BMJ Open

Predictors of cerebrovascular event reoccurrence in patients with depression: a retrospective cohort study

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To cite: Cai W, Mueller C, Shetty H, *et al*. Predictors of cerebrovascular event reoccurrence in patients with depression: a retrospective cohort study. *BMJ Open* 2020;**10**:e031927. doi:10.1136/bmjopen-2019-031927

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-031927).

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Received 26 May 2019
Revised 22 November 2019
Accepted 25 November 2019

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ABSTRACT

Objectives To identify predictors of recurrent cerebrovascular morbidity in a cohort of patients with depression and a cerebrovascular disease (CBVD) history.

Methods We used the Maudsley Biomedical Research Centre Case Register to identify patients aged 50 years or older with a diagnosis of depressive disorder between 2008 and 2017 and a previous history of hospitalised CBVD. Using depression diagnosis as the index date we followed patients until first hospitalised CBVD recurrence or death due to CBVD. Sociodemographic data, symptom and functioning scores of Health of the Nation Outcome Scales, medications and comorbidities were extracted and modelled in multivariate survival analyses to identify predictors of CBVD reoccurrence.

Results Of 1292 patients with depression and CBVD (mean age 75.6 years; 56.6% female), 264 (20.4%) experienced fatal/non-fatal CBVD recurrence during a median follow-up duration of 1.66 years. In multivariate Cox regression models, a higher risk of CBVD recurrence was predicted by older age (HR, 1.02; 95% CI, 1.01 to 1.04) (p=0.002), physical health problems (moderate to severe HR, 2.47; 95% CI, 1.45 to 4.19) (p=0.001), anticoagulant (HR, 1.40; 95% CI, 1.01 to 1.93) (p=0.041) and antipsychotic medication (HR, 0.66; 95% CI 0.44 to 0.99) (p=0.047). Neither depression severity, mental health symptoms, functional status, nor antidepressant prescribing were significantly associated with CBVD recurrence.

Conclusions Approximately one in five patients with depression and CBVD experienced a CBVD recurrence over a median follow-up time of 20 months. Risk of CBVD recurrence was largely dependent on age and physical health rather than on severity of depressive symptoms, co-morbid mental health or functional problems, or psychotropic prescribing.

Strengths and limitations of this study

- A relatively large sample was generated from a specialist mental care provider.
- Near-complete follow-up was achieved through linkage to national hospitalisation records.
- The cohort was from a secondary care sample, thus limiting generalisability to community cases of depressive disorder.
- Outcome ascertainment was limited to International Classification of Diseases-10 (ICD-10) diagnoses applied to hospitalisation episodes, and types of CBVD could not be differentiated.
- The measurement of some potential risk factors for adverse outcomes such as health behaviours, level of education, socioeconomic status and comorbidity ascertainment was limited.

INTRODUCTION

Depression is common in patients with cerebrovascular diseases (CBVDs) and predicts adverse outcomes such as physical limitations and poor quality of life, as well as higher healthcare costs.[1 2] CBVD includes stroke, carotid stenosis, vertebral/intracranial stenosis, aneurysms and vascular malformations, among which stroke has the highest incidence rate.[3] Two meta-analyses have concluded that depression is present in approximately 30% of stroke survivors.[4 5]

Few studies have explored stroke recurrence in stroke survivors with depression,[6–9] and these have reported inconsistent results: three studies[6 8 9] found that the presence of depression was associated with an increased hazard for stroke recurrence, while Ayerbe *et al*[7] found that depression at 3 months after stroke was not associated with higher risk of total stroke recurrence over a 5-year follow-up (HR: 0.98). Furthermore, although a number of previous studies have reported findings on possible risk factors such as older age,[8] physical illness,[10] medications[9 11 12] and comorbidities[13–15] predicting first or recurrent CBVD in community samples, few have investigated prediction in people with both depression and CBVD history, despite the likelihood that this is a high risk group. Given this gap in evidence, a cohort study was assembled to investigate potential predictors of CBVD recurrence in a cohort of patients with depression and a history of CBVD.

METHODS

Study setting and data source

We conducted a retrospective observational study using data from the South London

and Maudsley NHS Foundation Trust (SLaM) Biomedical Research Centre (BRC) case register. SLaM serves a geographic catchment of four South London boroughs (Lambeth, Lewisham, Southwark and Croydon) with a population of over 1.3 million residents. The data for this study were extracted using the clinical record interactive search (CRIS) application, which renders a de-identified version of SLaM's electronic health record accessible for research projects within a robust and patient-led governance framework.[16 17] CRIS has been linked to a number of other informative data sources, including data on all hospitalisations regardless of specialty or location in England (national hospital episode statistics (HES)). The SLaM BRC case register contains data on more than 400 000 patients with a range of mental disorders and CRIS-supported investigations have included several longitudinal cohort studies of depression and other mental disorders of later life.[18–20] The database has full approval for secondary analysis from Oxford Research Ethics Committee (Oxford Research Ethics Committee C, reference 18/SC/0372). Data from CRIS have been extensively supplemented through natural language processing applications using generalised architecture for text engineering (GATE) software, applying information extraction techniques to derive structured information from the text fields held in the mental health record.[17 21]

Participants

All patients aged 50 years or older, who received a depressive disorder diagnosis according to International Classification of Diseases-10 (ICD-10) criteria[22] (F32x and F33x ICD-10 codes) from SLaM services between 1 January 2008 and 31 March 2017, were identified and were restricted to those who had a hospitalisation with CBVD (I60x-I69x ICD-10 codes in HES) prior to the depression diagnosis. Date of first depression diagnosis after the age of 50 served as the index date for analysis. We ascertained the first depression diagnosis within the secondary mental healthcare service but were unable to determine the length/duration of depressive symptoms before this diagnosis was established.

Outcomes

For outcomes, the linkage with HES was used to ascertain CBVD re-hospitalisation until March 2017. A hospitalised non-fatal CBVD recurrence was defined when an ICD-10 code of I60x-I69x was recorded as a primary or secondary diagnosis for a hospital admission. Fatal CBVD recurrence was ascertained if an underlying cause of death with an ICD-10 code of I60x-I69x was recorded on the patient's death certificate. The two outcomes were combined to define CBVD recurrence and the sample was followed until the first fatal or non-fatal CBVD event, death from any other cause or a censoring point on 31 March 2017.

Predictors

Independent variables were extracted from CRIS based on values recorded closest to the index date of first depression diagnosis. Extracted demographic information included age (at index date), gender, ethnic group, cohabiting status and index of multiple deprivation (IMD).[23] Ethnic group was extracted from structured fields and grouped into white and non-white. Cohabiting status was dichotomised into cohabiting (civil partnership, married, cohabiting) and non-cohabiting (single, divorced, civil partnership dissolved, widowed, separated). The IMD reflects neighbourhood-level deprivation, derived from 2011 Census data across several domains including income, employment, health, education, barriers to housing and services, living environment and crime,[23] and applied to lower super output area level.

Mental, physical and functional problems were identified via the Health of the Nation Outcome Scales 6 months before and after the index date, which are routinely recorded at significant patient encounters in UK mental healthcare.[24] We included items measuring problematic agitation, self-injury, substance use, cognitive impairment, psychosis, depressed mood, physical illness, relationships, activities of daily living (ADL) problems, living conditions and occupation/activities. Items are scored between 0 (no problem) and 4 (moderate-severe problem). Of these, scores of depressed mood were classified into 'minor or transient changes in mood' (score 0–1), 'definite depression on subjective and objective measures' (score 2) and 'marked or severe depressive symptoms' (score 3–4). Besides, we classified scores of physical illness/disability into 'No or minor problem' (score 0–1), 'mild problem' (score 2) and 'moderate to severe problem' (score 3–4). Scores of the other scales were dichotomised into 'no or mild problem' (score 0–1) and 'problem present' (score 2–4) to facilitate interpretation.

We further ascertained medications recorded within a time window from 6 months before to 6 months after the index date through a GATE-supported natural language processing algorithm,[17 21] supplemented by mentions in relevant structured fields from the record, as follows: antidepressants, anticoagulants, antihypertensives, antihyperglycaemics, antipsychotics, lipid lowering medication. Antidepressants were further categorised as serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and mirtazapine. We also calculated the total number of different medications prescribed and ascertained the presence or not of recorded diabetes in the mental health record. The 6-month window around the index date was chosen, as medication prescription is not always recorded close to the index date in routinely collected data, and ascertainment in this window has provided good predictive validity in previous studies from this data source.[18 25 26]

Finally, hospitalisation records were used to ascertain whether the patient had a hospitalisation prior to the index depression diagnosis for which non-CBVD cardiovascular disease was coded as a discharge diagnosis (ICD-10 codes I00x-52x & I70x-I99x).

Statistical analysis

We used STATA software (V.13) in all statistical analyses with a significance level of 5%. Demographic and clinical characteristics were initially compared by outcome status using t tests or $\chi 2$ tests as appropriate. Next, Cox proportional HRs and 95% CI were calculated for potential risk factors affecting time to the first fatal or non-fatal stroke reoccurence. Variables of interest (predictors/risk factors for CBVD reoccurrence) were examined in multivariate models: first controlling for age and gender (Model I), then controlling for age, gender, ethnic group, cohabiting status, IMD score, depressed mood and physical illness problem scores (Model II) and finally all covariates were included (Model III) to determine independent associations. In our study sample, 28% had missing data on at least one of the other covariates. Applying an assumption of missingness at random, we imputed missing values using chained equations to maximise statistical power.[27] Using the *mi* package in STATA we created 28 imputed data sets, replacing missing values through simulated values assembled from all potential covariates and outcome values. The number of complete imputed data sets was based on the rule of thumb that the number of imputations ought to be at least equal to the proportion of incomplete cases.[28 29] Rubin's rules[30] were applied to combine coefficients in final analyses.

Patient and public involvement

A patient-led committee provides operational oversight of the CRIS resource and ensures that the proposed study has both scientific value as well as benefit for patients and carers.[16 17] The project was approved by this committee with an outline of the proposed analysis, including data linkages. There was no further patient and public involvement in the design of this register-based study.

RESULTS

Sample characteristics of the study population

During the observation period 10 892 patients aged over 50 years old with a diagnosis of depression were identified. Of these, 1292 had a previous history of hospitalised CBVD and these comprised the sample for final analysis. Mean age at depression diagnosis was 75.6 (SD: 11.5) years and 56.6% of the sample were women. Of the analysed sample, 264 (20.4%) had a recorded CBVD recurrence within a median follow-up period of 1.66 years (IQR: 0.49–3.86 years; maximum: 9.24 years) representing an incidence rate of 84.2 per 1000 person years. In 83 (31.4% of 264 patients with CBVD reoccurence) this first CBVD recurrence was fatal.

Table 1 presents sample characteristics grouped according to the presence of cerebrovascular reoccurence in the follow-up period. Patients who suffered from CBVD recurrence were more likely to be cohabiting, to have worse physical health, more difficulties with ADL and were more frequently receiving anticoagulants and lipid-lowering medication, but less frequently recorded with substance use or receiving mirtazapine.

Predictors of cerebrovascular recurrence

HRs for potential predictors of CBVD recurrence are presented in table 2. In models adjusted for age, gender, ethnic group, cohabiting status, deprivation index, severity of depression and physical health problems (Model II), older age at depression diagnosis, mild and moderate-severe physical illness, anticoagulant medication and lipid-lowering medications were associated with a higher risk of CBVD recurrence. In the fully adjusted model (Model III; using all potential predictors) older age, moderate-severe physical health problems and anticoagulant medication remained statistically significant predictors of CBVD recurrence. Notably antipsychotic prescription was associated with a borderline significant lower risk of these outcomes, while no significant associations were found in relation to other medications, depression severity, other psychiatric symptoms or functional problems.

DISCUSSION

In a large sample of more than a thousand patients with a clinical diagnosis of depression and a past record of hospitalised CBVD, fatal/non-fatal recurrence of CBVD occurred in one in five patients over a median 20-month follow-up period. CBVD recurrence was independently predicted by older age, moderate-severe physical illness/disability and anticoagulant prescription in a fully adjusted model, while antipsychotic prescription was associated with lower risk. No evidence was found that key clinical parameters (eg, depression severity), social/functional problems (eg, relationship problems, ADL problems, living condition problems, problems of occupation/activities) or antidepressant use (SNRIs, SSRIs, TCAs) and non-CVD circulatory diseases were independently associated with CBVD recurrence.

Older age was identified as an independent risk factor for the outcomes of interest, consistent with previous reports for stroke reoccurrence[8]; however, female gender was not a significant predictor of stroke reoccurrence. An interesting finding in our study was the lack of association of depression severity with CBVD recurrence, which contrasts with several previous reports of associations between post-CBVD depression with recurrent CBVD.[6 8 9] Depression after stroke is recognised to be associated with dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, which accentuates inflammation, consequently increasing risk of stroke recurrence.[31–33] However, the fact that the patients in our cohort were receiving specialist mental healthcare and intervention might have diluted any association between depression severity and fatal/non-fatal CBVD recurrence; alternatively, the HoNOS scale chosen for approximating severity may not have been sufficient to pick up an independent effect on outcome.

Table 1 Sample characteristics by cerebrovascular recurrence status

Risk factors	Whole cohort (n=1292)	Recorded CBVD recurrence (n=264)	No recorded CBVD recurrence (n=1028)	P value*
Sociodemographic status†				
Mean age (SD)	75.6 (11.5)	76.3 (10.8)	75.4 (11.6)	0.295
Female gender, %	56.6	54.6	57.1	0.455
Non-white ethnic group, %‡	23.9	26.5	23.2	0.255
Cohabiting status,%§	32.9	39.0	31.3	**0.022**
Mean IMD score (SD)‡	28.1 (12.2)	28.2 (12.8)	28.1 (12.0)	0.947
HoNOS symptoms/disorders, %¶**				
Agitation	15.2	11.2	16.3	0.056
Self-injury	10.7	7.1	11.6	0.053
Substance use	5.2	1.8	6.1	**0.010**
Cognitive problem	41.2	37.8	42.1	0.255
Hallucination problem	10.3	8.2	10.8	0.248
Depressed mood				0.097
Minor or transient changes in mood	29.5	26.5	30.2	
Definite depression on subjective and objective measures	39.9	46.2	38.2	
Marked or severe depressive symptoms	30.7	27.4	31.5	
Physical illness or disability				**0.001**
No or minor problem	14.8	8.9	16.3	
Mild problem	23.5	19.2	24.7	
Moderate-severe problem	61.7	71.9	59.0	
HoNOS functional problems, %¶**				
Relationship problem	21.6	17.2	22.7	0.075
Activity of daily living problem	70.9	78.3	68.9	**0.007**
Living condition problem	15.4	17.5	14.9	0.350
Problem of occupation/activities	42.2	43.8	41.7	0.584
Medication prescription¶				
Anticoagulant, %	37.7	45.5	35.7	**0.004**
Antihypertensive, %	43.0	45.8	42.3	0.303
Antihyperglycaemic, %	11.2	14.0	10.4	0.097
Antipsychotic, %	17.5	13.6	18.5	0.064
Antidepressant, %	83.4	83.7	83.4	0.893
Mirtazapine, %	39.2	33.3	40.8	**0.028**
SNRI, %	9.9	8.3	10.3	0.337
SSRI, %	53.1	56.8	52.1	0.174
TCA, %	9.6	11.4	9.1	0.275
Lipid lowering, %	37.5	43.2	36.0	**0.031**
Number of medications (median (IQR))	4 (1–9)	5 (1–9)	4 (1–9)	0.724
Comorbidities, %				
Non-CBVD circulatory diseases ††	75.9	76.5	75.8	0.803
Diabetes mellitus ¶	13.0	16.3	12.2	0.075

Bold values indicate statistical significance: P<0.05.
*t test or χ^2 test; due to skewness Wilcoxon rank sum test was applied for number of medications.
†At the time of depression diagnosis.
‡Missing data:<5%.
§Missing data: 5%–10%.
¶Six months before or after the time of depression diagnosis.
**Missing data:>10%.
††Any time before the time of depression diagnosis.
CBVD, cerebrovascular disease; HoNOS, Health of the Nation Outcome Scales; IMD, index of multiple deprivation; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants.

Table 2 Adjusted Cox regression models showing HRs for CBVD recurrence

Risk factors	Model I	P value	Model II	P value	Model III	P value
Sociodemographic status‡						
Age (1-year increase)	**1.02 (1.01–1.04)**	**<0.001**	**1.03 (1.02–1.04)**	**<0.001**	**1.02 (1.01–1.04)**	**0.002**
Female gender	0.79 (0.62–1.01)	0.059	0.80 (0.63–1.02)	0.077	0.80 (0.62–1.03)	0.078
Non-white ethnic group	1.26 (0.95–1.66)	0.107	1.22 (0.92–1.61)	0.175	1.10 (0.81–1.48)	0.556
Cohabiting status	**1.41 (1.09–1.82)**	**0.009**	1.29 (0.99–1.68)	0.056	1.27 (0.97–1.67)	0.085
IMD score (10 unit increase)	1.01 (0.92–1.12)	0.777	1.01 (0.91–1.12)	0.886	0.97 (0.88–1.08)	0.625
HoNOS symptoms/disorders†						
Agitation	0.71 (0.47–1.06)	0.096	0.67 (0.45–1.02)	0.061	0.72 (0.45–1.13)	0.150
Self-injury	0.67 (0.40–1.13)	0.134	0.73 (0.43–1.23)	0.240	0.75 (0.44–1.28)	0.290
Substance use	**0.38 (0.15–0.96)**	**0.041**	0.40 (0.16–1.02)	0.055	0.43 (0.17–1.12)	0.084
Cognition	1.07 (0.82–1.40)	0.619	1.03 (0.78–1.35)	0.860	0.98 (0.73–1.32)	0.907
Psychosis	0.94 (0.58–1.54)	0.812	0.94 (0.58–1.54)	0.813	1.07 (0.64–1.79)	0.803
Depressed mood						
Minor or transient changes in mood	Reference		Reference		Reference	
Definite depression on subjective and objective measures	**1.50 (1.10–2.04)**	**0.011**	1.35 (0.99–1.85)	0.059	1.27 (0.92–1.75)	0.149
Marked or severe depressive symptoms	1.18 (0.83–1.66)	0.360	0.98 (0.69–1.39)	0.902	0.97 (0.66–1.42)	0.870
Physical illness or disability						
No or minor problem	Reference		Reference		Reference	
Mild problem	**1.79 (1.05–3.03)**	**0.032**	**1.76 (1.03–2.99)**	**0.038**	1.64 (0.94–2.85)	0.080
Moderate-severe problem	**3.14 (1.97–5.00)**	**<0.001**	**2.95 (1.83–4.76)**	**<0.001**	**2.47 (1.45–4.19)**	**0.001**
HoNOS functional problems†						
Relationship problem	0.81 (0.56–1.16)	0.242	0.76 (0.53–1.10)	0.148	0.74 (0.50–1.11)	0.151
Activity of daily living problem	**1.75 (1.28–2.39)**	**<0.001**	1.28 (0.91–1.80)	0.154	1.30 (0.90–1.87)	0.159
Living condition problem	1.32 (0.92–1.90)	0.131	1.18 (0.80–1.72)	0.404	1.25 (0.85–1.86)	0.260
Problem of occupation/activities	1.25 (0.96–1.63)	0.092	1.07 (0.81–1.41)	0.634	1.08 (0.80–1.47)	0.601
Medication prescription†						
Anticoagulant	**1.41 (1.10–1.80)**	**0.006**	**1.40 (1.09–1.79)**	**0.008**	**1.40 (1.01–1.93)**	**0.041**
Antihypertensive	1.12 (0.88–1.43)	0.367	1.14 (0.89–1.45)	0.312	0.89 (0.63–1.24)	0.487
Antihyperglycaemic	1.40 (0.99–1.98)	0.061	1.25 (0.87–1.79)	0.224	0.89 (0.57–1.40)	0.623
Antipsychotic	**0.69 (0.48–0.98)**	**0.037**	0.74 (0.52–1.06)	0.102	**0.66 (0.44–0.99)**	**0.047**
Antidepressant	1.17 (0.84–1.62)	0.362	1.09 (0.78–1.53)	0.600	1.04 (0.63–1.70)	0.887
Mirtazapine	0.91 (0.70–1.18)	0.488	0.94 (0.73–1.23)	0.667	0.94 (0.68–1.31)	0.735
SNRI	0.71 (0.46–1.10)	0.123	0.80 (0.52–1.25)	0.334	0.84 (0.52–1.36)	0.487
SSRI	1.18 (0.92–1.50)	0.185	1.11 (0.87–1.42)	0.402	1.01 (0.71–1.46)	0.938
TCA	1.43 (0.98–2.10)	0.066	1.37 (0.93–2.00)	0.112	1.39 (0.91–2.10)	0.127
Lipid-lowering medication	1.22 (0.95–1.55)	0.114	**1.29 (1.01–1.66)**	**0.044**	1.13 (0.80–1.61)	0.484
Number of medications	1.01 (0.98–1.03)	0.548	1.01 (0.99–1.03)	0.381	1.01 (0.97–1.04)	0.743
Comorbidities						
Non-CBVD circulatory diseases*	1.20 (0.90–1.60)	0.210	1.03 (0.77–1.38)	0.829	1.02 (0.76–1.38)	0.887
Diabetes mellitus†	**1.56 (1.12–2.16)**	**0.008**	1.38 (0.98–1.96)	0.065	1.47 (0.98–2.19)	0.061

Bold values indicate statistical significance: p<0.05; the numbers in brackets represent 95% CI.
Model I—variable of interest (risk factor) controlling for age and gender.
Model II—variable of interest (risk factor) controlling for age, gender, ethnic group, cohabiting status, IMD score, depressed mood, physical illness and disability.
Model III—adjusted for all the variables.
*Any time before the time of depression diagnosis.
†Six months before and after the time of depression diagnosis.
‡At the time of depression diagnosis.
CBVD, cerebrovascular disease; HoNOS, Health of the Nation Outcome Scales; IMD, index of multiple deprivation; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants.

We also found that physical illness or disability significantly predicted CBVD reoccurence, in line with conclusions from a previous meta-analysis[10] that history of stroke associated with worse physical state was associated with higher risk of recurrent ischaemic stroke (pooled risk ratio (RR): 2.5, 95% CI, 2.1 to 3.1). In terms of functional scores, relationship problems were not associated with recurrent CBVD in the fully adjusted model, although it is possible that lack of support may prompt higher independence, and reduced unhealthy behaviours, reducing risk of relapse.[34]

We found that anticoagulant prescription was an independent predictor of adverse cerebrovascular outcomes, which is consistent with a previous finding of an association between anticoagulants and secondary haemorrhagic stroke.[11] Of interest is the finding that antipsychotic prescription was associated with a small, but statistically significant (p=0.047) reduced risk of CBVD recurrence. This is surprising as previous studies have suggested an antipsychotic-related increased stroke risk in unselected primary care populations,[12] as well as the well-documented antipsychotic-associated stroke risk in patients with dementia.[35] This raises the possibility that addressing target symptoms such as psychosis or agitation related to depression and CBVD might be associated with benefits that outweigh potential risks; however, this clearly requires further investigation. Although mirtazapine has also been associated with a more benign cardiovascular risk profile[36] and less blood-thinning effects than SSRIs,[37] thus theoretically reducing risk of further haemorrhagic stroke, we found no evidence of a significant association in our cohort. However, antidepressants were not significantly associated with higher risk of stroke recurrence, consistent with a previous study.[9] Oza *et al*[14] recommended use of lipid-lowering medication to lower the risk of recurrent stroke; however, we found that lipid-lowering medication was if anything associated with a significantly increased risk for CBVD recurrence in Model II, which might be explained by a previous finding that 5-year use of statin therapy increased the risk of haemorrhagic stroke.[38] In line with previous studies,[13–15] we found higher prevalences of other comorbidities including diabetes (0.7% higher) and non-CBVD circulatory diseases (4.1% higher) in the cohort with recurrent CBVD than those without CBVD recurrence; however, these were not independent in the fully adjusted model, and the measure of global health status in the HoNOS showed a stronger and more consistent association.

Strengths of our study included the relatively large sample from a specialist mental care provider and the near completeness of follow-up achieved through linkage to national hospitalisation. When interpreting the findings, some limitations should, however, be noted. First, the cohort in this study comprises patients receiving secondary mental healthcare and are thus likely to have relatively severe and/or treatment-resistant syndromes compared with community cases, limiting generalisability. Second, we were not able to distinguish between different subtypes of cerebrovascular diseases, most notably not between ischaemic and haemorrhagic events, which have different mechanisms and treatment approaches (eg, anticoagulants); non-CBVD circulatory diseases as comorbidities were also not characterised into specific conditions. Third, other potential risk factors for outcomes of interest were not directly captured, such as obesity, smoking, alcohol use, hyperlipidaemia, antiplatelet medications, health behaviours or level of education and socioeconomic status was only approximated through an index of neighbourhood-level deprivation.[23] Fourth, we were unable to present data on the duration of depressive symptoms before patients entered the cohort. As this is a cohort under a specialist mental health service, primary care providers might have differing thresholds for referring into specialist psychiatric care.

Fifth, while we are able to capture through free-text and structured fields which medications a patient is prescribed around index date, we have no information whether they were adhering to their medication regime over the study period. Finally, comorbidity ascertainment was limited to hospitalisation discharge diagnoses and the relatively crude HoNOS physical illness subscale. However, although the latter as is relatively brief without details on the specific long-term conditions defining its score, it has been shown to have strong predictive validity for adverse outcomes in this data source.[25 26]

CONCLUSIONS/RELEVANCE

In patients with a diagnosis of depression and previous hospitalised CBVD, risk of a recurrent CBVD event was largely predicted by age, worse general physical health, and anticoagulant prescription rather than mental health-related factors such as severity of depressive symptoms, comorbid mental disorders, functional problems or psychotropic prescribing. Considering the potential for preventing CBVD recurrence, it may be more appropriate to focus on improving physical health in people with depression, or at least focusing known stroke prevention initiatives on the groups with worse general health, although any interventions need to be developed to acceptable levels of feasibility and acceptability, followed by formal evaluation of efficacy.

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Contributors RS, WC and CM conceptualised the study. HS and GP contributed to data acquisition. RS, WC and CM designed the analyses, and CM performed the analyses. WC drafted the manuscript. All authors revised the manuscript for important intellectual content.

Funding WC is supported by China Scholarship Council and postgraduate innovation training program, Shanghai University of traditional Chinese Medicine (Grant No. Y201805). CM, GP and RS are funded in part by the National Institute for Health Research Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London.

Competing interests RS has received research funding from Roche, GSK, Takeda and Janssen.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article.

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