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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# Supplementary Table 1: ICD codes for mental health conditions

|  |  |  |  |
| --- | --- | --- | --- |
| **Position in hierarchy** | **Mental health condition** | **ICD-9 codes** | **ICD-10 codes** |
| 1 | Schizophrenia: schizophrenia and schizoaffective disorders | 295.0-295.3,295.6-295.9 | F20, F25 |
| 2 | Other psychoses: schizotypal disorders, acute and transient psychosis, delusional disorders, and other psychotic disorders | 295.4, 295.5,297.0-297.9298.3, 298.4, 298.8, 298.9   | F21-F24, F28, F29 |
| 3 | Bipolar disorder: manic episode or bipolar affective disorder | 296.0296.2-296.6 | F30-F31 |
| 4 | Major depression: depressive episode or recurrent depressive disorder | 296.1298.0, 300.4,  311 | F32-F33 |
| 5 | Other mental health conditions: including other mood disorders, neuroses, dissociative disorders, somatoform disorders, eating disorders, non-organic sleep disorders and other behavioural syndromes associated with physiological disturbances and physical factors, disorders of adult personality and behaviour, disorders of psychological development, behavioural and emotional disorders with onset in childhood and adolescence and unspecified mental disorders | 293.8,296.8, 296.9, 298.1, 298.2,299.0-301.9,302.1-302.9,305.9,306.0-309.9,312.0-315.9316 | F34-F69,F80-F99 |

# Supplementary Table 2: ICD-10 codes for cause-specific mortality

|  |  |  |
| --- | --- | --- |
| **Cause-specific mortality** | **ICD-10 codes** | **Description** |
| CVD-specific mortality | I20-I25 | Ischaemic heart diseases |
| I60-I69 | Cerebrovascular diseases   |
| G45 | Transient cerebral ischaemic attacks and related syndromes |

# Supplementary Table 3: ICD codes for history of CVD and alcohol use disorder

|  |  |  |  |
| --- | --- | --- | --- |
| **Condition** | **Code type** | **Code** | **Description** |
| CVD | ICD-9 | 410-414 | Ischaemic heart disease |
| 430-438 | Cerebrovascular disease |
| ICD-10a | I20-I25 | Ischaemic heart diseases |
| I60-I69 | Cerebrovascular diseases  |
| G45 | Transient cerebral ischaemic attacks and related syndromes |
| Alcohol use disorder | ICD-9 | 291.0 | Delirium tremens |
| 291.1 | Korsakov's psychosis, alcoholic |
| 291.2 | Other alcoholic dementia |
| 291.5 | Alcoholic jealousy |
| 303 | Alcohol dependence syndrome |
| 571.0 | Alcoholic fatty liver |
| 571.1 | Acute alcoholic hepatitis |
| 571.2 | Alcoholic cirrhosis of liver |
| 571.3 | Alcoholic liver damage, unspecified |
| 357.5 | Alcoholic polyneuropathy |
| 425.5 | Alcoholic cardiomyopathy |
| 535.3 | Alcoholic gastritis |
| E947.3 | Drugs, medicaments and biological substances causing adverse effects in therapeutic use: alcohol deterrents |
| ICD-10 | F10.1 | Mental and behavioural disorders due to use of alcohol: Harmful use |
| F10.2 | Mental and behavioural disorders due to use of alcohol: Dependence syndrome |
| F10.3 | Mental and behavioural disorders due to use of alcohol: Withdrawal state |
| F10.4 | Mental and behavioural disorders due to use of alcohol: Withdrawal state with delirium |
| F10.6 | Mental and behavioural disorders due to use of alcohol: Amnesic syndrome |
| K70 | Alcoholic liver disease |
| E24.4  | Alcohol induced Pseudo-Cushing’s syndrome |
| E51.2  | Wernicke’s Encephalopathy |
| G31.2  | Degeneration of nervous system due to alcohol |
| G62.1  | Alcoholic polyneuropathy |
| G72.1  | Alcoholic myopathy |
| I42.6  | Alcoholic cardiomyopathy |
| K29.2  | Alcoholic gastritis |
| K85.2 | Alcohol-induced acute pancreatitis |
| K86.0  | Alcohol-induced chronic pancreatitis |
| O35.4  | Maternal care for (suspected) damage to foetus from alcohol |
| Y57.3  | Drugs, medicaments and biological substances causing adverse effects in therapeutic use: alcohol deterrents |
| Z50.2  | Alcohol rehabilitation |
| Z71.4  | Alcohol abuse counselling and surveillance |

1. Note that these are the same ICD-10 codes used to identify CVD-specific mortality

# Supplementary Text 1: Adaptation of the Charlson Index

We measured comorbidity at the time of diabetes diagnosis using an adaptation of the Charlson Index (1). The Charlson Index is a weighted count of a person’s morbidities. The original index accounted for 19 conditions, with weights approximately equal to the hazard ratio of mortality for people with the condition versus those without the condition.

We based our comorbidity score on a version of the Charlson Index (2) that has been used by NHS Scotland to calculate standardised morality ratios for Scottish hospitals (3). This version is based on only 17 conditions, because the original tumour, leukaemia and lymphoma groups have been combined into a single cancer group. The weights have been updated to reflect current risks of mortality.

We adapted the updated version of the Charlson Index as follows:

* We excluded diabetes and diabetes complications because our intention is measure other comorbidities at the time of diabetes diagnosis.
* We excluded acute myocardial infarction and cerebral vascular accident because these conditions are covered in a separate history of CVD variable.
* We excluded ICD-10 codes K70.2 (alcoholic fibrosis and sclerosis of liver) and K70.3 (alcoholic cirrhosis of liver) from liver disease because these codes are used in the ascertainment of a separate history of alcohol use variable.

We ascertained morbidities from primary and secondary diagnoses in acute hospital records using a 10 year look-back period from the date of diabetes diagnosis. We excluded records before the person’s 18th birthday. We used the ICD-10 codes defined in the updated version of the Charlson Index and mapped the ICD-10 codes to ICD-9 codes. We only included an ICD-9 code if all the conditions it indicated were also indicated by the ICD-10 codes. The table below details the conditions, codes and weights that we used. Each person’s total Charlson Index was calculated by summing the weights associated with their conditions.

**Conditions, ICD codes and weights for the adapted version of the Charlson Index used in this study**

|  |  |  |  |
| --- | --- | --- | --- |
| Condition name | ICD-10 codes | ICD-9 codes | Weight |
| Congestive heart failure | I50 | 428 | 13 |
| Connective tissue disorder | M05, M06.0, M06.3, M06.9, M32, M33.2, M34, M35.3 | 710.0, 710.1, 710.4,714.0, 714.1, 714.2,725 | 4 |
| Dementia | F00, F01, F02, F03, F05.1 | 290, 294.1 | 14 |
| Liver disease | K71.7, K73, K74 | 571.4, 571.5, 571.6 | 8 |
| Peptic ulcer | K25 – K28 | 531 – 534 | 9 |
| Peripheral vascular disease | I71, I73.9, I79.0, R02, Z95.8, Z95.9 | 440, 441.7, 443.9, 785.4, V43.4 | 6 |
| Pulmonary disease | J40-J47, J60-J76 | 490 – 496, 500 – 508 | 4 |
| Cancer | C00 – C76, C80 – C97 | 140 – 195, 199  – 208 | 8 |
| Paraplegia | G04.1, G81, G82.0, G82.1, G82.2 | 342, 344.1 | 1 |
| Renal disease | I12, I13, N01, N03, N05.2-N05.6, N07.2-N07.4, N18, N19, N25 | 403, 404, 580.4, 582,583.1, 583.2, 583.4,585, 586, 588 | 10 |
| Metastatic cancer | C77, C78, C79 | 196-198 | 14 |
| Severe liver disease | K72.1, K72.9, K76.6, K76.7 | 572.2, 572.3, 572.4 | 18 |
| HIV | B20, B21, B22, B23, B24 | 043, 044, 045\* | 2 |

\* The ICD 9 codes were published in 1977, but AIDS and HIV were not discovered until the early 1980s. Prior to 1995 no specific AIDS or HIV codes existed. ICD 9 codes for AIDS and HIV were introduced in 1996.

# Supplementary Text 2: Additional information on derivation of hypertension, high cholesterol, HbA1c and body mass index

We ascertained hypertension, high cholesterol, HbA1c and body mass index (BMI) from SCI-Diabetes using records from within 180 days of type 2 diabetes diagnosis date. We identified hypertension using a combination of systolic and diastolic blood pressure measurements and prescriptions for hypertension medicines. Likewise, we identified high cholesterol using a combination of total cholesterol measurements and prescriptions for cholesterol medication.

For all continuous measurements (systolic blood pressure, diastolic blood pressure, total cholesterol, HbA1c and BMI, if there was more than one record within the window +/- 180 days from type 2 diabetes diagnosis date, we took the median.

# Supplementary Text 3: Multiple imputation

We used multiple imputation by chained equations (MICE) to account for missing data in seven covariates (deprivation, ethnicity, hypertension, high cholesterol, log HbA1c, BMI and smoking), assuming that data was missing at random. The imputation models included the outcomes and all covariates (including the quadratic terms for the continuous variables). We incorporated the survival and competing risk outcomes in the imputation models by including the failure indicators and the Nelson–Aalen estimators of the cumulative hazard functions (4-6). Overall, 29.7% of participants had a missing value for at least one variable. Hence, we conducted 30 imputations (7). Each imputed dataset was analysed and we used Rubin’s rules to pool the results (8).

# Supplementary Figure 1: Flow diagram of the study population - sensitivity analysis (major depression based on psychiatric hospital admission records only)



# Supplementary Table 4: Baseline characteristics of patients with type 2 diabetes, by history of mental health admission – sensitivity analysis (major depression based on psychiatric hospital admission records only)

|  | No mental health condition (N=251,139) | Schizophrenia (N=2,621) | Bipolar disorder (N=1,211) | Major depression (N=4,014) |
| --- | --- | --- | --- | --- |
| Follow-up time (years)[mean (SD)] | 7.1 (4.2) | 6.8 (4.0) | 6.7 (4.0) | 6.8 (4.0) |
| Male | 142477 (56.7%) | 1590 (60.7%) | 498 (41.1%) | 1674 (41.7%) |
| Age at diabetes diagnosis (years) [mean (SD)] | 60.7 (13.4) | 52.1 (12.7) | 57.5 (12.4) | 58.9 (12.2) |
| Ethnicity\* |  |  |  |  |
|  White | 209311 (83.3%) | 2298 (87.7%) | 1108 (91.5%) | 3616 (90.1%) |
|  Ethnic minority groups | 17860 (7.1%) | 149 (5.7%) | 53 (4.4%) | 171 (4.3%) |
|  Missing | 23968 (9.5%) | 174 (6.6%) | 50 (4.1%) | 227 (5.7%) |
| SIMD quintile |  |  |  |  |
|  5 (least deprived) | 35774 (14.2%) | 169 (6.4%) | 139 (11.5%) | 367 (9.1%) |
|  4 | 45430 (18.1%) | 275 (10.5%) | 178 (14.7%) | 511 (12.7%) |
|  3 | 51297 (20.4%) | 494 (18.8%) | 248 (20.5%) | 792 (19.7%) |
|  2 | 57932 (23.1%) | 699 (26.7%) | 282 (23.3%) | 1038 (25.9%) |
|  1 (most deprived) | 60288 (24.0%) | 984 (37.5%) | 364 (30.1%) | 1303 (32.5%) |
|  Missing | 418 (0.2%) | 0 (0.0%) | 0 (0.0%) | 3 (0.1%) |
| History of CVD | 37273 (14.8%) | 264 (10.1%) | 199 (16.4%) | 828 (20.6%) |
| Modified Charlson Index |  |  |  |  |
|  0 | 207218 (82.5%) | 2136 (81.5%) | 911 (75.2%) | 2872 (71.5%) |
|  1-8 | 25041 (10.0%) | 320 (12.2%) | 183 (15.1%) | 705 (17.6%) |
|  >8 | 18880 (7.5%) | 165 (6.3%) | 117 (9.7%) | 437 (10.9%) |
| Hypertension at diabetes diagnosis |  |  |  |  |
|  No hypertension | 48390 (19.3%) | 1086 (41.4%) | 354 (29.2%) | 889 (22.1%) |
|  Hypertension | 186914 (74.4%) | 1320 (50.4%) | 797 (65.8%) | 2935 (73.1%) |
|  Missing | 15835 (6.3%) | 215 (8.2%) | 60 (5.0%) | 190 (4.7%) |
| Cholesterol at diabetes diagnosis |  |  |  |  |
|  No high cholesterol | 39220 (15.6%) | 393 (15.0%) | 164 (13.5%) | 517 (12.9%) |
|  High cholesterol | 187743 (74.8%) | 1967 (75.0%) | 950 (78.4%) | 3149 (78.5%) |
|  Missing | 24176 (9.6%) | 261 (10.0%) | 97 (8.0%) | 348 (8.7%) |
| 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) | 60.0 (18.7) |
|  Missing | 30206 (12.0%) | 355 (13.5%) | 130 (10.7%) | 452 (11.3%) |
| History of alcohol use disorder | 6240 (2.5%) | 451 (17.2%) | 180 (14.9%) | 763 (19.0%) |
| BMI |  |  |  |  |
|  < 25 kg/m2 | 19151 (7.6%) | 160 (6.1%) | 66 (5.5%) | 234 (5.8%) |
|  ≥ 25 and < 30 kg/m2 | 62238 (24.8%) | 453 (17.3%) | 216 (17.8%) | 772 (19.2%) |
|  ≥ 30 and < 35 kg/m2 | 66877 (26.6%) | 750 (28.6%) | 349 (28.8%) | 1087 (27.1%) |
|  ≥ 35 and < 40 kg/m2 | 37440 (14.9%) | 496 (18.9%) | 206 (17.0%) | 706 (17.6%) |
|  ≥ 40 kg/m2 | 28202 (11.2%) | 392 (15.0%) | 196 (16.2%) | 623 (15.5%) |
|  Missing | 36543 (14.6%) | 358 (13.7%) | 171 (14.1%) | 581 (14.5%) |
| Smoking |  |  |  |  |
|  Never smoked | 112183 (44.7%) | 669 (25.5%) | 368 (30.4%) | 1335 (33.3%) |
|  Ex-smoker | 86629 (34.5%) | 550 (21.0%) | 349 (28.8%) | 1145 (28.5%) |
|  Current smoker | 51387 (20.5%) | 1391 (53.1%) | 490 (40.5%) | 1523 (37.9%) |
|  Missing | 940 (0.4%) | 11 (0.4%) | 4 (0.3%) | 11 (0.3%) |

**\*** 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.

# Supplementary Table 5: Risk of major CVD event, all-cause mortality and CVD-specific mortality in people with a history of a severe mental illness versus people without a history of a severe mental illness. Complete case analysis (N = 182,764). Hazard ratios and 95% CIs.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcome | Model | Schizophrenia | Bipolar disorder | Major depression |
| Major CVD event | Model 1 | 1.02 (0.85, 1.23) | 1.41 (1.14, 1.74) | 1.46 (1.34, 1.58) |
| Model 2 | 0.92 (0.77, 1.12) | 1.28 (1.04, 1.58) | 1.14 (1.05, 1.24) |
| Major CVD event amongst people without a history of a major CVD event at baseline | Model 1 | 1.04 (0.86, 1.27) | 1.45 (1.16, 1.81) | 1.41 (1.28, 1.55) |
| Model 2 | 0.93 (0.77, 1.14) | 1.30 (1.04, 1.62) | 1.14 (1.04, 1.26) |
| All-cause mortality | Model 1 | 2.29 (2.06, 2.55) | 2.00 (1.74, 2.29) | 1.69 (1.59, 1.79) |
| Model 2 | 1.81 (1.63, 2.02) | 1.59 (1.39, 1.83) | 1.22 (1.15, 1.30) |
| CVD-specific mortality | Model 1 | 2.19 (1.72, 2.79) | 1.59 (1.13, 2.22) | 1.80 (1.58, 2.04) |
| Model 2 | 1.92 (1.50, 2.45) | 1.36 (0.97, 1.91) | 1.27 (1.12, 1.45) |

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).

# Supplementary Table 6: Risk of major CVD event, all-cause mortality and CVD-specific mortality in people with a history of a severe mental illness versus people without a history of a severe mental illness. Sensitivity analysis (major depression based on psychiatric hospital admission records only) (N = 258,985). Hazard ratios and 95% CIs.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcome | Model | Schizophrenia | Bipolar disorder | Major depression |
| Major CVD event | Model 1 | 1.22 (1.05, 1.41) | 1.57 (1.32, 1.86) | 1.48 (1.34, 1.62) |
| Model 2 | 1.07 (0.92, 1.24) | 1.37 (1.15, 1.62) | 1.21 (1.11, 1.34) |
| Major CVD event amongst people without a history of a major CVD event at baseline | Model 1 | 1.27 (1.08, 1.48) | 1.59 (1.32, 1.91) | 1.44 (1.30, 1.60) |
| Model 2 | 1.10 (0.94, 1.29) | 1.41 (1.17, 1.69) | 1.20 (1.08, 1.33) |
| All-cause mortality | Model 1 | 2.44 (2.25, 2.65) | 1.93 (1.72, 2.16) | 1.70 (1.59, 1.81) |
| Model 2 | 1.88 (1.73, 2.05) | 1.49 (1.33, 1.68) | 1.30 (1.22, 1.38) |
| CVD-specific mortality | Model 1 | 2.37 (1.97, 2.85) | 1.69 (1.30, 2.19) | 1.66 (1.46, 1.90) |
| Model 2 | 2.00 (1.66, 2.41) | 1.37 (1.05, 1.78) | 1.29 (1.12, 1.48) |

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).

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