Severe mental illness and type 2 diabetes outcomes and complications

Severe mental illness and type 2 diabetes outcomes and complications: a nationwide cohort study

Running title: Severe mental illness and diabetes outcomes

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Twitter summary: People with type 2 diabetes and schizophrenia, bipolar disorder or major depression have poorer cardiovascular and mortality outcomes compared to those with type 2 diabetes alone.

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ABSTRACT

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 (HR) for associations between SMI and outcomes, adjusting for baseline sociodemographic and clinical characteristics, including history of CVD, comorbidity, hypertension, high cholesterol, HbA1c, BMI, alcohol use disorder and smoking.

RESULTS

Amongst 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, 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 to people without a history of mental illness. SMI was also associated with approximately two-fold 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 to those without mental illness. Whilst the underlying mechanisms are further investigated, effective prevention and management of cardiovascular risk factors is needed in this high-risk group.

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 adjustment for sociodemographic characteristics, risk of major CVD events, CVD-specific mortality and all-cause mortality was higher in people with schizophrenia, bipolar disorder and major depression compared to 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.

INTRODUCTION

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 three-fold increased risk of type 2 diabetes (5-8), a health gap which may be widening (6). Multiple factors play a role in this increased risk, including lifestyle factors, psychotropic medication side 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 under-studied (14-21). In the handful of existing studies, SMI is reasonably 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 (for example, 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 effect of each 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 article 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). It is estimated that this dataset includes 99% of people diagnosed with diabetes in Scotland (29). It is a broad dataset 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 18 years of age or older before the end of the follow-up period (30 April 2019) and whose data could be linked to Scottish hospital and death records (Figure 1).

Severe mental illness

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 prior to 1996 and ICD-10 codes for morbidity records from 1996 onwards. 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 categorised 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 sub-group of people without a history of a major CVD event, CVD-specific mortality (comprising ischaemic 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 programme to identify people whose screening result indicated referral to an eye clinic for assessment of suspected retinopathy or maculopathy. Data from the screening programme is 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 onwards. Receipt of renal replacement therapy was ascertained from linkage to the Scottish Renal Registry. Lower limb amputations were identified from hospital records using OPCS-4 operation 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 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 is then divided into quintiles based on the entire Scottish population. Ethnicity was categorised as White; Asian, Asian Scottish or Asian British; mixed or multiple ethnic groups or other. NHS Scotland is comprised of 14 regional health boards. We used ICD-9 and ICD-10 codes (Supplementary Table 3) to ascertain 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, HbA1c and BMI from the SDRN-NDS using records from within 180 days of 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 in order 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 in order to ascertain whether the person had either previous or current cholesterol. We categorized BMI using cut-offs of 25, 30, 35 and 40 kg/m^2. We defined smoking status from the SDRN-NDS using the record closest to 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 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 adjusts 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 adjusts for these confounders plus baseline values of potential mediators including history of CVD, comorbidity, hypertension,

high cholesterol, HbA1c, 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 HbA1c 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).

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

All analyses were conducted in R version 3.6.0. We used the mice package version 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 was 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 a multi-centre research ethics committee (reference 11-AL-0225).

Data and resource availability

The Scottish Diabetes Research Network epidemiology group welcomes 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 over-represented in the bipolar disorder and depression groups (Table 1). Mean age of diabetes diagnosis was lower in people with a history of schizophrenia (52.1 years), bipolar disorder (57.5 years) or depression (58.9 years) compared to those without a history of 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, over a 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 to 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 HbA1c 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 to 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 time 24,873 CVD events occurred (Table 2). In the model adjusting for sociodemographic characteristics only, compared to people without mental illness, the risk of a major CVD event was higher amongst people with each of 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) (Figure 2). In the fully adjusted model (adjusting for sociodemographic characteristics as well as history of CVD, comorbidity, hypertension, high cholesterol, HbA1c, 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 (Figure 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 amongst people with each SMI, compared to 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). Whilst estimates attenuated slightly in the fully adjusted model, a marked increased risk of CVD mortality persisted in all groups (Figure 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 (Figure 2).

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 proportions of major CVD events in people with schizophrenia and missing data (9.4%), compared to those with schizophrenia and complete data (6.0%). For people without a history of

SMI similar proportions had major CVD events amongst 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, 1540 (0.6%) of our cohort had a lower limb amputated, including 1462 (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

Amongst 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 amongst those with bipolar disorder and major depression, whereas relative risks of CVD-

specific mortality and all-cause mortality were highest amongst 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 on 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 each of schizophrenia, bipolar disorder and depression (21). Similarly a Taiwanese study reported an association between clinically diagnosed depression and increased risk of acute coronary syndrome and stroke (24). Our results partially align with those of a national Danish study that found that SMI (as a composite exposure) was associated with 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 each of schizophrenia (18) and major depression (16). The latter study has various shortcomings including inclusion of prevalent diabetes cases and lack of adjustment for diabetes duration and short follow-up, whilst 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 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 which 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, just two previous studies have reported on 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 to no mental illness is consistent with previous literature (14, 19-24, 26). Our study adds to the scarce data on bipolar disorder, which, in comparison to schizophrenia and major depression has been less completely studied in this context (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 play 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 amongst 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 in part 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 of 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 HbA1c and cholesterol targets in people with versus without SMI (35). However, disparities in diabetes care do not explain the findings in our study, since, in Scotland (with the exception of retinopathy screening) receipt of type 2 diabetes processes of care is similar or better in people with an SMI 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 sub-optimal 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 to those without mental illness, patients with an SMI were less likely to receive coronary revascularisation 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 side 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 under-investigated (40).

Our study makes an important contribution to a relatively under-studied 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, analyse 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 over-estimating 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 dataset includes a narrow set of primary care records specific to diabetes and so the definition of SMI was based on hospital records only. Our findings may not, therefore, 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 pre-existing SMI and diabetes outcomes, we have not accounted for incident SMI after diabetes diagnosis. We could not evaluate microvascular complications due to small number of events. Whilst 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 and 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 HbA1c 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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in Scotland, 1-2 November 2018 and Royal College of Psychiatrists International Congress, England, 1-4 July 2019.

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DUALITY OF INTEREST

The authors have no conflicts of interests.

AUTHOR CONTRIBUTIONS

CAJ conceived the study, CAJ, SHW, KL, DJS, SWM and CLMS obtained grant funding, all authors contributed to the study design, KF conducted the statistical analysis, all authors contributed to data interpretation, KF and CAJ drafted the manuscript which all authors commented on. CAJ is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiatry. 2015;72(4):334-41. doi: 10.1001/jamapsychiatry.2014.502.
2. Momen NC, Plana-Ripoll O, Agerbo E, Benros ME, Børglum AD, Christensen MK, et al. Association between Mental Disorders and Subsequent Medical Conditions. N Engl J Med. 2020;382(18):1721-31.
3. Plana-Ripoll O, Pedersen CB, Agerbo E, Holtz Y, Erlangsen A, Canudas-Romo V, et al. A comprehensive analysis of mortality-related health metrics associated with mental disorders: a nationwide, register-based cohort study. Lancet. 2019;394(10211):1827–35.
4. Dal Canto E, Ceriello A, Rydén L, Ferrini M, Hansen TB, Schnell O, et al. Diabetes as a cardiovascular risk factor: An overview of global trends of macro and micro vascular complications. Eur J Prev Cardiol. 2019;26(2_suppl):25-32.
5. Bai YM, Su TP, Chen MH, Chen TJ, Chang WH. Risk of developing diabetes mellitus and hyperlipidemia among patients with bipolar disorder, major depressive disorder, and schizophrenia: a 10-year nationwide population-based prospective cohort study. J Affect Disord. 2013;150(1):57-62. doi: 10.1016/j.jad.2013.02.019.
6. Jackson CA, Fleetwood K, Kerssens J, Smith DJ, Mercer S, Wild SH. Incidence of Type 2 Diabetes in People With a History of Hospitalization for Major Mental Illness in Scotland, 2001-2015: A Retrospective Cohort Study. Diabetes care. 2019;42(10):1879-85. doi: 10.2337/dc18-152.
7. Lindekilde N, Rutters F, Erik Henriksen J, Lasgaard M, Schram MT, Rubin KH, et al. Psychiatric disorders as risk factors for type 2 diabetes: An umbrella review of systematic reviews with and without meta-analyses. Diabetes Res Clin Pract. 2021;176:108855.
8. Lindekilde N, Scheuer SH, Diaz LJ, Rubin KH, Plana-Ripoll O, Henriksen JE, et al. Risk of Developing Type 2 Diabetes in Individuals With a Psychiatric Disorder: A Nationwide Register-Based Cohort Study. Diabetes care. 2022;45(3):724-33.
9. Holt RI, Mitchell AJ. Diabetes mellitus and severe mental illness: mechanisms and clinical implications. Nat Rev Endocrinol. 2015;11(2):79–89.
10. Farooqi A, Khunti K, Abner S, Gillies C, Morriss R, Seidu S. Comorbid depression and risk of cardiac events and cardiac mortality in people with diabetes: A systematic review and meta-analysis. Diabetes Res Clin Pract. 2019;156:107816. doi: 10.1016/j.diabres.2019.
11. Nouwen A, Adriaanse MC, van Dam K, Iversen MM, Viechtbauer W, Peyrot M, et al. Longitudinal associations between depression and diabetes complications: a systematic review and meta-analysis. Diabet Med. 2019;36(12):1562-72.
12. Hofmann M, Köhler B, Leichsenring F, Kruse J. Depression as a Risk Factor for Mortality in Individuals with Diabetes: A Meta-Analysis of Prospective Studies. PLoS One. 2013;8(11):e79809.
13. van Dooren FEP, Nefs G, Schram MT, Verhey FRJ, Denollet J, Pouwer F. Depression and Risk of Mortality in People with Diabetes Mellitus: A Systematic Review and Meta-Analysis. PLoS One. 2013;8(3):e57058.
14. Chan JKN, Wong CSM, Or PCF, Chen EYH, Chang WC. Diabetes complication burden and patterns and risk of mortality in people with schizophrenia

and diabetes: A population-based cohort study with 16-year follow-up. Eur Neuropsychopharmacol. 2021;53:79-88.
15. Kurdyak P, Vigod S, Duchen R, Jacob B, Stukel T, Kiran T. Diabetes quality of care and outcomes: Comparison of individuals with and without schizophrenia. Gen Hosp Psychiatry. 2017;46:7–13.
16. Leung G, Zhang J, Lin W-C, Clark RE. Behavioral disorders and diabetes-related outcomes among Massachusetts Medicare and Medicaid beneficiaries. Psychiatr Serv. 2011;62(6):659-65. doi: 10.1176/ps.62.6.pss6206_0659.
17. Scheuer SH, Kosjerina V, Lindekilde N, Pouwer F, Carstensen B, Jørgensen ME, et al. Severe mental illness and the risk of diabetes complications. A nationwide register-based cohort study. J Clin Endocrinol Metab. 2022;107(8):e3504–e14. doi: 10.1210/clinem/dgac204.
18. Toender A, Vestergaard M, Munk-Olsen T, Larsen JT, Kristensen JK, Laursen TM. Risk of diabetic complications and subsequent mortality among individuals with schizophrenia and diabetes - a population-based register study. Schizophr Res. 2020;218:99-106.
19. Vinogradova Y, Coupland C, Hippisley-Cox J, Whyte S, Penny C. Effects of severe mental illness on survival of people with diabetes. Br J Psychiatry. 2010;197(4):272–7.
20. Wu S-I, Chen S-C, Liu S-I, Sun F-J, Juang JJM, Lee H-C, et al. Relative Risk of Acute Myocardial Infarction in People with Schizophrenia and Bipolar Disorder: A Population-Based Cohort Study. PLoS One. 2015;10:e0134763.
21. Kim H, Lee KN, Shin DW, Han K, Jeon HJ. Association of comorbid mental disorders with cardiovascular disease risk in patients with type 2 diabetes: A nationwide cohort study. Gen Hosp Psychiatry. 2022;79:33-41.
22. Mai Q, Holman CD, Sanfilippo FM, Emery JD, Preen DB. Mental illness related disparities in diabetes prevalence, quality of care and outcomes: a population-based longitudinal study. BMC Med. 2011;9:118.
23. Sullivan MD, O'Connor P, Feeney P, Hire D, Simmons DL, Raisch DW, et al. Depression predicts all-cause mortality: epidemiological evaluation from the ACCORD HRQL substudy. Diabetes care. 2012;35(8):1708–15.
24. Wu CS, Hsu LY, Wang SH. Association of depression and diabetes complications and mortality: a population-based cohort study. Epidemiol Psychiatr Sci. 2020;29:e96.
25. Han L, Doran T, Holt RIG, Hewitt C, Jacobs R, Prady SL, et al. Impact of severe mental illness on healthcare use and health outcomes for people with type 2 diabetes: a longitudinal observational study in England. Br J Gen Pract. 2021;71(709):e565-e73.
26. Rohde C, Nielsen JS, Schöllhammer Knudsen J, Thomsen RW, Østergaard SD. Risk factors associated with mortality among individuals with type 2 diabetes and depression across two cohorts. European Journal of Endocrinology. 2022;187(4):567-77.
27. Lin EHB, Rutter CM, Katon W, Heckbert SR, Ciechanowski P, Oliver MM, et al. Depression and Advanced Complications of Diabetes: A prospective cohort study. Diabetes care. 2010;33(2):264–9.
28. Ting RZ, Lau ES, Ozaki R, Lau WW, Kong AP, Luk AO, et al. High risk for cardiovascular disease in Chinese type 2 diabetic patients with major depression--a

7-year prospective analysis of the Hong Kong Diabetes Registry. J Affect Disord. 2013;149(1-3):129-35.
29. McGurnaghan SJ, Blackbourn LAK, Caparrotta TM, Mellor J, Barnett A, Collier A, et al. Cohort profile: the Scottish Diabetes Research Network national diabetes cohort – a population-based cohort of people with diabetes in Scotland. BMJ Open. 2022;12(10):e063046.
30. Scottish Government. Introducing the Scottish Index of Multiple Deprivation 2016. 2016 [Available from: http://www.gov.scot/Resource/0050/00504809.pdf.
31. Walker ER, Druss BG. Mental and Addictive Disorders and Medical Comorbidities. Current Psychiatry Reports. 2018;20(10):86.
32. Campbell I, Campbell H. Mechanisms of insulin resistance, mitochondrial dysfunction and the action of the ketogenic diet in bipolar disorder. Focus on the PI3K/AKT/HIF1-a pathway. Med Hypotheses. 2020;145:110299.
33. Guest PC. Insulin Resistance in Schizophrenia. Adv Exp Med Biol. 2019;1134:1-16.
34. Mitchell AJ, Malone D, Doebbeling CC. Quality of medical care for people with and without comorbid mental illness and substance misuse: systematic review of comparative studies. BJPsych. 2009;194(6):491–9.
35. Knudsen L, Scheuer SH, Diaz LJ, Jackson CA, Wild SH, Benros ME, et al. Indicators of quality of diabetes care in persons with type 2 diabetes with and without severe mental illness: A Danish nationwide register-based cohort study. The Lancet Regional Health - Europe. 2022:100565.
36. Chan JKN, Chu RST, Hung C, Law JWY, Wong CSM, Chang WC. Mortality, Revascularization, and Cardioprotective Pharmacotherapy After Acute Coronary Syndrome in Patients With Severe Mental Illness: A Systematic Review and Meta-analysis. Schizophr Bull. 2022;48(5):981-98.
37. Fleetwood K, Wild SH, Smith DJ, Mercer SW, Licence K, Sudlow CLM, et al. Severe mental illness and mortality and coronary revascularisation following a myocardial infarction: a retrospective cohort study. BMC Med. 2021;19(1):67.
38. Pillinger T, McCutcheon RA, Vano L, Mizuno Y, Arumuham A, Hindley G, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry. 2020;7(1):64-77.
39. Zhu J, Hou W, Xu Y, Ji F, Wang G, Chen C, et al. Antipsychotic drugs and sudden cardiac death: A literature review of the challenges in the prediction, management, and future steps. Psychiatry Res. 2019;281:112598.
40. Greene C, Penny-Ward H, Ionnou MF, Wild SH, Wu H, Smith DJ, et al. Antidepressant and antipsychotic medications and cardiovascular risk in people with diabetes: a systematic review medRxiv. 2023;2023.01.27.23285097.

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

	No 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)
Male	141302 (56.9%)	1590 (60.7%)	498 (41.1%)	3181 (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	206596 (83.3%)	2298 (87.7%)	1108 (91.5%)	7155 (90.5%)
Ethnic minority groups	17734 (7.1%)	149 (5.7%)	53 (4.4%)	331 (4.2%)
Missing	23810 (9.6%)	174 (6.6%)	50 (4.1%)	417 (5.3%)
SIMD quintile				
5 (least deprived)	35517 (14.3%)	169 (6.4%)	139 (11.5%)	683 (8.6%)
4	45019 (18.1%)	275 (10.5%)	178 (14.7%)	1027 (13.0%)
3	50700 (20.4%)	494 (18.8%)	248 (20.5%)	1569 (19.9%)
2	57223 (23.1%)	699 (26.7%)	282 (23.3%)	1986 (25.1%)
1 (most deprived)	59264 (23.9%)	984 (37.5%)	364 (30.1%)	2634 (33.3%)
Missing	417 (0.2%)	0 (0.0%)	0 (0.0%)	4 (0.1%)
History of CVD	36315 (14.6%)	264 (10.1%)	199 (16.4%)	2118 (26.8%)
Modified Charlson Index				
0	205445 (82.8%)	2136 (81.5%)	911 (75.2%)	5117 (64.7%)
1-8	24334 (9.8%)	320 (12.2%)	183 (15.1%)	1660 (21.0%)
>8	18361 (7.4%)	165 (6.3%)	117 (9.7%)	1126 (14.2%)
History of hypertension				
No hypertension	47821 (19.3%)	1086 (41.4%)	354 (29.2%)	1633 (20.7%)
Hypertension	184626 (74.4%)	1320 (50.4%)	797 (65.8%)	5913 (74.8%)
Missing	15693 (6.3%)	215 (8.2%)	60 (5.0%)	357 (4.5%)
History of raised cholesterol				
No high cholesterol	38834 (15.7%)	393 (15.0%)	164 (13.5%)	1025 (13.0%)
High cholesterol	185414 (74.7%)	1967 (75.0%)	950 (78.4%)	6150 (77.8%)
Missing	23892 (9.6%)	261 (10.0%)	97 (8.0%)	728 (9.2%)
HbA1c at diabetes diagnosis				
Mean (SD) (%)	7.6 (1.7)	7.8 (2.0)	7.5 (1.8)	7.6 (1.7)
Mean (SD) (mmol/mol)	60.1 (18.4)	61.9 (21.7)	58.6 (19.3)	59.7 (18.6)
Missing	29868 (12.0%)	355 (13.5%)	130 (10.7%)	887 (11.2%)

	No mental illness (N=248,140)	Schizophrenia (N=2,621)	Bipolar disorder (N=1,211)	Major depression (N=7,903)
History of alcohol use disorder	5774 (2.3%)	451 (17.2%)	180 (14.9%)	1435 (18.2%)
BMI (kg/m^2)				
Median (IQR)	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 kg/m^2	19619 (7.9%)	172 (6.6%)	73 (6.0%)	514 (6.5%)
≥ 25 and < 30 kg/m^2	61693 (24.9%)	453 (17.3%)	216 (17.8%)	1485 (18.8%)
≥ 30 and < 35 kg/m^2	66184 (26.7%)	750 (28.6%)	349 (28.8%)	1970 (24.9%)
≥ 35 and < 40 kg/m^2	36918 (14.9%)	496 (18.9%)	206 (17.0%)	1387 (17.6%)
≥ 40 kg/m^2	27713 (11.2%)	392 (15.0%)	196 (16.2%)	1291 (16.3%)
Missing	36013 (14.5%)	358 (13.7%)	171 (14.1%)	1256 (15.9%)
Smoking				
Never smoked	111183 (44.8%)	669 (25.5%)	368 (30.4%)	2633 (33.3%)
Ex-smoker	85671 (34.5%)	550 (21.0%)	349 (28.8%)	2349 (29.7%)
Current smoker	50364 (20.3%)	1391 (53.1%)	490 (40.5%)	2891 (36.6%)
Missing	922 (0.4%)	11 (0.4%)	4 (0.3%)	30 (0.4%)

***** The statistical models adjust for an ethnicity variable with 4 categories (Asian, Asian Scottish or Asian British; White; Mixed or multiple ethnic groups; any other ethnic group). In this table, the last 3 categories are grouped in order to ensure that this table does not risk the anonymity of individuals by including cells with very small numbers.

IQR = interquartile range; SD = standard deviation

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	Schizophrenia	Bipolar disorder	Major depression
N	248,140	2,621	1,211	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
Number of people with a major CVD event	20,302 (8.7%)	165 (6.6%)	114 (10.0%)	688 (9.7%)
Number of deaths (%)	48,261 (19.4%)	573 (21.9%)	303 (25.0%)	1,892 (23.9%)
Number of 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
Number of people screened at least once (%)	151,347 (93.3%)	1,593 (88.4%)	745 (89.4%)	5,067 (89.9%)
Number of people with referable disease (% of screened)	7435 (4.9%)	50 (3.1%)	25 (3.4%)	152 (3.0%)

* Number of people without a history of a major CVD event at baseline

† Data from the retinopathy screening programme is 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 onwards.

CVD = cardiovascular disease; SD = standard deviation

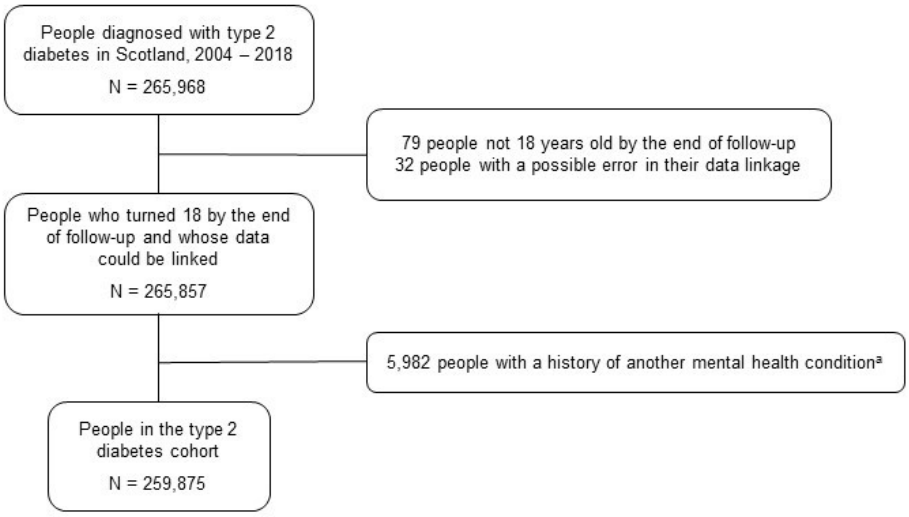
FIGURE LEGENDS

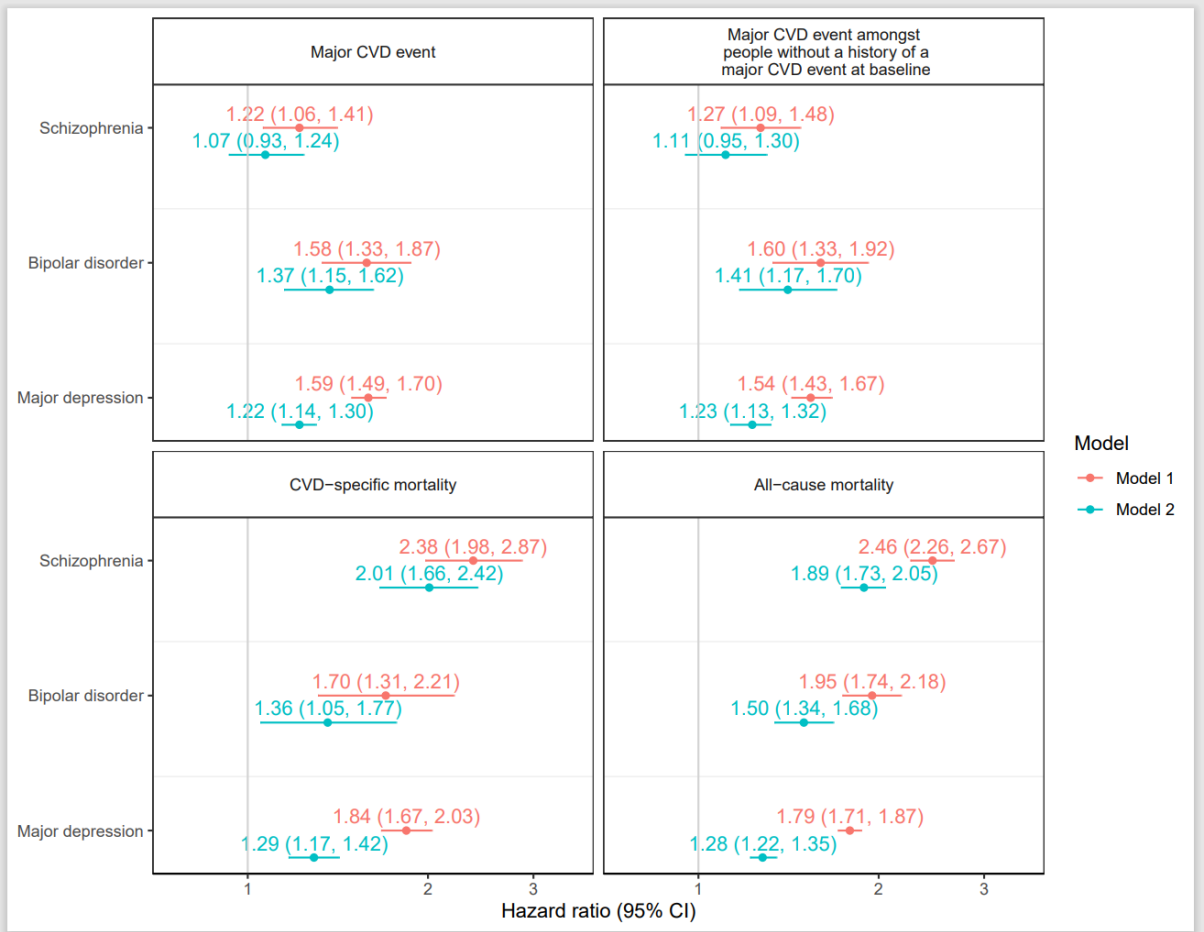
Figure 1: Flow diagram describing the selection of the study population

a. Including other psychoses, other mood disorders, disorders of adult personality and behaviour, eating disorders, neuroses, dissociative and somatoform disorders, behavioural and emotional disorders with onset in childhood and adolescence, non-organic sleep disorders, disorders of psychosocial development and unspecified mental disorders.

Figure 2: Risk of major CVD events, CVD-specific mortality and all-cause mortality in people with a hospital record of severe mental illness versus no mental illness

Estimates 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 HbA1c, body mass index, alcohol use disorder and smoking).
CVD = cardiovascular disease


People diagnosed with type 2 diabetes in Scotland, 2004 – 2018
N = 265,968
79 people not 18 years old by the end of follow-up
32 people with a possible error in their data linkage
People who turned 18 by the end of follow-up and whose data could be linked
N = 265,857
5,982 people with a history of another mental health condition[a]
People in the type 2 diabetes cohort
N = 259,875


Major CVD event
Major CVD event amongst people without a history of a major CVD event at baseline
CVD−specific mortality
All−cause mortality
Schizophrenia
Bipolar disorder
Major depression
1.22 (1.06, 1.41)
1.07 (0.93, 1.24)
1.27 (1.09, 1.48)
1.11 (0.95, 1.30)
1.58 (1.33, 1.87)
1.37 (1.15, 1.62)
1.60 (1.33, 1.92)
1.41 (1.17, 1.70)
1.59 (1.49, 1.70)
1.22 (1.14, 1.30)
1.54 (1.43, 1.67)
1.23 (1.13, 1.32)
2.38 (1.98, 2.87)
2.01 (1.66, 2.42)
2.46 (2.26, 2.67)
1.89 (1.73, 2.05)
1.70 (1.31, 2.21)
1.36 (1.05, 1.77)
1.95 (1.74, 2.18)
1.50 (1.34, 1.68)
1.84 (1.67, 2.03)
1.29 (1.17, 1.42)
1.79 (1.71, 1.87)
1.28 (1.22, 1.35)
1
2
3
Hazard ratio (95% CI)
Model
Model 1
Model 2