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Prevalence of pre-stroke depression and its association with post-stroke depression; a systematic review and meta-analysis.

Cover Title: Pre-stroke depression: a systematic review.

Author List: Martin Taylor-Rowan¹, Oyiza Momoh¹, Luis Ayerbe², Jonathan J Evans³, David J Stott¹ & Terence J Quinn¹

1. Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK
2. Centre of Primary Care and Public Health, Queen Mary University of London, UK
3. Institute of Health and Wellbeing, University of Glasgow, UK

Correspondence to:

Martin Taylor-Rowan
Institute of Cardiovascular and Medical Sciences, University of Glasgow
New Lister Building, Glasgow Royal Infirmary
Glasgow, UK G4 0SF
Email: m.taylor-rowan.1@research.gla.ac.uk
Tel: +44 141 211 8510

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Tables/Illustrations:

Table 1. Summary of included studies describing pre-stroke depression

Table 2. Risk of bias assessment for studies describing prevalence of pre-stroke depression

Table 3. Risk of bias assessment of multiple logistic regression models employed to evaluate pre-stroke depression/post-stroke depression association

Figure 1. Flow chart of systematic search

Figure 2. Forest plot of pooled pre-stroke depression prevalence

Figure 3. Forest plot of prevalence by assessment method

Figure 4. Funnel plot assessing publication bias of odds ratio data reported in studies

Figure 5. Forest plot of odds ratios for developing post-stroke depression (PSD) based upon presence of pre-stroke depression

Keywords

- Pre-stroke depression
- Post-stroke depression
- Stroke
- Risk
- Prevalence

Abstract

Background: Depression is a common post-stroke complication. Pre-stroke depression may be an important contributor, however the epidemiology of pre-stroke depression is poorly understood. Using systematic review and meta-analysis we described prevalence of pre-stroke depression and its association with post-stroke depression.

Methods: We searched multiple cross-disciplinary databases from inception to July 2017 and extracted data on prevalence of pre-stroke depression and association with post-stroke depression. We assessed risk of bias using validated tools. We described summary-estimates of prevalence and summary-odds-ratio for association with post-stroke depression, using random effects models. We performed subgroup-analysis describing effect of depression assessment method. We used a funnel plot to describe potential publication bias. Strength of evidence presented in this review was summarised via 'GRADE'.

Results: Of 11884 studies identified, 29 were included (total participants n=164993). Pre-stroke depression pooled-prevalence was 11.6%(95%CI:9.2-14.7);range:0.4%-24%(I^2 :95.8). Prevalence of pre-stroke depression varied by assessment method ($p=0.02$) with clinical interview suggesting greater pre-stroke depression prevalence (~17%) than case-note review (9%) or self-report (11%). Pre-stroke depression was associated with increased odds of post-stroke depression; summary OR:3.0(95%CI:2.3-4.0). All studies were judged to be at risk of bias: 59% of included studies had an uncertain risk of bias in stroke assessment; 83% had high or uncertain risk of bias for pre-stroke depression assessment. Funnel plot indicated no risk of publication bias. Strength of evidence based on GRADE was 'very low'.

Conclusions: One-in-six stroke patients have had pre-stroke depression. Reported rates may be routinely underestimated due to limitations around assessment. Pre-stroke depression significantly increases odds of post-stroke depression.

Protocol identifier: PROSPERO identifier: CRD42017065544

INTRODUCTION

Depression is the most common psychological consequence of a stroke. Depression after stroke (post-stroke depression) occurs in around half of all stroke patients (Ayerbe et al., 2013). This figure contrasts with the 12% mood disorder prevalence reported in the general population (Kessler et al., 2009). The presence of post-stroke depression is associated with adverse outcomes including increased mortality, functional impairment and institutionalisation (Williams et al., 2004). These associations may arise due to a combination of differences in comorbidities, lifestyle factors, neurobiological factors such as immunologic and inflammatory disorders, and reduced compliance with medication or post-stroke therapy (Ayerbe et al., 2014; Gianotti et al., 2001).

In order to better understand the natural history and mechanistic development of post-stroke depression, it is important to have an understanding of pre-stroke mood problems. Moreover, knowledge of pre-stroke depression may aid treatment decisions and guide policy regarding, for instance, risk factor screening (Towfighi et al., 2016). However, prevalence rates of pre-stroke depression are not well established and highly cited papers on the topic have reported differing estimates. Reported rates of pre-stroke depression prevalence within studies have ranged from <1% - 52% (Liu et al., 2017; Wulsin et al 2001). This stark variability in reported rates may in part reflect differing assessment methods employed. Indeed, when utilising the same patient cohort, but adopting differing pre-stroke depression assessment methods, McCarthy et al., (2016) and Wulsin et al., (2001) reported differing rates (13% vs 52%).

Pre-stroke depression is often cited as a risk factor for post-stroke depression (DeRyck et al., 2014; Kutlubayev & Hackett, 2014; Robinson & Jorge 2016); yet there is also inconsistency in this regard. Several recent studies (DeRyck et al., 2013; Lewin-Richter et al., 2015; Schottke & Giabbiconi, 2015; White et al., 2014) have failed to find significant associations between pre-stroke depression and post-stroke depression, prompting suggestions that no meaningful risk association actually exists (Schottke & Giabbiconi, 2015). It is currently unclear why some studies have found associations between pre-stroke depression and post-stroke depression, where others have failed. Inadequate regression-model power and differences in covariate control or assessment method may be contributing factors to the inconsistency.

In a literature that is seemingly disparate with potentially biased papers, a comprehensive review, critical appraisal and synthesis can aid our understanding of the topic. The primary aim of this review was to summarise the prevalence of pre-stroke depression reported across the literature. Our secondary aim was to summarise the association between pre-stroke depression and post-stroke depression.

METHODS

A systematic review of the literature based upon a pre-registered protocol (PROSPERO identifier: CRD42017065544) was conducted. All aspects of planning, conduct and reporting were guided by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) consensus statement (Stroup et al., 2000). All aspects of title searching, data extraction and risk of bias assessment were performed

by two independent researchers trained in systematic review (MT, OM). Decisions were made by consensus with recourse to a third arbitrator as necessary (TQ).

Search Strategy

Initial scoping of the literature suggested that pre-stroke depression was rarely the primary focus of original research and was more often described as a co-variate in studies that investigate post-stroke mood disorder. Thus, our search strategy adopted two complementary approaches to the literature. A specific search with a focus on pre-stroke depression was performed (search A) as well as a more sensitive search with a focus on post-stroke depression, to identify papers from which data on pre-stroke depression could be obtained (search B; see supplementary materials).

As our emphasis was on published, peer-reviewed journals, we did not search grey-literature beyond the scope of the included search engines and hand searches. There were no restrictions placed on the basis of language; however foreign-language studies were only included if they could be translated into English.

Search A: A search syntax incorporating commonly used terms to describe pre-stroke depression (see supplementary materials) was created and multidisciplinary databases across a variety of platforms were searched: Medline (OVID), Embase (OVID), PsychInfo (EBSCO), Web of Science (Thomson Reuters), Cinahl (EBSCO) from inception to July 2017. This was supplemented by hand searches of references of identified papers and relevant reviews.

Search B: For our review of post-stroke depression, we used a search strategy that had informed a recently published systematic review on the topic (Ayerbe et al., 2013). Studies and relevant reviews identified via the search were hand searched for additional studies. We then screened the studies reporting prevalence of pre-stroke depression.

Inclusion/Exclusion criteria

Study designs: Observational studies, published in peer reviewed journals, that had a focus on mood, and that reported pre-stroke depression prevalence were included. The focus was on studies assessing pre-stroke depression retrospectively, and over a period that could reasonably be thought to encapsulate life-course depression prevalence.

As we were interested in the natural population frequency of pre-stroke depression, any studies that recruited exclusively from clinical trials or that artificially enriched the population with 'cases' to allow matched case-control analyses were not included. Studies that prospectively assessed depression at a pre-stroke baseline and then followed patients up until an index stroke were also excluded if they did not assess depression at least every 2 years or more. Due to the typically sporadic time-frame covered for assessment of depression before stroke occurrence, prolonged periods with no assessment are liable to underestimate overall pre-stroke depression prevalence by systematically missing interim incident depression.

Exposures: Studies were accepted if they defined depression according to recognised clinical criteria that were current at the time of the primary paper (for example, Diagnostic and Statistical Manual of Mental Disorders version III/IV; International Classification of Diseases version 10); or if they defined depression using a cut-off point on a validated scale designed for assessing depression or depressive symptoms. Any defined form of depression, including minor depression, was included. Due to the often lax reporting of pre-stroke depression, it can be unclear how a study has defined the depression prevalence that they present (e.g. DSM IV major depression prevalence only or a combination of major depression, minor depression and dysthymia). Therefore, where studies did not operationalise the pre-stroke depression definition, but defined post-stroke depression consistent with our criteria, the pre-stroke depression data were included and coded on the assumption that pre-stroke depression was defined according to the same criteria that was applied for post-stroke depression. Moreover, data were included if the pre-stroke depression assessment method employed was likely to include a definition that was consistent with our criteria (e.g. utilisation of medical records to determine a prior clinical diagnosis of 'depression'; self-report of a prior clinical diagnosis of 'depression').

Patients/participants: Studies were included where patients had a stroke or Transient Ischaemic Attack (TIA) of any form consistent with the World Health Organisation (WHO) definition (Hatano, 1976). Studies were excluded if they: 1) excluded patients with depression; 2) were restricted to a selected stroke cohort (e.g. females only; highly restricted age groups); 3) had mixed populations (e.g. stroke and non-stroke populations in study sample) unless the stroke specific data could be extracted separately; 4) only used antidepressant prescription as evidence of depression; 5) if the depression rates could not be separated from other mental health disorders (e.g. "psychiatric history"); 6) had excessively non-generalisable exclusion criteria (e.g. exclusion of vascular risk factors, such as hypertension or diabetes, common to the typical stroke population).

Study selection

Studies identified from electronic databases were exported to Covidence software (version 1.0, Veritas Health Innovation, Australia) for screening. After de-duplication, titles and abstracts were screened for relevance. Potentially relevant full texts were reviewed against the inclusion/exclusion criteria.

To assess validity of the search strategy, a third researcher (TQ) who was independent of the search pre-specified five important papers or reviews that were relevant to the pre-stroke depression topic - Ayerbe et al., 2013; De Ryck et al., 2014; Hackett et al., 2005; Robinson & Jorge., 2016; Reid et al., 2010. Validity was assessed by describing how many of these titles were returned on initial searching.

Assessment of risk of bias

Risk of bias (RoB) was assessed at study level. The potential important biases vary for our two review aims, so we used differing approaches to RoB assessments for each. For our first aim of describing prevalence of pre-stroke depression, we utilised the Critical Appraisal Skills Programme (CASP) cohort study tool, adapting it for our purpose. Specifically, we judged potential RoB based upon the focus of

the paper, cohort recruitment method, stroke diagnosis method, pre-stroke depression assessment method and study population inclusion/exclusion criteria.

For our secondary aim of describing association between pre-stroke depression and post-stroke depression, a stroke-specific RoB assessment tool was adopted for use in studies describing risk factors (Counsell & Dennis, 2001). This tool assessed RoB according to the following criteria: covariates controlled for; event-covariate ratio; control for collinearity; and, as a secondary category, we incorporated control for post-stroke care pathway. Rationale for our model assessment can be seen in the supplementary materials.

Data extraction and analyses

The reported numbers of patients with pre-stroke depression along with the total sample size, setting, time-frame covered, country, first ever stroke (yes/no), means for assessment of pre-stroke depression, and definition of pre-stroke depression were extracted from each study. Where studies defined multiple forms of pre-stroke depression in their sample (e.g. major depression, minor depression, dysthymia), each subtype of depression was grouped together to form one whole depression sample. Additional data regarding post-stroke depression assessment method and covariates controlled were extracted only for studies included in our investigation into the risk association between pre-stroke and post-stroke depression.

All data were extracted to a pre-specified template and stored on an electronic spreadsheet (Excel, version 2016, Microsoft, USA). Where data were not available from the primary paper, author teams were contacted.

Meta-analyses were conducted using Comprehensive Meta-Analysis software version 3 (Biostat, USA).

Our primary meta-analysis was designed to give a summary estimate of prevalence of pre-stroke depression. Due to our expectation that the true pre-stroke depression prevalence rate will vary within the population, we created a random-effects model to generate a pooled estimate of prevalence.

Our second meta-analysis pooled adjusted odds ratios and confidence intervals of pre-stroke depression association with post-stroke depression from all studies utilising multiple regression analysis into a random effects model.

Heterogeneity was assessed through visual inspection of forest plots and by describing I^2 .

Publication bias for pre-stroke depression/post-stroke depression association analysis was determined by visually examining a funnel plot.

The overall strength of our summary data on prevalence rates and the pre-stroke depression/post-stroke depression association was judged using GRADE criteria. (Atkins et al., 2004)

Pre-specified subgroup analysis describing the effect of method of assessment for pre-stroke depression on prevalence rate was conducted. Studies were separated by assessment and data pooled where the assessment method utilised had relevant data from a minimum of five studies.

Random-effects ANOVA was run, to explore the contribution of assessment method to observed heterogeneity of reported prevalence rates between studies.

If any study was overly influential on pooled pre-stroke depression rate or odds ratios, and presented 'outlier' data then sensitivity analysis was performed, removing the outliers and re-running the analyses. We also conducted pooled-prevalence-related sensitivity analyses based on time-frame covered in studies, utilisation of a screening method only to assess pre-stroke depression, and type of depression included within the sample (e.g. major depression only).

[insert Figure 1]

RESULTS

After excluding duplicates, our combined searches identified a total of 11884 studies. A total of 29 studies (Aben et al., 2006; ; Bara et al., (2016); Caeiro et al., 2006; Castellanos-Pinedo et al., 2011; De Ryck et al., 2013; Dou et al., 2015; Gillen et al., 2001; Hackett et al., 2006; Jorgensen et al., 2016; Kim et al., 2014; Kocer et al., 2011; Kootker et al., 2016; Liu et al., 2017; McCarthy et al., 2016; Ng et al., 1995; Paolucci et al., 2006; Pohjasvarra et al., 1998; Prinsie et al., 2016; Schottke et al., 2015; Sienkiewicz-Jarosz et al., 2010; Singh et al., 2000; Slater et al., 2012; Tang et al., 2005; Tang et al., 2011; Tse et al., 2017;Verdelho et al., 2004; Vermeer et al., 2017; White et al., 2014; Zhang et al., 2010) met our inclusion criteria (164993 patients; see Table 1). We requested additional data from seven authors and received data from one (Acknowledgements). Validity of our search strategy was supported as all pre-specified papers were identified in the initial search.

[insert Table 1]

Prevalence of pre-stroke depression

Pooled prevalence of pre-stroke depression was 11.6% (95%CI=9.2-14.7; 29 studies; total participants n=164993). There was substantial heterogeneity across studies ($I^2=95.8$) (see Figure 2).

[insert Figure 2]

RoB assessment of studies suggested potential bias in reported pre-stroke depression rates in all included studies (see Table 2). Particular issues were around validity of the pre-stroke depression assessment (25 studies--83%-- were at high or uncertain risk of bias) and external validity of the included participants (25 studies--83%--were at high or uncertain risk of bias), the latter primarily due

to excluding patients with pre-stroke dementia/cognitive impairment (13 studies; 44%). 17 (59%) studies had an uncertain risk of bias in stroke assessment.

[insert Table 2]

GRADE evaluation suggested that the strength of evidence to support our summary estimate of prevalence was 'very low' (see Supplementary Materials).

There was substantial variation in the method of pre-stroke depression assessment employed across studies. Pre-stroke depression was assessed using at least five different methods; eight studies utilised more than one method for assessing depression (see Table 1). The most commonly used methods were medical records/charts (utilised in 14 studies) and self-reports (utilised in 12 studies). The standard of reporting of assessment method within studies was mixed; most studies provided only minimal details of assessment method employed.

We described summary estimates of pre-stroke depression based on assessment method for self-reports, medical records/charts and clinical interviews. Prevalence was 10.7% (95%CI=7.4-15.2); 9.4% (95%CI=6.2-14.0) and 17.3% (95%CI=13.1-22.6) respectively (see Figure 3). Random-effects ANOVA suggested that method of assessment was an important contributor to between-study heterogeneity ($P=0.02$).

[insert figure 3 here]

Sensitivity analysis

No outliers were apparent in our analyses; however, three studies were identified that were restricted in duration of pre-stroke assessment (i.e. ≤ 1 year) and hence had been excluded, but otherwise met our inclusion criteria (Burville et al., 2010; Dossa et al., 2011; Nuyen et al., 2008). Sensitivity analysis was performed by inserting these three studies into our primary pre-stroke depression prevalence meta-analysis; the resultant pooled rate (11.8%; 95%CI= 9.6-14.5,) suggests that excluding such studies had minimal impact upon our reported rate. In addition, as one study (Tse et al., 2017) established a pre-stroke depression prevalence rate via a screening method, which could be more indicative of depressive symptoms, rather than depression *per se*, we performed sensitivity analysis by removing this study; resultant pooled rates (11.4; 95%CI= 8.9-14.5) suggest inclusion of this study did not bias our analysis. Only two studies explicitly reported that they limited their reported sample to major depression only (Kocer et al., 2011; Schottke et al., 2015); hence we also removed these two studies. Again, resultant pooled rate (11.4; 95%CI= 8.9-14.6) suggests that restriction to major depression only had minimal impact upon overall pooled rate.

Association with post-stroke depression

The association between pre- and post-stroke depression was described in 24 studies (83%) (see supplementary materials); 14 (58%) reported significant associations (see supplementary materials). Multiple logistic regression analyses were described in 15 studies (see supplementary materials) and 11 (73%) reported significant associations (see supplementary materials). The resulting funnel plot did not suggest reporting bias (see Figure 4). Assessment methods employed to assess pre and post-stroke depression were variable, as were chosen covariates included in regression models (see supplementary materials).

[Insert Figure 4]

The papers describing association models were at risk of bias (see Table 3). In particular, no studies controlled for post-stroke care-pathway. Three out of four studies employing multiple regression models that failed to observe a risk association were underpowered (Aben et al., 2006; White et al., 2014) or failed to control for important covariates (Schottke & Gabbiconi, 2015); one study had a very small pre-stroke depression prevalence (Bara et al., 2016).

[insert Table 3]

Odds ratio data were available for nine studies in total. However, one study was removed from analysis due to a lack of symmetry of log values. (McCarthy et al., 2016) This left eight studies with a combined sample size of 37483 for meta-analysis. Random-effects analysis suggested a pooled odds ratio of 3.03 (95% CI of 2.30-3.98) (Figure 5). One study (Tang et al., 2011) appeared to be a clear outlier; hence sensitivity analysis was performed by removing this study and rerunning analysis. This did not meaningfully alter the strength of association (2.85; 95%CI=2.70-3.02).

GRADE evaluation suggested that the strength of evidence to support our summary estimate of association was 'very low' (see Supplementary Materials).

[Insert Figure 5]

DISCUSSION

Prevalence

The primary aim of our review was to describe the natural stroke population prevalence of pre-stroke depression based upon data from typical stroke settings. Our results suggest a pooled pre-stroke

depression prevalence rate of ~12%, which is identical to the 12% mood disorder prevalence rate most commonly reported in the general population (Kesler et al., 2009). This is somewhat surprising given that depression is a risk factor for stroke (Barlind et al., 2014). We note that pre-stroke depression was assessed in diverse ways across studies and that there was a significant trend towards increasing prevalence with increasing complexity of testing. This indicates that the more one looks for pre-stroke depression, the more it is discovered, which is in keeping with research suggesting variable detection of pre-stroke depression according to assessment method employed (McCarthy et al., 2016; Prisnie et al., 2016; Wulsin et al., 2012; Zhang et al., 2010). On this basis, the 17% pre-stroke depression rate, evident when in-depth interviews were utilised to investigate presence of pre-stroke depression, may be more reflective of the actual pre-stroke depression prevalence, existent within the stroke population.

Comparing pre-stroke depression rates (17%) to recent estimates of post-stroke depression (39-52%; Ayerbe et al., 2013) demonstrate that rates of depression after stroke are several multiples higher than the rates of depression present before a stroke. These results suggest that the majority of cases of post-stroke depression are not simply the re-manifestation or 'unmasking' of pre-stroke depression. Our findings are therefore in line with suggestions that the majority of cases of post-stroke depression are the product of the experience and consequences of the stroke itself (Ayerbe et al., 2013).

Risk Association

As a secondary aim, we described the association between pre-stroke depression and post-stroke depression. Recent findings prompted suggestions that the pre-stroke state is "not a meaningful predictor" of depression after stroke (Schottke & Gabbiconi, 2015). Our meta-analysis results suggest that pre-stroke depression at any point over the life-time increases odds of post-stroke depression by as much as 3.0 (95%CI=2.3-4.0), when compared to those without pre-stroke depression. Notably, of the fifteen studies that utilised multiple logistic regression analysis to investigate the association, two of the four studies that failed to find an association were underpowered in their event-per variable ratio (Aben et al., 2006; White et al., 2014); one study (Schottke & Gabbiconi, 2015) failed to control for important covariates, and one reported a very low rate of pre-stroke depression (Bara et al., 2016). We would therefore suggest it is inaccurate to conclude that the pre-stroke state is not a meaningful predictor of depression after stroke and would encourage researchers to include pre-stroke depression as a case-mix adjuster in all future studies of post-stroke depression.

Strengths and Limitations

We present a methodologically robust synthesis of the published literature, following best practice in conduct of observational systematic review. However, quality of primary data mandated a low GRADE rating: prevalence rates reported across studies were heterogeneous and studies had risk of bias. Specifically, the limitations of the available papers may risk underestimating pre-stroke depression rates. Particular issues were regarding sensitivity of pre-stroke depression assessment and exclusion of patients with pre-stroke cognitive impairment. The pooled rate may alternatively be *inflated* by inclusion of rates that reflect depressive symptoms rather than depression *per se*; although, our sensitivity analysis indicates that such rates were not overly influential towards the pooled prevalence that we report. More significantly, we cannot say for certain what form of depression our pooled rate describes, as explicit definitions of pre-stroke depression were lacking. Typically employed assessment methods (i.e. medical records, self-reported prior diagnosis, clinical interview) could

conceivably incorporate any form of clinical depression (e.g. major depression, minor depression and dysthymia all inclusive), or may be predominantly constrained to major depression only. Clearer reporting in this regard would benefit the field.

Similarly, our assessment of the pre-stroke/post-stroke depression association has methodological limitations. Authors may have been more likely to give odds-ratios where an association was apparent; hence our summary quantitative analysis is at risk of reporting bias, albeit this was not evident in the corresponding funnel plot. Studies were heterogeneous in both covariates controlled for and assessment method utilised for both pre and post-stroke depression assessment, which could potentially bias or confound reported associations; for instance, strength of reported odds ratios may be heightened or diluted due to differences in control for stroke severity, or ability to accurately detect pre-stroke depression within a sample. Taking all this into account, our GRADE estimate of confidence in this evidence was 'very low'. We also note that no included studies controlled for the possible influence of alterations in care pathway following assessment of pre-stroke depression. It seems plausible that recording pre-stroke depression, clinically, would result in greater use of pharmacological treatment, likelihood of referral for psychological assessment, or more frequent assessment for post-stroke depression (Reid et al., 2010; Slater et al., 2012). As a result, although current evidence is favourable regarding a relevant risk association between pre-stroke depression and post-stroke depression, we must remain cautious and changes to the approach for investigating this association are needed. In particular, we would advise future studies seeking to assess risk factors for post-stroke depression to be aware of the potential care-pathway related confound and encourage greater consistency of depression assessment (both pre and post stroke).

Finally, we used two complementary approaches to inform our literature search, one specific search designed to find papers with a focus on pre-stroke depression and a more sensitive search with a post-stroke depression focus. Through various internal and external validity checks we believe we have captured all the relevant studies. However, it is possible that we may have missed prospective cohort studies with depression and stroke data where these variables are only available as secondary outcomes data and there have been no specific publications relating to depression and stroke.

Future Directions

Our findings suggest avenues for further research. Optimal methods for assessing pre-stroke depression should be established, particularly as differences in assessment tool properties could interfere with correct identification of risk associations or result in improper patient care plans. Secondly, it would be beneficial to ascertain whether depression severity (e.g. major depression only vs "any depression") is a source of variance for the risk of developing depression after stroke. Finally, the literature presents a clear correlation between pre-stroke depression and post-stroke depression; however, the specific aetiology of this association remains unknown. Previous studies have suggested that genetic factors may play a role (Ayerbe et al., 2013). The presence of particular psychological characteristics may also be relevant. For instance, selective attention towards negative attributes can lead to depression following disease (Rodin et al., 1991) and is also a characteristic attributable to depression. Hence, a prior history of this cognitive style may increase the likelihood that this way of thinking will arise post-stroke, thus heightening risk of developing depression after stroke. Understanding the nature of the pre-stroke/post-stroke depression association should therefore help to tailor better treatment methods.

Clinical Implications

Stroke patients are at considerable risk of developing depression, and having depression prior to the stroke event only serves to further heighten this risk. On this basis, it is important that clinicians are aware of the relevance of pre-stroke depression to the potential development of depression after a stroke, as well as the prevalence of the condition within their patient population (likely 1 in 6).

Clinicians should also be aware of the potential limitations of relying upon medical records or patient self-reported diagnoses as means of identifying pre-stroke depression. It is likely that reliance upon such methods will fail to identify a substantial number of patients with the condition.

Conclusions

It seems clear from the existent literature that the prevalence of pre-stroke depression is strikingly lower than the depression prevalence observed after a stroke. Nevertheless, it appears that pre-stroke depression is an important and relevant clinical variable regarding the development of post-stroke depression.

We would suggest that in those patients where pre-stroke depression is apparent, a high index of suspicion for post-stroke depression would be appropriate.

In a research context, efforts to investigate pre-stroke depression are currently hampered by the challenge of reliably assessing it: the most commonly employed methods utilised to detect pre-stroke depression are at risk of underestimating the prevalence of the condition. Utilisation of more thorough assessments of pre-stroke depression along with a careful consideration of relevant confounds and adequately powered statistical models are essential to the enablement of a more developed and nuanced understanding of pre-stroke depression and its relationship with post-stroke depression.

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DISCLOSURES

None.

CONTRIBUTORS

MT and TJQ conceived the study. OM was the second reviewer on the paper. DJS, LA & JE contributed to supervision, interpretation of results and critical review of draft manuscripts. MT and TJQ drafted the paper. All authors contributed to the writing of the paper. MT is the guarantor.

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