quadratic terms; all other variables were categorical. We used multiple imputation to account for missing data in seven covariates (see Supplementary Text 3).

Owing to small numbers of secondary outcome events, these data were summarized descriptively only. Results for lower-limb amputations and renal replacement therapy are summarized for those with any SMI versus those without a history of mental illness to avoid reporting very small numbers, which may compromise the anonymity of individuals.

All analyses were conducted in R 3.6.0 software. We used the mice package 3.14.0 to perform multiple imputation.

Sensitivity Analyses

Our primary analysis defined major depression based on both general and psychiatric hospital admission records. Since this may identify some people with mild depression, we repeated the multiple imputation and subsequent analyses with major depression defined based on psychiatric hospital admission records only.

Our primary analysis used multiple imputation to account for missing data. As a sensitivity analysis, we repeated the analyses including only individuals without missing data and compared findings from this complete case analysis to the results of the multiple imputation.

Ethics Approval

Approval for the linkage of the administrative health data sets used in this study was provided by the NHS Scotland Public Benefit and Privacy Panel for Health and Social Care. Approval for the use of diabetes data were obtained from the Public Benefit and Privacy Panel for Health and Social Care in Scotland (reference 1617-0147), and ethical approval for use of the linked database for research was obtained from the Scotland A Research Ethics Committee (reference 11-AL-0225).

Data and Resource Availability

The Scottish Diabetes Research Network epidemiology group welcomes research proposals for collaborations but cannot provide access to data. Applications for data access can be made to the Public Benefit and Privacy Panel for Health and Social Care in Scotland (<https://www.informationgovernance.scot.nhs.uk/pbpphsc/>).

RESULTS

Our cohort included 259,875 people with type 2 diabetes. Of these, 2,621 (1.0%), 1,211 (0.5%), and 7,903 (3.0%) had a prior hospital admission record for schizophrenia, bipolar disorder, and depression, respectively. Mean follow-up to death or the end of the study was 7.1 years. Overall, our cohort included slightly more men than women; however, women were overrepresented in the bipolar disorder and depression groups (Table 1). Diabetes was diagnosed at a younger mean age in people with a history of schizophrenia (52.1 years), bipolar disorder (57.5 years), or depression (58.9 years) compared with those without a history of

Table 1—Baseline characteristics of patients with type 2 diabetes by history of hospital record for mental illness

	No mental illness (<i>n</i> = 248,140)	Schizophrenia (<i>n</i> = 2,621)	Bipolar disorder (<i>n</i> = 1,211)	Major depression (<i>n</i> = 7,903)
Follow-up time (years), mean (SD)	7.1 (4.2)	6.8 (4.0)	6.7 (4.0)	6.3 (4.0)
Male sex	141,302 (56.9)	1,590 (60.7)	498 (41.1)	3,181 (40.3)
Age at diabetes diagnosis (years), mean (SD)	60.8 (13.4)	52.1 (12.7)	57.5 (12.4)	58.9 (12.7)
Ethnicity*				
White	206,596 (83.3)	2,298 (87.7)	1,108 (91.5)	7,155 (90.5)
Ethnic minority groups	17,734 (7.1)	149 (5.7)	53 (4.4)	331 (4.2)
Missing	23,810 (9.6)	174 (6.6)	50 (4.1)	417 (5.3)
SIMD quintile				
5 (least deprived)	35,517 (14.3)	169 (6.4)	139 (11.5)	683 (8.6)
4	45,019 (18.1)	275 (10.5)	178 (14.7)	1,027 (13.0)
3	50,700 (20.4)	494 (18.8)	248 (20.5)	1,569 (19.9)
2	57,223 (23.1)	699 (26.7)	282 (23.3)	1,986 (25.1)
1 (most deprived)	59,264 (23.9)	984 (37.5)	364 (30.1)	2,634 (33.3)
Missing	417 (0.2)	0 (0.0)	0 (0.0)	4 (0.1)
History of CVD	36,315 (14.6)	264 (10.1)	199 (16.4)	2,118 (26.8)
Modified Charlson Index				
0	205,445 (82.8)	2,136 (81.5)	911 (75.2)	5,117 (64.7)
1–8	24,334 (9.8)	320 (12.2)	183 (15.1)	1,660 (21.0)
>8	18,361 (7.4)	165 (6.3)	117 (9.7)	1,126 (14.2)
History of hypertension				
No hypertension	47,821 (19.3)	1,086 (41.4)	354 (29.2)	1,633 (20.7)
Hypertension	184,626 (74.4)	1,320 (50.4)	797 (65.8)	5,913 (74.8)
Missing	15,693 (6.3)	215 (8.2)	60 (5.0)	357 (4.5)
History of raised cholesterol				
No high cholesterol	38,834 (15.7)	393 (15.0)	164 (13.5)	1,025 (13.0)
High cholesterol	185,414 (74.7)	1,967 (75.0)	950 (78.4)	6,150 (77.8)
Missing	23,892 (9.6)	261 (10.0)	97 (8.0)	728 (9.2)
HbA _{1c} at diabetes diagnosis				
HbA _{1c} (%), mean (SD)	7.6 (1.7)	7.8 (2.0)	7.5 (1.8)	7.6 (1.7)
HbA _{1c} (mmol/mol), mean (SD)	60.1 (18.4)	61.9 (21.7)	58.6 (19.3)	59.7 (18.6)
Missing	29,868 (12.0)	355 (13.5)	130 (10.7)	887 (11.2)
History of alcohol use disorder	5,774 (2.3)	451 (17.2)	180 (14.9)	1,435 (18.2)
BMI (kg/m ²)	31.6 (28.0, 36.2)	33.3 (29.5, 38.1)	33.3 (29.6, 38.2)	33.2 (29.1, 38.3)
<25	19,619 (7.9)	172 (6.6)	73 (6.0)	514 (6.5)
≥25 and <30	61,693 (24.9)	453 (17.3)	216 (17.8)	1,485 (18.8)
≥30 and <35	66,184 (26.7)	750 (28.6)	349 (28.8)	1,970 (24.9)
≥35 and <40	36,918 (14.9)	496 (18.9)	206 (17.0)	1,387 (17.6)
≥40	27,713 (11.2)	392 (15.0)	196 (16.2)	1,291 (16.3)
Missing	36,013 (14.5)	358 (13.7)	171 (14.1)	1,256 (15.9)
Smoking				
Never smoked	111,183 (44.8)	669 (25.5)	368 (30.4)	2,633 (33.3)
Former smoker	85,671 (34.5)	550 (21.0)	349 (28.8)	2,349 (29.7)
Current smoker	50,364 (20.3)	1,391 (53.1)	490 (40.5)	2,891 (36.6)
Missing	922 (0.4)	11 (0.4)	4 (0.3)	30 (0.4)

Data are presented as *n* (%) or median (interquartile range), unless indicated otherwise. *The statistical models adjust for an ethnicity variable with four categories: Asian, Asian Scottish, or Asian British; White; mixed or multiple ethnic groups; any other ethnic group. In this table, the last three categories are grouped to ensure that this table does not risk the anonymity of individuals by including cells with very small numbers.

a mental illness (60.8 years). Our cohort was predominantly of White ethnicity, with the area-based deprivation distribution reflecting the higher prevalence of type 2 diabetes among more deprived populations. This pattern was even more

striking among those with an SMI; for example, more than one-third of people with schizophrenia came from the most deprived fifth of areas in Scotland. History of prior CVD, comorbidity, and high cholesterol at diabetes diagnosis were more

common in those with depression and bipolar disorder compared with those without mental illness. A similar pattern was not observed for schizophrenia, perhaps in part reflecting the younger age at diabetes diagnosis. History of hypertension

and mean HbA_{1c} at baseline were similar across comparison groups. Smoking, history of alcohol use disorder, and overweight/obesity were more common in people with SMI than in those without mental illness.

In the sensitivity analysis, we found that only 1.5% of the cohort had depression based on psychiatric hospital records compared with 3.0% when depression was defined from both acute and psychiatric hospital records. However, the distribution of baseline characteristics was similar to that observed in the primary analysis (Supplementary Table 4).

Major CVD Events

Mean follow-up (to the earliest of major CVD event, death, or end of study) was 6.9 years, during which 24,873 CVD events occurred (Table 2). In the model adjusting

for sociodemographic characteristics only, compared with people without mental illness, the risk of a major CVD event was higher among people with each of schizophrenia (hazard ratio [HR] 1.22, 95% CI 1.06–1.41), bipolar disorder (HR 1.58, 95% CI 1.33–1.87), and major depression (HR 1.59, 95% CI 1.49–1.70) (Fig. 2). In the fully adjusted model (adjusting for sociodemographic characteristics as well as history of CVD, comorbidity, hypertension, high cholesterol, HbA_{1c}, BMI, alcohol use disorder, and smoking), effect estimates were attenuated: schizophrenia (HR 1.07, 95% CI 0.93–1.24), bipolar disorder (HR 1.37, 95% CI 1.15–1.62), and major depression (HR 1.22, 95% CI 1.14–1.30). When we restricted the analysis to people without a history of a major CVD event at baseline, the associations were similar (Fig. 2).

CVD-Specific and All-Cause Mortality

During a mean follow-up time of 7.1 years, 51,029 deaths occurred (Table 2). CVD-specific mortality rates were higher among people with each SMI compared with those with no history of hospital admission for a mental illness. After adjusting for sociodemographic characteristics, schizophrenia was associated with the greatest excess risk of CVD-specific death (HR 2.38, 95% CI 1.98–2.87), followed by bipolar disorder (HR 1.70, 95% CI 1.31–2.21) and major depression (HR 1.84, 95% CI 1.67–2.03). While estimates attenuated slightly in the fully adjusted model, a marked increased risk of CVD mortality persisted in all groups (Fig. 2).

All-cause mortality was also higher among people with a history of an SMI versus no mental illness, with estimates very similar to those for CVD-specific mortality (Fig. 2).

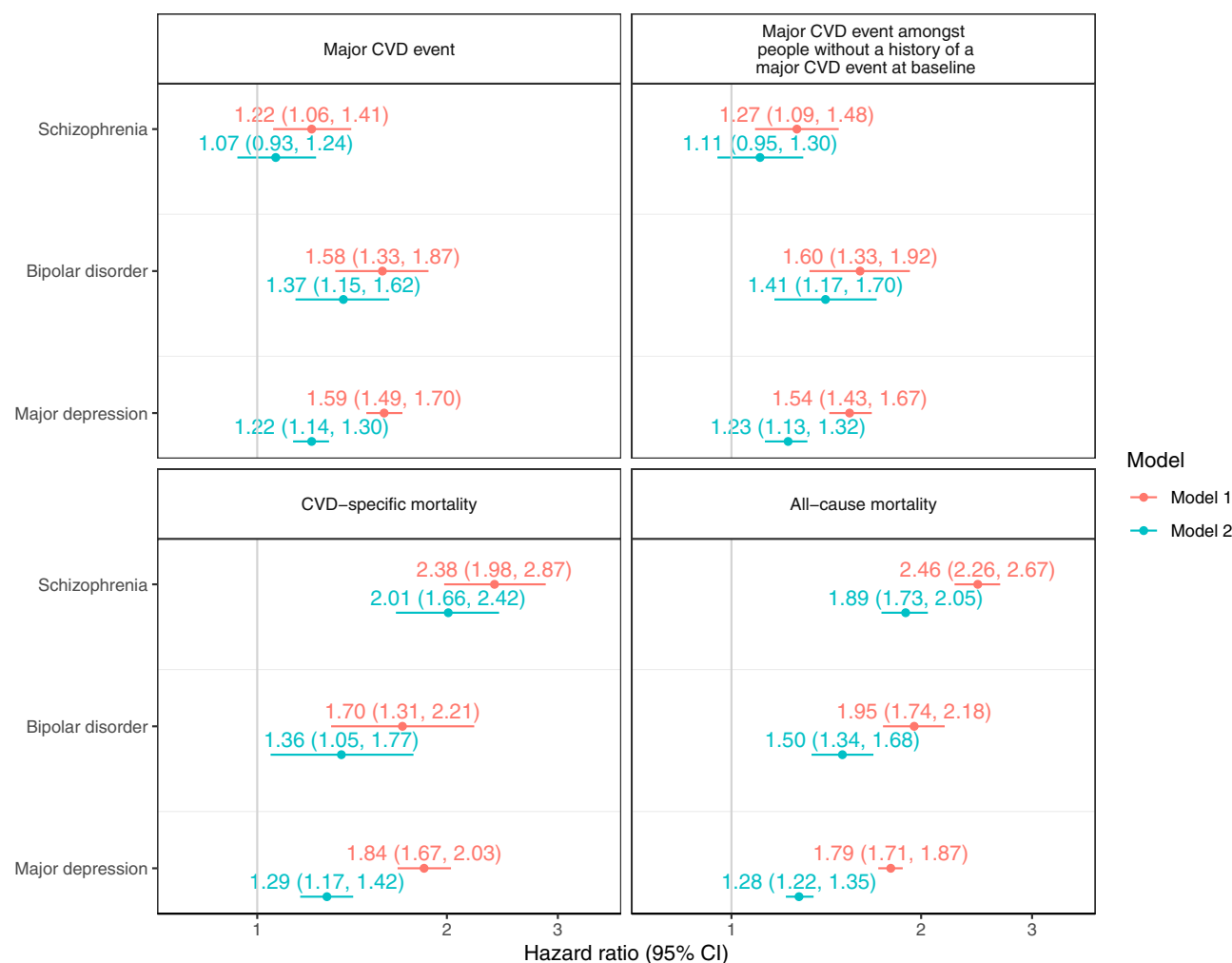


Figure 2—Risk of major CVD events, CVD-specific mortality, and all-cause mortality in people with a hospital record of severe mental illness vs. no mental illness. Estimates were obtained using multiple imputation by chained equations. Model 1 adjusts for sociodemographic characteristics (sex, age at type 2 diabetes diagnosis, calendar year of type 2 diagnosis, deprivation, ethnicity, and health board). Model 2 additionally adjusts for clinical characteristics at baseline (history of CVD, comorbidity, hypertension, high cholesterol, log HbA_{1c}, BMI, alcohol use disorder, and smoking).

Table 2—Frequency of macrovascular, microvascular, and mortality outcomes in people with type 2 diabetes, stratified by hospital record for mental illness

	No history of any mental illness (n = 248,140)	Schizophrenia (n = 2,621)	Bipolar disorder (n = 1,211)	Major depression (n = 7,903)
Follow-up time (years), mean (SD)	7.1 (4.2)	6.8 (4.0)	6.7 (4.0)	6.3 (4.0)
Major CVD event	23,686 (9.5)	184 (7.0)	132 (10.9)	871 (11.0)
Incident major CVD event (people without a history of a major CVD event at baseline)				
n*	233,130	2,513	1,144	7,122
People with a major CVD event	20,302 (8.7)	165 (6.6)	114 (10.0)	688 (9.7)
Deaths	48,261 (19.4)	573 (21.9)	303 (25.0)	1,892 (23.9)
CVD deaths	11,071 (4.5)	116 (4.4)	57 (4.7)	426 (5.4)
Referable retinopathy or maculopathy				
n†	162,167	1,803	833	5,636
People screened at least once	151,347 (93.3)	1,593 (88.4)	745 (89.4)	5,067 (89.9)
People with referable disease (of those screened)	7,435 (4.9)	50 (3.1)	25 (3.4)	152 (3.0)

Data are presented as n (%) unless indicated otherwise as mean (SD) or n. *Number of people without a history of a major CVD event at baseline. †Data from the retinopathy screening program are available for all health boards in Scotland from 2009; hence, we restricted our analyses of retinopathy to people diagnosed with type 2 diabetes from 2009 onward.

Sensitivity Analyses

Generally, the results of the complete case analysis were similar to those based on multiple imputation (Supplementary Table 5). For major CVD events, based on the complete case analysis, the model adjusting for sociodemographic factors only did not find a statistically significant difference between people with schizophrenia and those without a history of SMI. This may be due to a higher proportion of major CVD events in people with schizophrenia and missing data (9.4%) compared with those with schizophrenia and complete data (6.0%). For people without a history of SMI, similar proportions had major CVD events among those with missing data (9.1%) and those with complete data (9.7%).

When major depression was defined based on psychiatric hospital records only, the effect estimates were very similar to those for major depression defined based on all hospital records (Supplementary Table 6).

Secondary Outcomes

Overall, a lower-limb amputation occurred in 1,540 (0.6%) of our cohort, including 1,462 (0.6%) without a history of a mental illness and 78 (0.7%) with a history of SMI. Of those who attended eye screening at least once, 4.8% had referable retinopathy or maculopathy identified (Table 2). Of the 259,486 individuals without a history of renal replacement therapy at baseline, 462 (0.2%)

required renal replacement therapy during follow-up, including 441 (0.2%) without a history of mental illness and 21 (0.2%) with a history of mental illness. Numbers were too small to formally compare complication rates across comparison groups, which are thus confounded by age and diabetes duration. Rates of referable retinopathy or maculopathy and renal replacement therapy may also be affected by differential access to eye screening and renal replacement programs, respectively.

CONCLUSIONS

Among people with type 2 diabetes, schizophrenia, bipolar disorder, and major depression were associated with increased risks of major CVD events, CVD-specific mortality, and all-cause mortality. Relative to people with no history of hospital admission with mental illness, risks of major CVD events were highest among those with bipolar disorder and major depression, whereas relative risks of CVD-specific mortality and all-cause mortality were highest among those with schizophrenia. Differences in clinical characteristics at baseline explained some, but not all, of the disparity in outcomes. There were too few microvascular events in our cohort to allow formal comparisons by SMI status.

Previous studies of SMI and macrovascular complications among people with diabetes report conflicting findings. In line with our results, a South Korean study found a similar excess risk of

heart attack and stroke among those with diabetes and schizophrenia, bipolar disorder, or depression (21). Similarly, a Taiwanese study reported an association between clinically diagnosed depression and an increased risk of acute coronary syndrome and stroke (24). Our results also partially align with those of a national Danish study that found that SMI (as a composite exposure) was associated with a higher CVD risk (defined more broadly than in our study) (17). This was, however, driven largely by an excess CVD risk in people with major depression, with little difference observed in people with schizophrenia or bipolar disorder, even in minimally adjusted models. In contrast, two studies reported lower risks of cardiovascular events in people with schizophrenia (18) or major depression (16). The latter study had various shortcomings, including inclusion of prevalent diabetes cases and lack of adjustment for diabetes duration and short follow-up, while the former defined diabetes using hospital diagnosis codes and prescription data.

One study found no difference in macrovascular complications among those with versus without schizophrenia, but it was limited by analysis of only the first year post diabetes diagnosis (14). Our study aligns with some, but not all, findings from a recent, smaller study in England that compared both primary care-recorded CVD conditions and emergency hospital admissions by SMI status in people with diabetes

(25). A combined definition of SMI was associated with a higher risk of stroke but a lower risk of emergency admission for MI and no difference in primary care-recorded MI diagnosis. Differences in outcome definitions and inclusion of people with SMI diagnosed after diagnosis of diabetes could contribute to the discrepant findings (25).

To our knowledge, only two previous studies have reported the association between SMI and cardiovascular-specific mortality in people with diabetes, with similar findings reported (21,25). Our results also align with those from a meta-analysis of studies that examined depression of any severity and risk of cardiovascular mortality in people with diabetes (10).

The observed excess all-cause mortality among people with diabetes and SMI compared with no mental illness is consistent with previous literature (14,19–24, 26). Our study adds to the scarce data on bipolar disorder, which has been studied less in this context compared with schizophrenia and major depression (19,21).

The mechanisms underlying the excess cardiovascular morbidity and mortality in people with comorbid diabetes and SMI are multifactorial and poorly understood. Shared risk factors for poor physical and mental health include low socioeconomic status, adverse childhood experiences, and lifestyle factors (31). The higher prevalence of smoking, overweight/obesity, and comorbidities in people with SMI plays a role, as reflected by the attenuation of effect estimates upon adjustment for these factors in our analyses. A Danish study of people with type 2 diabetes concluded that excess mortality among those with depression was largely explained by physical inactivity, smoking, and comorbidities (26). There is also emerging evidence suggesting that brain insulin resistance may be part of the core pathophysiology of schizophrenia and bipolar disorder (32,33) and could partially explain the observed poorer diabetes outcomes in people with SMI. Inequalities in care for physical disease is thought to partly explain the observed increased risk and poorer outcomes of physical diseases, including diabetes, in people with SMI (34), with a recent Danish study reporting lower rates of diabetes monitoring and achievement of HbA_{1c} and cholesterol targets in people with versus without SMI (35). However, disparities in diabetes care do not explain

the findings in our study, since receipt of type 2 diabetes processes of care (with the exception of retinopathy screening) is similar or better in people with an SMI in Scotland versus no mental illness (17). Nevertheless, optimal monitoring may not translate into optimal treatment of cardiovascular risk factors and/or established CVD.

Furthermore, previous studies of general populations of people with and without diabetes have demonstrated suboptimal cardiovascular risk management in those with SMI (34,36). The excess risk of cardiovascular death in people with diabetes and SMI might also reflect more severe cardiovascular events and potential differences in cardiac care, both in the acute phase and subsequently. Previous research from our group and others found that, among people with an MI and compared with those without mental illness, patients with an SMI were less likely to receive coronary revascularization procedures, less likely to survive 30-days post-MI, and more likely to experience a further vascular event (36,37). The adverse cardiac and metabolic adverse effects of some antipsychotic medications may also play a role in the poorer outcomes (38,39). Evidence on the adverse effects of antipsychotic and antidepressant drugs on cardiovascular and mortality outcomes in people with diabetes is notably underinvestigated (40).

Our study makes an important contribution to a relatively understudied area where existing studies are scarce or contradictory. Our study has multiple strengths, which together address some of the limitations and gaps in the existing literature. We included people with diabetes from a national population-based diabetes register, thereby including an unselected and nationally representative cohort. The large study population and long follow-up period allowed us to investigate individual SMIs, analyze specific CVD outcomes separately, and obtain reliable, precise effect estimates for outcomes. We also included people with incident diabetes to avoid survival bias. The richness of the diabetes register allowed associations to be adjusted for key lifestyle factors that previous studies have not always adjusted for. We avoided introducing bias and possibly overestimating effect estimates by accounting for competing risks of death and death from other causes, as appropriate, in our

analyses. Finally, our study adds to the scarce data on associations between SMI and CVD-specific mortality in people with diabetes and on all-cause mortality in those with bipolar disorder specifically.

The main limitation of our study is that the diabetes data set includes a narrow set of primary care records specific to diabetes, so the definition of SMI was based on hospital records only. Therefore, our findings may not be generalizable to people with schizophrenia, bipolar disorder, or depression who have not had an inpatient stay and whose condition may be less severe. This limitation is mitigated by the fact that the hospital records extend back to 1981. There may have been selection bias in that people with less severe depression may have only been included because they were admitted to a general hospital for another health condition. Reassuringly, sensitivity analyses based on psychiatric hospital records only suggest that the depression group was reasonably homogeneous in severity or that our findings apply to people with different severity of depression. Since the aim of this study was to examine the association between preexisting SMI and diabetes outcomes, we have not accounted for incident SMI after a diabetes diagnosis. We could not evaluate microvascular complications due to the small number of events.

While the diabetes register collects information on a range of key factors, data on individual socioeconomic status are unavailable. Area-based deprivation does not necessarily reflect individual socioeconomic status, so there may be residual confounding. We also did not have data on other lifestyle factors, including diet, physical activity, and sleep. Almost one-third of our cohort had some missing data, with BMI and HbA_{1c} at diabetes diagnosis having the most missing values. However, to address this, we used multiple imputation to estimate our effect estimates, with the assumption that the probability of a covariate being missing can be predicted based on the other variables we included.

In conclusion, among people with new-onset diabetes, those with a prior history of SMI have a markedly higher risk of major CVD events, CVD-specific mortality, and all-cause mortality than people with no mental illness. Our findings suggest that some of this excess risk is due to modifiable risk factors, including smoking, alcohol

misuse, and obesity, highlighting the particular need for effective lifestyle modification in people with SMI. However, other emerging mechanisms, including the possible shared pathophysiology between SMI and diabetes, require further investigation. Future research should also clarify the role of psychotropic medication use and receipt of optimal cardiac care in primary and secondary care settings. Meanwhile, effective prevention and management of cardiovascular risk factors is needed in this high-risk group.

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