Aus dem Institut „Centrum für Schlaganfallforschung“
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DISSERTATION

Schlaganfallnachsorge, Depressionen und deren Assoziation mit Langzeitkomplikationen und gesundheitsassoziierter Lebensqualität

Post-stroke aftercare, depression and its association with screening, long-term complications and health related quality of life

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

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aus Hamburg

Datum der Promotion: .....17.09.2021.....

Inhalt

1 Abstract Deutsch

1.1 Hintergrund

Depression ist eine der häufigen Langzeitfolgen eines Schlaganfalls. Depressionen haben tiefgreifende Auswirkungen auf die Entwicklung chronischer Krankheiten. Die ambulante, chronische Nachsorgephase eines Schlaganfalls ist gekennzeichnet durch einen komplexen Bedarf an medizinischer und sozialer Unterstützung, die eine Voraussetzung für eine gute Langzeitbehandlung und angemessene Hilfe bei Anpassungen in Alltag, Arbeit und Wohnen darstellt. Die Organisation dieser Unterstützung kann jedoch insbesondere für Patienten mit Post-Schlaganfall-Depressionen eine Herausforderung sein. Trotzdem fehlen im ambulanten Umfeld Daten zur Prävalenz, zur Langzeitüberwachung und Behandlung von Depressionen und zu deren weiteren Konsequenzen nach Schlaganfall. Wir wollten erheben, ob Patienten zwei bis drei Jahre nach einem Schlaganfall in Bezug auf Depressionen untersucht, diagnostiziert und angemessen unterstützt wurden und wie sich dies ggf. auf die Entwicklung weitere Komplikationen auswirkte.

1.2 Methoden

In einer Querschnittsstudie, die Schlaganfall-Patienten zwei bis drei Jahre nach Beginn der Erkrankung einschloss, wurden Komplikationen und Therapien nach Schlaganfall bewertet. Die Depression wurde anhand der Hamilton Depression Rating Scale (HDRS) definiert und die Patienten wurden gefragt, ob sie zuvor auf Depressionen untersucht worden waren oder nicht. Darüber hinaus wurden die soziale Situation, die Lebensqualität und Empfehlungen zur weiteren Beratung im Bereich des sozioökonomischen Bedarfs sowie des ungedeckten emotionalen Bedarfs anhand standardisierter Scores bewertet.

1.3 Ergebnisse

Nur eine Minderheit (36%) der Patienten gab an, auf Depressionen untersucht worden zu sein und auch bei den Patienten bei denen ein Screening stattfand war dies mehrheitlich bereits im Krankenhaus erfolgt. Zwei bis drei Jahre nach Schlaganfall hatten Patienten ohne Screening höhere Depressionsraten als Patienten mit Screening (5 vs. 29%). Depressionen im ambulanten Umfeld waren signifikant mit einem ungedeckten Bedarf an Hilfe bei emotionalen Problemen, mangelndem sozialen Kontakt, erhöhtem sozioökonomischem Bedarf und höheren Empfehlungsraten für weitere Beratung und Interventionen in diesem Bereich verbunden. Darüber hinaus wiesen Punkt 2 (Schuldgefühle) und Punkt 7 (Verlust des Interesses an Arbeit / anderen Aktivitäten) der HDRS hohe negative Vorhersagewerte und relativ hohe positive Vorhersagewerte für die Erkennung von Depressionen auf.

1.4 Fazit

Depressionen in der chronischen Phase des Schlaganfalls werden nicht ausreichend diagnostiziert. Weitere Studien sollten prüfen, ob effiziente Screening-Maßnahmen und die verbesserte Behandlung von Depressionen im Rahmen der Schlaganfall-Nachsorge dazu beitragen können, den Zugang des Patienten zu sozioökonomischer Unterstützung, die langfristigen Behandlungsergebnisse, die Lebensqualität und die Teilhabe am Leben nach einem Schlaganfall zu verbessern.

2 Abstract, english

2.1 Background

Depression is a common complication of stroke. It can have a profound impact on development of chronic diseases. The out-patient, chronic aftercare phase of stroke is characterized by a complex need for medical and social support to receive long-term treatment as well as to make appropriate adjustments in daily routines, work and housing. Organizing this support however can be challenging especially for patients suffering from post-stroke depression. Despite of this in the out-patient setting there is a lack of data on the prevalence, long-term monitoring and treatment of depression after stroke. Here, we aimed to better understand whether patients had been screened, diagnosed and appropriately supported with regard to depression two to three years after stroke and how that might relate to depression and development of longer term complications.

2.2 Methods

Patients were assessed in the first cross-sectional phase of complex post stroke intervention study. Two to three years after stroke onset, post-stroke complications and therapies were evaluated. Depression was defined using the Hamilton Depression Rating Scale (HDRS) and patients were asked whether or not they had previously been screened for depression. Furthermore, the social situation, quality of life, recommendations with regard to further counselling in the area of socio-economic need and unmet emotional need were assessed using standardized scores.

2.3 Results

Only a minority (36%) of patients reported to have been screened for depression and of those who had been screened only a minority had received that screening during outpatient aftercare. Two to three years after stroke patients without screening had higher depression rates compared to patients with screening (5 vs. 29%). Depression in the out-patient setting was significantly

associated with unmet need for help with emotional problems, lack of social contact, higher socio-economic need and higher rates of recommendations for further counselling and interventions in this area. Furthermore, item 2 (feelings of guilt) and item 7 (loss of interest in work/other activities) of the Hamilton depression scale had high negative predictive values and reasonably high positive predictive values for detecting depression in our sample.

2.4 Conclusion

Post-stroke depression in the chronic phase of stroke is underdiagnosed. Future studies should help to further evaluate whether screening measures and treatment of depression as part of stroke aftercare may also help to improve patient's access to socio-economic support and help in improving long-term outcomes, quality of life and participation after stroke.

3 Manteltext

3.1 Introduction

3.1.1 Epidemiology, etiology, and long term compilations of stroke

Stroke today is the fifth leading causes of death and the leading cause of disability in western countries such as the united states (1). Adverse long-term outcomes after stroke include but are not limited to reduced mobility, dysphagia, aphasia, chronic pain, cognitive problems, a secondary stroke event and depression.

For acute ischemic stroke important factors with regard to the severity of long-term outcomes are the time until treatment (thrombolysis and thrombectomy) as well as –partly related to this- the size and location of the ischemic lesion. Additional factors discussed to be involved in the development of such adverse long-term outcomes after stroke include but are not limited to a history of prior stroke or diabetes mellitus, sex, congestive heart failure, fever >38 C after acute stroke and age (2). The identification of determining additional factors that are involved in a higher long-term risk for complications following stroke is complex. One reason for this is the fact that the complications of the stroke itself may interact with one another as well as with socio demographic and with certain biological characteristics of the patients. These may include differences in education, social and financial resources as well as potential individual differences in regenerative capacity and susceptibility to ischemia, rendering some of the stroke patients more vulnerable than others.

3.1.2 Prevention

While being highest immediately after the initial stroke the risk of a recurrent secondary event in stroke survivors is about 11.1% per year (3). Despite of a decrease in risk some time after the initial stroke secondary prevention is suggested to be maintained indefinitely, turning stroke essentially into chronic disease with recommended life-long treatment and prevention.

Major modifiable general risk factors that can help in the prevention of secondary as well as of primary stroke include age, previous symptomatic vascular disease, hypertension, diabetes mellitus, tobacco smoking, hyperlipidemia and lifestyle factors, such as obesity, poor diet/nutrition, and physical inactivity. Depending on the cause of primary stroke recommended medication after stroke therefore includes intake of station anticoagulants and anti-platelets and medication based blood sugar control (1). Benefits of anti-coagulation therapy thereby have to be weighed against the risk for bleeding with shared risk predictors such as older age and previous stroke (3).

Interventions with the most favorable risk benefit ratio are changing life style risk factors such as adhering to a more healthy diet, smoking cessation and taking up sport. Despite of being very

effective in principle this intervention is also one that highly depends on the patient's understanding, motivation, trust, cooperation and endurance to follow through with the suggested behavioral adaptations.

3.1.3 Challenges of acute and long-term stroke treatment and prevention

As can be derived from the above described risk factors for acute and secondary stroke and the measures involved in their prevention, stroke treatment can be separated into an acute and a chronic phase. The acute phase is characterized by in hospital early thrombolysis or thrombectomy and the treatment of acute complications such as pneumonia. The chronic phase is characterized by medical and behavioral interventions in the rehabilitation hospital and out-patient setting to prevent or reduce long-term complications and secondary events. Challenges that are typical for the chronic phase especially during out-patient therapy are the successful exchange of information during interdisciplinary care due the scattered nature of out-patient service provision and getting the patients in need to access the appropriate care available to them.

Out-patient benefits that -in many western countries- are in principal supported by social and health insurances thereby include long-term financial support, help with reintegration into the workplace, housing adaptations, obtaining mobility aids and more (4).

However, seeking help can be time consuming and complex and therefore potentially represents a burden especially for certain subgroups of patients such as those with a lower level of education or with psychiatric comorbidities. For example, a lack of family support or insufficient health insurance may drastically affect the patients access to the medically appropriate resources. Furthermore, without actively seeking adequate social counselling on therapeutic options supported by general health insurance and/or on benefits granted for reintegration into work and for adaptations at home, such support may never be obtained. This may result in a higher grade of medical and social deteriorations with potential mutual influences reinforcing a negative feedback.

Additionally, differences in volition and trust in medical doctors or the medical system per se may affect how well the available resources are accepted by the patients, how well life style recommendations are followed through and how well the patients may be able to get hold of medical and social support that would be available in principle

However, as long-term complications of stroke are representing a severe challenge for the patient's future participation and social and professional functioning, identifying modifiable factors that help to prevent the development of complications and adverse events and increase

all patients access to the appropriate treatment and care to prevent complications is important from a public health as well as from the individual patient's perspective.

3.1.4 Depression as a potentially underdiagnosed complication of stroke that may affect long term out-comes

Some of the variability in obtaining effective out-patient treatment may be caused by a frequently observed complication of the stroke which is depression. Typical symptoms of depression include fatigue or loss of energy, indecisiveness and a general pessimism about the future (5) that may lead patients to passively accept an unideal medical or social situation without seeking the help that is needed and also might make adherence to medication and behavioural changes in the course of secondary prevention more difficult.

Generally, adverse outcomes associated with depression could therefore be the result of an interaction of physiological aspects involved in the development of depression (6) in combination with behavioral changes induced by depression. Furthermore, depression and anxiety might interact with physiological factors and smoking producing supra-additive effects on mortality (7).

Even though a large number of post stroke deaths can be attributable to depression the importance monitoring for it -for example by organizing a psychiatric aftercare for stroke survivors- does not seem to be as much in focus as the somatic aftercare for stroke (8).

A reason for this might partly be the fact that depression after stroke is considered a psychiatric problem that may often been overlooked by medical doctors with a somatic focus during aftercare. It could be that neurologists and also general practitioners see their expertise rather in the more somatic topics of stroke aftercare and may feel that they lack the time as well as the skill set to diagnose complications outside of this frame of reference. However, psychiatric problems still tend to be stigmatized which also may represent a burrier for patients when it comes to report symptoms of depression when not explicitly asked for them.

3.1.5 Modern approaches directed to the study and improvement of out-patients aftercare

Due to the complex nature of the treatment of depression in the context of chronic disease, novel treatment concepts include collaborative care to effectively and optimally manage the patients in all aspects of their disease (9). These approaches aim to avoid a loss of information at the intersections from inpatient to out-patient care as well as between different out-patient service providers which currently are major obstacles for a continued and coherent long-term aftercare of stroke.

Modern approaches to study the treatment of out-patient stroke also take this complexity into account trying to develop interventions enabling multidisciplinary diagnosis, treatment and help

with social, medical and psychological complications after stroke. For example the study “New Start” aims for needs identification, exploration of social networks and components of problem-solving and self-management to improve stroke survivors' quality of life by addressing unmet needs and increasing participation (10).

3.1.6 Aims of the current study

The current study was designed as a first step to develop a complex intervention to enable comprehensive care for stroke patients after release from the hospital. In the first phase of the study (MAS-1) we aimed to better understand the complexity of the longer term complications such as the state of motor, cognitive, and emotional functioning after stroke. Furthermore, we wanted to understand whether social care and counselling had been appropriate after stroke and whether there was an open need with regard to help with the socio-economic situation of the patients. Due to small numbers of patients and even fewer patients with depression in the current study we focused on socio-economic associations and in the present study did not aim for an analysis of potentially partially secondary effects on the patient somatic complications. Here a larger, longitudinal follow up-analysis might help to assess potential differences.

We specifically wanted to test the following hypothesis:

1. Stroke survivors are under diagnosed for depression
2. Prevalent depression is associated with a worse socioeconomic situation and lower health related quality of life.

Furthermore, an explorative analysis was directed to assess if depression could be more efficiently screened for in the out-patient setting. Specifically, we wanted to confirm how the post stroke checklist (PSC) or a reduced version of the Hamilton score might represent a useful tool in the out-patient setting (11).

3.2 Methods/Description of the study:

3.2.1 Complex intervention

The MAS-1 dataset represents a first step in a more complex overall project aiming to gain information on open medical and social needs and their efficient interventions in ambulant stroke aftercare.

In MAS-1 information on the out-patient situation of the patients was collected and open needs and medical information was assessed to determine where additional support would be needed most. This first phase of the study was thought to inform the development of a complex intervention in the second stage of the MAS project. Here patients would again be screened for deficits in care but then would also be guided to optimize medication and acquire physiotherapy, neuropsychology, behavioral therapy, speech therapy and counselling on socio-economic problems, depending on the individual need. Data collected in MAS 1 will be used to develop a complex intervention and to guide out-patient stroke aftercare. Complex interventions are defined to a large degree by the complexity of the underlying disorder targeted, the complexity, number of steps and interaction of the components of the intervention itself and the variability of targeted outcomes (12).

The exact nature of the individual intervention thereby would depend of course on the "objective" medical and social needs of each patients but as well had to be based on the individual personal preferences, main objectives and capabilities. Furthermore, parallel treatment and training of different areas of deficits has sometimes even been shown to be counter-productive which may require identifying the most urgent areas of intervention and start there with a stepwise approach with improved health related quality of life as the main long-term outcome to be addressed (13).

3.2.2 Description of the dataset

Data on the social situation, medical care and open need, depression and quality of life were obtained by reinventing interviewing patients on site using standardized scores. Data in previous screening and quality of previous care were collected retrospectively. Similarly, data on prescribed medication were collected retrospectively but hospital records on medication given during initial hospital stay were checked in addition.

MAS patients were recruited from patient populations that previously took part in studies on acute stroke care at the Charité in Germany (Stroke Adverse Outcome and association with nosocomial infections (STRAWINSKI) or prediction of stroke associated pneumonia

(PREDICT) as also described in the publication on which this thesis is based upon as described previously (11).

3.2.3 Assessment of validated scores

The main outcome depression was classified according to the Hamilton 17 depression scale as follows: Subjects having 0-8 points were classified as not depressed, 9-16 point = mild depression, 15-24 points = medium depression, >24 points = severe depression (11, 14). Technical details and background on additional scores can be found in the supplementary methods section of our publication (11).

With regard to the Hamilton score, the interviews were performed by two different persons. Inter-rater variability was calculated across 5 interviews of the study which were rated by both interviewers independently. The average measures intraclass correlation (cronbachs alpha) for a two way mixed model tested for absolute agreement was 0.886 (p-value=0.029) suggesting good agreement between the two raters.

3.2.4 Statistical analysis

Statistical analysis were performed using SPSS software version 22 and STATA 14. Further details on the major statistical analysis can be found in Padberg et al. (11).

3.2.5 Logistic regression and confounder correction

As an additional analysis -despite the small sample size and based on a reviewers suggestions- associations between depression and screening were tested by logistic regression including factors outlined in results table 2 as confounders, to see whether this would result in a relevant reduction of effect size. This can be important to differentiate between effects that are due to a direct association between exposure and outcome and those that are not. To know whether a treatment or a risk factor is causally associated with an outcome ideally one would like to observe the individual outcome under different exposure levels. However, in reality the individuals outcome can only be observed under one condition, then also called the factual outcome. The outcomes expected under the non-observed conditions are called the counterfactual or potential outcomes (15, 16). In observational population based studies where persons are not randomly assigned to a treatment and a test group observed associations may actually be caused by factors both influencing the outcome and the exposure independently, thereby creating a non-causal association between the two. To correct for such confounders and to correctly estimate their effects, they should be included in statistical models of observational data. It has to be noted however that confounder correction also has limits. First of all not all

potential confounders might be measured and included in the model. Furthermore, a more reliable establishment of causality would essentially of course require a longitudinal study design and a much larger study size to minimize selection bias. Never the less correction for confounders in our study should provide some additional indication on whether observed associations were stable.

Confounders that may both impact health behaviors (such as the frequency of screening/prevention) as well as of depression include sex (17-19), age (20, 21), parameters of physical and cognitive disability (modified Rankin scale/Moca) and potentially also indicators of secondary prevention (intake of statins etc.). This impact may be mediated either by a direct influence on depression and/or on cardiovascular disease known to be associated with depression and furthermore by representing a surrogate for getting appropriate after-care treatment by out-patient practitioners and/or being at higher risk for insufficient care which would be a perquisite for depression screening.

3.2.6 Correction for multiple testing

To avoid a type 1 statistical error when doing multiple comparisons in a small dataset we corrected for a false positive rate using the Benjamini-Hochberg procedure.

We chose Benjamini-Hochberg instead of other procedures such as Bonferoni correction as this is a relatively small dataset. This reduces the power for statistical analysis and might lead to a type 2 statistical error of not rejecting the 0 hypothesis although it is actually false due to a lack of statistical power.

The Benjamini-Hochberg procedure is a false discovery rate (FDR) controlling procedure (22) that provides greater power than more conservative methods to correct for familywise error rate (FWER) such as the Bonferoni procedure (23).

To control for the false discovery rate using the Benjamini-Hochberg procedure, the p-values given for each group comparison for our primary and secondary research questions were given a rank that reflected their adjacent order and then compared to a critical value given by (i/m) Q, where Q,i = the individual p-value's rank, m = total number of tests and Q = the false discovery rateas as described for example also here: https://www.statisticshowto.com/benjamini-hochberg-procedure/).

3.3 Results

3.3.1 Depression and it's associations in post stroke aftercare

Recalled screening rates were lower in patients with depression as also described in our corresponding publication (11)(Table 1). The other way around in patients with recalled screening we observed lower depression rates than in those without screening (5 vs 29%). Patients with depression furthermore also reported higher levels of unmet need with emotional problems (11)/(Table1). Furthermore, we found a short screening tool for depression to maybe be similarly effective as the full version of the HDRS in detecting depression (11).

3.3.2 Analysis of effect sizes

We additionally calculated a logistic regression model with and without correction for confounding factors as also outlined in the material and methods section above and in the associated manuscript (11). Out of the confounders included only female gender was significantly associated with depression (OR: 8.11, 95% CI: 1.05-62.7, p-value 0.045). The odds ratio for a previous screening for depression in patients with depression was 0.13 (95% CI: 0.02-1.12) without correction for confounders and actually decreased to 0.03 (95% CI: 0.002-0.46, p-value=0.01) after confounder correction. Especially inclusion of age and sex let to a relevant further reduction in the odds ratio for the association of screening and depression. So correcting for these variables did not reduce but actually slightly increased the effect sizes of the association between these two variables. We hereby saw slightly higher screening rates in women (39.13 vs 34.38%) and –according to HRDS value- lower depression rates in man compared to woman (12.5 vs 30.43 %). Patients with depression according to the Hamilton depression scale had a significantly lower reported social support and a worse socio-economic situation than patients without depression (11)/(Table 1).

3.3.3 Anti-depressant medication and long-term prevalence of depressive symptoms

Anti-depressant medication had been prescribed to a minority of patients (11). However, mean Hamilton score in patients with medication were slightly higher than in those without medication (7.55 (SD=4.68) vs 5.39 (SD=4.91)) and about 2/3 of the approximately 30% of all stroke patients in our study, who according to medication intake and/or score based diagnosis at one point might have had a problem with depression after stroke, still would have been diagnosed with depression 2-3 years after the stroke according to their Hamilton Score result. Thereby, our study also provides some indication on the dynamics of disease preservation and efficiency of treatment. Our results suggest that, even if medical treatment for depression was once initiated its efficiency may not have been adequately monitored during out-patient aftercare as symptoms of depression also occurred frequently in the patients already receiving

medication. However, also here, due to the sample study size conclusion that can be drawn from the current data are limited.

3.3.4 Presentation of depression after stroke

When looking at the overall distribution of the values of single items of the Hamilton score in patients with and without depression a couple of things might be interesting to note. First of all: with regard to insight (item 17), only a minority of the patients classified as depressed would have confirmed depression by themselves. This could be a further indication that patients were not educated well with regard to such a potential complication that occurs often after stroke. On the other hand it is important to note that most of the patients in our study would have been classified only as mildly or moderately affected with score values ranging from 9-17 points. Patients who were suspecting to have depression had Hamilton score values >=12.

Furthermore, in our small study we did not find that somatic symptoms such as loss of weight or appetite did discriminate well between stroke survivors with and without depression with a very low overall positivity for these items (11)/(Ref 9, Figure 1). Also with regard to insomnia- even though there was a general difference between the patients with and without depression- the focus on early hour insomnia which is usually typical for depression was not seen in our study (11)/(Ref. 9, Figure 1).

3.4 Discussion

3.4.1 Summary and limitations

We have shown previously that there is a significant unmet need with regard to social care (4, 24) as well as with regard to general health related aftercare in life after stroke (25). Here we now focus specifically on depression related problems.

Stroke survivors appear to be poorly screened in out-patient aftercare and a lack of screening was associated with manifest symptoms of depression and was associated with a worse socioeconomic situation, need for additional social support despite being easily detected by a short screening (11).

The data collected here will inform the second phase of our study where we try to see whether an improvement in screening and treatment of depression really will affect longer-term outcome scores such as self-reported quality of life.

Despite the potential relevance of our data for a better long-term treatment in post stroke aftercare it is also important to remember that depressed individuals may perceive themselves as more ill or more disadvantaged than they are (11). Consequently, depressed patients may over-report symptoms of physical illness. This would have to be investigated in more detail in

future studies which are including a longitudinal detailed physical examination by medical doctors and not only self-reported symptoms. In the current study we collected baseline physical parameters which currently were mainly used to inform the longitudinal second phase of the study with regard to open medical need during aftercare. However, we also hope our data will can inform further larger studies to investigate the association of depression with symptoms such as motor performance, spasticity or aphasia after stroke.

Moreover, effect sizes for variates associated with depression as presented above have to be interpreted with great caution as single outlies may have a disproportionate influence on our results in this a small dataset. Similarly, also the distribution of symptoms for depression in stroke survivors presented in the results section of the "Manteltext" above may not be representative for stroke survivors in general. Especially as out small study might be biased towards patients with more mild depression. This of course may also effect the accuracy of the small screening tool described in the current published manuscript. Future larger studies need to confirm sensitivity and specificity of our two-item screening and provide AUC values that can be validated using cross validation and internal and external test and training datasets.
Further limitation are out lined in more detail in the corresponding manuscript (11).

3.4.2 Applications of our data

The data collected in the current study were thought to inform the second phase of the MAS-project where an intervention directed to an improved provision of out-patient screening and treatment of depression was to be tested for its effects on outcomes such as self-reported quality of life.

3.4.2.1 Guidance for general practitioners and public health decision makers with regard to focusing diagnostic and treatment interventions in chronic aftercare of stroke

However, our data-provided they can be confirmed in larger studies- may be useful to inform medical practitioners and public health decision makers in general out-patient aftercare on the importance of psychiatric and social interventions that are needed to ensure the most optimal long term out-come of the disease.

Namely, our data underline the importance to check for depression and especially in patients with depression to investigate open medical and social need. The association between depression and a lack in social support is concerning as this could also make it more difficult for this patients to get the access to the medical and therapeutic support they need in the chronic phase of the disease. Furthermore, out data demonstrate that there could be a short and efficient way for general practitioners to address screening for depression.

Since depression generally represents a well treatable condition (26) and since the consequences of undertreatment can be severe our study furthermore may help to better allocate public health resources to areas where they are needed most and might have the greatest treatment effect. Thereby it hopefully helps to improve patient relevant long-term outcomes after stroke such as social and professional reintegration as well as long-term quality of life of the stroke survivors.

3.4.2.2 Generating awareness for post stroke depression and potential gender specific underdetection in men

We hope that our study may contribute to further increase the awareness for potential under detection of depression in man. Continuous monitoring for symptoms of depression may be necessary to see whether adaptation in medication is needed (11). When looking at the distribution of depression between man and woman we saw lower depression rates according to HRDS value in man compared to woman (12.5 vs. 30.43 %). It might also be important to look into such gender differences in more detail in larger studies as this could indicate further underlying gender differences with regard to health behaviors including secondary prevention (as attending check-ups by out-patient practitioners maybe one of the prerequisites to get screened in the first place). Alternatively these data could indicate a bias in general practitioners to screen male patients for depression, especially as man less often may openly present typical symptoms of depression and have a higher reluctance to report on them. Such a reporting bias could lead to an underestimation of the true rate of post-stroke depression in the current study. However, the mechanisms related to potential underdetection in the current study may also apply to the general outpatient setting, and even more so without screening. It has been previously reported that depression in man may be underdetected but that depression associated risk behavior such as alcoholism a less healthy diet, less physical activity and lower levels of health care is seen more frequently in men (27, 28). This in turn can lead to a diverse burden of additional complications and long-term complications such as amongst others cardiovascular disease, cancer, liver disease, malnutrition and cognitive problems and further underlines the need for sufficient screening to enable a correct and timely diagnosis in both genders. To enable sufficient detection and better treatment we hope that our data help to inform future studies to also look into these gender specific aspects in underdetection of depression in more detail.

3.4.3 Open questions

3.4.3.1 Associations between physical illness and depression

Depression may cause physical illness but it has also been described a consequence of physical illness (28). To better decipher causes and consequences of depression longitudinal studies are needed that extensively follow up upon the interplay between physical illness and depression. Depression in this context was found to be generally associated with abdominal obesity and dyslipidemia as well as with systemic inflammation and HPA-axis dysregulation (29). Regardless if these associations indicate depression to be a cause or a consequence of stroke or just being associated with it by a common risk factor, this raises the question whether there maybe differences in the presentation of the disease that correlate with differences in this somatic symptoms. In this context it has been described that hypercortisolimia was associated with the melancholic subtype while hyperinflamation and metabolic syndrome were associated with more atypical presentations of depression (29). Atypical depression is observed in about 15-30% of all cases and is characterized by hypersomnia, fatigue, weight gain and increased appetite (29).

Our study was too small to provide any reliable information on this regard. However, while we did not frequently observe major differences with regard to vegetative symptoms associated with depression, all patients in our study would have shown depressed mood and/or a loss of interest in activities in line with symptoms of a melancholic subtype. Whether this indicates that stroke survivors seen in our study also were prone to develop depression already prior to their stroke and depression less often represents a consequence of hyperinflamation after stroke would have to be further investigated in larger studies also specifically addressing these mechanistic aspects in more detail.

3.4.3.2 Causal networks and mutual influences associated with aspects of socio-economic and behavioural risk factors

Furthermore, a more detailed understanding of the relationship between open need with regard to socio-economic problems and its implication for long-term general health maybe essential. The fact that social inequalities have major implications on mortality is well known (30, 31). Furthermore material/structural living components have been described to shape the conditions of psychological resources and health behavior (30).

The underlying causes and mediators for these associations include but may not be limited to:

1. Underlying educational differences leading to income differences and at the same time to differences with regard to the understanding of need for secondary prevention, options for out-patient treatment etc.
2. Differences with regard to health risks related to working conditions (noise exposure to toxins and so on)

3. Differences with regard to nutrition (such as consumption of a high fat/high carbohydrate diet)
4. Living conditions (such as the ability to leave the flat /house with the help of elevators)
5. General mobility (for example car ownership)
6. Level of general stress (related to work, living conditions, understanding and feeling of control /helplessness) with regard to the remaining symptoms of the disease.

In a longitudinal study financial resources have been assessed for their associated with a lower likelihood of physical illness (28, 32). Here, respondents were asked at baseline to report their annual earnings before taxes (wages, salary, commissions) and whether or not they were currently employed either part or full time. Interestingly, despite a lot of evidence, that financial resources are linked to physical health and that depression may be associated with reduced financial resources the relationship between physical illness and previous depression was not found to be modified by this (28). So the prospective relationship between depression with physical illness did not vary with differences in financial resources, despite that fact that financial resources were associated with depression at baseline and also with development of physical illness (26). This might indicate that despite influencing both conditions separately the strength relationship between the two health outcomes seems not to be altered by baseline financial status in longitudinal manner. Meaning a lower baseline financial status does not seem to accelerate the way in which depression increased the risk for physical illness. However, if the financial status would change both outcomes would be expected to be influenced positively. To further untangle these association population wide longitudinal studies that start collecting financial data already before onset of depression may be helpful. Another interesting aspect might also be to investigate the relation between medication non-adherence and depression in more detail. An association is plausible and would further underline the importance of early diagnosis and screening. By decreasing medication adherence depression maybe a risk factor in the development of long-term somatic complications.

3.4.3.3 Use of SSRI treatment in the prevention of depression after stroke

Moreover, a general open question with regard to medication/treatment of depression after stroke concerns the general usefulness of prophylactic antidepressant medication intake. For example selective Serotonin Reuptake inhibitor (SSRI) intake hast been suggested to be associated with improved recovery, regardless of a diagnosis of depression after stroke (33). This was supported by increasing evidence from more high quality trials and indicates that post stoke intake of SSRI for a duration of three months can improve stroke recovery also in patients without depression with a favourable benefit/risk ratio (34). Specifically motor recovery was

found to be improved in a randomised, placebo controlled and double blinded study (FLAME) (35). Potential mechanistic explanations for this include a reduction of inflammatory damage, the induction of regenerative neurogenesis a better regulation of cerebral blood flow and a regulation of the adrenal hormone system (36). Specifically motor cortex excitability has been found to be decreased by SSRI and the beneficial effects of SSRIs have been explained by a beneficial effect of balanced bihemispheric motor cortex excitability on synaptic plasticity (36). In contrast to this other recent results from randomized controlled trials suggested that patients treated with fluoxetine had more bone fractures six and twelve months after stroke (37). More data describing the potential prophylactic and adverse effects of anti-depressants may be important to further inform and potentially eventually alter guideline recommendations for post stroke medical treatment.

3.4.3.4 Effectiveness of different non-pharmaceutical interventions after stroke

Finally, in the future it might also be of interest to generate a better knowledge with regard to the effectiveness of different non-pharmaceutical interventions in treating psychological and cognitive complications after stroke. Such interventions-for example neuropsychological training- may have the benefit of a more comprehensive treatment approach allowing for a combination of cognitive training, treatment of depression and addressing behavioral and social consequences after stroke. Combining these kind of approaches could lead to supra-additive effects on outcomes, for example when cognitive training also supports depression treatment by allowing patients the experience of self-efficacy with documented improvements of cognitive function after training. Furthermore, first data suggest that neuropsychological training may be essential for successful professional re-integration suggesting a high relevance also with regard to the socio-economic consequences of stroke (38). Keeping this in mind the benefits of cognitive rehabilitation training have also been shown to depend on the severity of the defects with more strong improvements seen for more mildly affected patients (39).

3.5 Contributions

Inken Padberg developed the primary and secondary research questions, generated the statistical analysis plan, performed all statistical analysis, generated all Figures and Tables, drafted the manuscript (introduction, material and methods, results and conclusion) , collected and coordinated input from co-authors wrote and finalized the manuscript, selected journal and implemented final formatting instructions, obtained final approval from all co-authors, submitted the manuscript, drafted response to reviewer comments and performed additional analysis suggested (namely Benjamini Hochberg correction and logistic regression), obtained input and approval from all co-authors, resubmitted the manuscript and corrected final proofs.

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4 Anteilserklärung

Eidesstattliche Versicherung

Ich, Inken Padberg, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema:

„ Schlaganfallnachsorge, Depressionen und deren Assoziation mit Langzeitkomplikationen und gesundheitsassoziierter Lebensqualität/Post-stroke aftercare, depression and its association with screening, long-term complications and health related quality of life"

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Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.
Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.
Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.
Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst."

Datum Unterschrift

Anteilserklärung an der erfolgten Publikation

Inken Padberg hatte folgenden Anteil an den folgenden Publikationen:
Publikation 1: Autoren: Inken Padberg, Benjamin Hotter, Andrea Liebenau, Petra Knispel, Sophie Lehnerer, Sabine Heel, [5]an Wellwood, Andreas Meisel
Titel; Unmet need for social and emotional support and lack of recalled screening is associated with depression in the long-term course after stroke
Journal: Risk Management and Healthcare Policy, 2019

Beitrag im Einzelnen
Entwicklung der Forschungsfragen, Ausarbeitung eines statistischen Analyseplans und Gesamtkonzeptes Durchführung der statistischen Analyse Auswertung der Daten zu allen Figures und Tabellen, Erstellung aller Figures und Tables, Einarbeitung Ides Inputs von Koauroten, Auswahl des Journals, Erstellen des Textes, Einarbeiten kritischer Kommentare der Reviewer und Koautoren, Ausarbeitung der Antworten an die Reviewer finale Formatierung, Einreichung und Korrektur

_____
Unterschrift, Datum und Stempel des/der erstbetreuenden Hochschullehrers/in

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Unterschrift des Doktoranden/der Doktorand

5 Journal Summary List

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI
Selected Categories: **"HEALTH POLICY and SERVICES"**
Selected Category Scheme: WoS
Gesamtanzahl: 81 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	MILBANK QUARTERLY	3,936	7.425	0.004600
2	BMJ Quality & Safety	5,234	7.043	0.017230
3	HEALTH AFFAIRS	17,240	5.711	0.053190
4	VALUE IN HEALTH	8,819	5.037	0.018200
5	Implementation Science	9,216	4.525	0.019280
6	International Journal of Health Policy and Management	1,140	4.485	0.003470
7	MEDICAL CARE	20,250	3.795	0.021130
8	PHARMACOECONOMICS	4,775	3.705	0.009090
9	FUTURE OF CHILDREN	2,013	3.500	0.002240
10	Journal of Patient Safety	940	3.386	0.002470
11	JOURNAL OF HEALTH ECONOMICS	7,220	3.352	0.014850
12	BMC Palliative Care	1,522	2.922	0.003880
13	HEALTH EXPECTATIONS	3,199	2.847	0.007740
14	HEALTH POLICY AND PLANNING	6,401	2.717	0.010110
15	HEALTH SERVICES RESEARCH	8,061	2.706	0.013670
16	Administration and Policy in Mental Health and Mental Health Services Research	2,888	2.681	0.005000
17	Patient-Patient Centered Outcomes Research	1,008	2.673	0.003090
18	Applied Health Economics and Health Policy	1,126	2.664	0.003350
19	HEALTH CARE MANAGEMENT REVIEW	1,660	2.636	0.001830
20	MEDICAL CARE RESEARCH AND REVIEW	2,431	2.577	0.004060
21	Human Resources for Health	2,504	2.547	0.005110

1

22	International Journal of Integrated Care	1,137	2.489	0.002010
23	QUALITY OF LIFE RESEARCH	13,192	2.488	0.019050
24	JOURNAL OF RURAL HEALTH	1,729	2.471	0.002630
25	Journal of Genetic Counseling	2,378	2.446	0.005110
26	Health and Quality of Life Outcomes	8,070	2.318	0.012120
27	Journal of Health Services Research & Policy	2,035	2.303	0.002050
28	Risk Management and Healthcare Policy	416	2.283	0.001270
29	PSYCHIATRIC SERVICES	10,947	2.253	0.015610
30	PSYCHOLOGY PUBLIC POLICY AND LAW	1,481	2.219	0.002180
31	Health Research Policy and Systems	1,766	2.218	0.004380
32	European Journal of Health Economics	2,028	2.169	0.005340
33	AIDS CARE-PSYCHOLOGICAL AND SOCIO-MEDICAL ASPECTS OF AIDS/HIV	6,484	2.105	0.012510
34	HEALTH POLICY	7,107	2.075	0.009910
35	Health Care Management Science	1,163	2.059	0.001340
36	HEALTH ECONOMICS	6,127	2.027	0.010350
37	JOURNAL OF AGING AND HEALTH	2,878	2.007	0.004100
38	Palliative & Supportive Care	1,609	1.965	0.003400
39	Health Economics Policy and Law	529	1.959	0.001140
40	HEALTH PROMOTION INTERNATIONAL	3,296	1.913	0.003800
41	HEALTH COMMUNICATION	3,135	1.846	0.005480
42	JOURNAL OF HEALTH POLITICS POLICY AND LAW	1,085	1.839	0.002250
43	HealthCare-The Journal of Delivery Science and Innovation	394	1.833	0.002570
44	INTERNATIONAL JOURNAL FOR QUALITY IN HEALTH CARE	4,709	1.829	0.004550

Selected JCR Year: 2018; Selected Categories: "HEALTH POLICY and SERVICES"

45	Expert Review of Pharmacoeconomics & Outcomes Research	1,645	1.828	0.003130
46	Journal of Interprofessional Care	2,977	1.772	0.003770
47	INTERNATIONAL JOURNAL OF HEALTH SERVICES	1,471	1.750	0.001600
48	Health Information Management Journal	320	1.742	0.000390
49	AMERICAN JOURNAL OF MANAGED CARE	4,414	1.706	0.009650
50	Cost Effectiveness and Resource Allocation	597	1.676	0.000790
51	JOURNAL OF PUBLIC HEALTH POLICY	1,076	1.675	0.001530
52	Israel Journal of Health Policy Research	338	1.662	0.000970
53	BMC International Health and Human Rights	958	1.656	0.002080
54	EVALUATION & THE HEALTH PROFESSIONS	1,209	1.604	0.001670
55	Health Sociology Review	529	1.591	0.000680
56	JOURNAL OF COMMUNITY HEALTH	2,864	1.572	0.006190
57	Disability and Health Journal	1,122	1.471	0.002690
58	COMMUNITY MENTAL HEALTH JOURNAL	2,714	1.460	0.003950
59	INTERNATIONAL JOURNAL OF HEALTH PLANNING AND MANAGEMENT	887	1.450	0.001310
60	Health Economics Review	460	1.374	0.001610
61	American Journal of Health Economics	129	1.349	0.001350
62	JOURNAL OF BEHAVIORAL HEALTH SERVICES & RESEARCH	1,113	1.343	0.002050
63	Journal of Health Organization and Management	914	1.306	0.001190
64	Australian Health Review	1,678	1.228	0.002310
65	Health Policy and Technology	277	1.225	0.000660
66	Journal of Pediatric Health Care	1,138	1.115	0.001800
67	Journal for Healthcare Quality	604	1.092	0.001650

68	HEALTH CARE ANALYSIS	508	1.043	0.000520
69	Australian Journal of Primary Health	844	1.024	0.001600
70	JOURNAL OF HEALTH CARE FOR THE POOR AND UNDERSERVED	2,496	0.966	0.004620
71	CAMBRIDGE QUARTERLY OF HEALTHCARE ETHICS	605	0.941	0.000740
72	Journal of Mental Health Policy and Economics	483	0.931	0.000490
73	Journal of Policy and Practice in Intellectual Disabilities	660	0.925	0.000750
74	JOURNAL OF HEALTHCARE MANAGEMENT	618	0.847	0.000840
75	INQUIRY-THE JOURNAL OF HEALTH CARE ORGANIZATION PROVISION AND FINANCING	617	0.769	0.000650
76	Quality Management in Health Care	458	0.759	0.000540
77	EASTERN MEDITERRANEAN HEALTH JOURNAL	2,228	0.694	0.001970
78	Asian Journal of WTO & International Health Law and Policy	77	0.433	0.000130
79	International Journal of Health Economics and Management	52	0.378	0.000260
80	JOURNAL OF PALLIATIVE CARE	984	0.364	0.000580
81	SCIENCES SOCIALES ET SANTE	143	0.154	0.000050

Risk Management and Healthcare Policy

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ORIGINAL RESEARCH

Unmet Need for Social and Emotional Support and Lack of Recalled Screening Is Associated with Depression in the Long-Term Course After Stroke

This article was published in the following Dove Press journal:
Risk Management and Healthcare Policy

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Purpose: Details on adequate care and prevalence of depression in long-term stroke aftercare are limited. We aimed to determine long-term depression rates after stroke and to test for an association between depression and inadequate screening, socio-economic complications and lack of sub-optimal care.

Patients and Methods: In this cross-sectional study, 57 patients were re-invited into the clinic 2–3 years after stroke. Patients were interviewed about recalled screening concerning depression and unmet needs. Depression, the patient's social situation, and confounders were assessed by standardized scores.

Results: In our study, 20% (n = 11) of patients were classified as depressed by the HDRS-17 score result. However, only 36% of all patients recalled to have been previously screened for depression and only 43% of those patients also recalled out-patient screening. Patients classified as depressed reported significantly lower recalled screening rates (9% vs 43%; $p = 0.036$) and higher rates of self-reported unmet need with emotional problems (72% vs 18%; $p < 0.001$). Depression in our study was further associated with a worse socio-economic situation, fewer social contacts, unmet needs with regard to emotional problems and higher rates of recommendations to apply for additional social support.

Conclusion: Our data suggest that systematic out-patient screening for depression is lacking in stroke aftercare. Furthermore, the high rate of unmet emotional needs, the poor socio-economic situation and the higher rates of recommendations for social counselling and application for benefits suggest an undersupply of care in the out-patient setting that is more prominent in patients with depression and warrants further studies to investigate the underlying causes.

Keywords: health-care quality, social-care, risk management, stroke, depression

Plain Language Summary

The study was done to better understand how frequently depression occurs 2–3 years post-stroke, whether it is continuously screened for and whether patients with post-stroke depression had more social problems than patients without depression.

We tested for depression by using a commonly used questionnaire asking for major symptoms of the disease. We also assessed the socio-economic situation, the social contacts and the housing situation of the patients and asked the patients whether a health-care professional had previously asked them for symptoms of depression after stroke.

We found that very few patients were tested for symptoms of depression after stroke during out-patient care. Compared to patients without depression, patients with a score result indicating depression less frequently reported to have previously been asked for symptoms of

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depression after stroke. Furthermore, patients with depression also had more social problems than patients without depression. Finally, we found that all patients classified as depressed by a questionnaire comprised of 17-items (HDRS-17) would also have been detected by using a reduced version of the questionnaire consisting of only two questions.

Introduction

Depression after stroke remains a major clinical challenge with a recent systematic review estimating a proportional frequency for post-stroke depression of approximately 30%.[1] It is associated with disability, poor quality of life, increased mortality, social isolation and slow recovery[2] as well as with non-adherence to medication in different medical conditions.[3,4] Despite this, depression often remains undertreated.[5,6] Depressive symptoms after stroke can occur directly after the event but also can arise in the course of long-term disease development and management.[1] Similar to other chronical diseases, the transfer from the hospital setting (acute or rehabilitation) to out-patient aftercare presents a challenge for continuous care in stroke patients. Here, deficits may limit the potential rehabilitation success as continuous care and training of function has been reported to result in improvements up to several years after stroke-event if provided with sufficient intensity.[7] Hereby, general health, opportunity and motivation for training are important factors influencing success. A recent review focused on depression as a general risk factor for organic disease and concluded, that by inducing unfavorable pathophysiological and behavioral processes, social and emotional loneliness contributes to the link between depression and physical illness.[8] Vice versa it is well known that depression also is a common complication caused by stroke.[1] Underdiagnosed or inadequately treated depression therefore may represent a risk factor for post-stroke complications. Current guidelines state there is a need for more research to determine if screening for depression – in conjunction with collaborative care – helps to reduce its prevalence.[9] In particular, there is a lack of evidence with regard to long-term care extending up to 2–3 years after stroke. Explicit recommendations on timing of screening for depression and its relation to long-term prevalence, as well as the development of potential complications do not exist. Current clinical guidelines highlight the need for time-efficient screening tools suitable to identify patients with post-stroke depression in the aftercare setting. Short dichotomous screening tools, such as the PHQ-9 score have been shown to be effective in the general population, however, have not yet been tested in stroke patients.[9,10]

Here, we aimed to investigate whether prevalent depression was associated with a self-reported lack of recalled screening for depression and care in the long-term course after stroke. Further, we sought to test the hypothesis that depression is associated with loss of social support, a worse housing and financial situation, insufficient care and lower quality of life 2–3 years after stroke. Moreover, we conducted exploratory tests of sensitivity and specificity of a potential simple screening tool for identifying patients with post-stroke depression.

Materials and Methods

Study-Design

The present analysis is part of the observational, cross-sectional MAS-I study (clinical trial registration number NCT02320994), which has been described previously.[11] Briefly, MAS-I aimed to assess the needs and disease burden of community-dwelling stroke patients and their carers and to compare their treatment to evidence-based guidelines by a stroke neurologist. We recruited participants employing purposive sampling of previous participants of two independent and completed hospital-based acute stroke studies (a randomised-controlled trial STRAWINSKI NCT0126454934 and an observational study PREDICT NCT0107972835). Inclusion criteria used in PREDICT were acute ischemic stroke of any severity (NIHSS ≥ 1 at study inclusion, TIA excluded) and any localization, symptom onset ≤ 36 h and age ≥ 18 years. Inclusion criteria used in STRAWINSKI were age ≥ 18 years and severe ischemic stroke in the middle cerebral artery (score of >9 on the National Institute of Health Stroke Scale). In MAS-1, all previous participants of STRAWINSKI and PREDICT living in the Berlin metropolitan area 2–3 years after the event were invited to take part and visit our out-patient clinic for a follow-up assessment. No financial incentive was provided.[11] The assessment included a comprehensive interview and an examination using the Post-Stroke-Checklist (PSC) as well as validated standard measures of (among other domains) depression, quality of life, secondary prevention and social needs. Current use of medication was assessed with a focus on secondary prevention. Recalled screening for depression and history of intake of anti-depressant medication was assessed based on self-reported information and review of discharge letters.

To counter selection bias, we offered to pay travel costs to and from our center.

Scores and Outcome Measures

In our primary research question, we attempted to understand which factors might contribute to the development of prevalent depression in the long-term aftercare after stroke. The main parameter of interest was self-reported recalled screening and its association with depression which was diagnosed using the HDRS-17 score. Further, scores used included the Stroke Survivor Need Scale, the Nikolaus Score and the EQ-5D-5L, the modified Rankin Scale, the MoCA and the Post-Stroke Checklist (PSC). Details on the above-described scores can be found in the Supplementary methods section.

Statistical Analysis

Statistical analyses were performed using SPSS software version 22.

Except for age where the assumption of normal distribution was not rejected by the Kolmogorov Smirnov test, all other group comparisons were subjected to non-parametric testing by Mann–Whitney-U, Fishers exact or chi-square test. Differences between frequency outcomes were calculated by Fisher's exact test where the expected frequency count was <5 and by chi-square where this was not the case. Correlations were calculated by Spearman's Rho. Missing data were subjected to listwise deletion. P-values related to primary and secondary research questions were controlled for multiple testing using the Benjamini-Hochberg procedure. Due to the small number of participants for most part of the analysis, we used simple parametric and non-parametric statistical testing. However, to clarify whether the association between recalled screening and depression may have been confounded by age, cognition, years of education, modified-Rankin scale and sex an explorative logistic regression model correcting for the factors was additionally carried out using Stata version 14.2.

Results

Prevalence, Recalled Screening and Care and Consequences of Depression

Overall 516 subjects were invited out of which 57 patients (11%) responded and were included in MAS-1.[11] For 56 of these patients depression was assessed using the HDRS-17 depression scale. Eleven (20%) of the assessed patients would be diagnosed as depressed according to the score result.

Data about recalled screening for depression after stroke were available from 55 of those 56 patients. According to the patient's self-report only a minority (n=20; 36%) recalled to have been screened for depression after stroke. To better understand whether the prevalence of depression might be associated with recalled screening we compared rates of self-reported prior screening and prevalent depression according to HDRS-17 score result. Recalled screening rates were 9% (n=1) in patients who were diagnosed as depressed and 43% (n=19) in non-depressed patients, resulting in a significant difference (p=0.036) (Table 1). Furthermore, even in the group of patients who indicated to have been previously screened for depression less than 43% indicated screening had been done during the out-patient phase of disease management. In order to exclude potential modifiers or confounders causing the observed association between recalled screening and prevalent depression, we additionally calculated a logistic regression model and corrected for current age, sex, years of education, cognition and modified Rankin scale (collected 3 months after stroke). Also after correction, the association remained significant. Also, in a direct comparison none of these factors differed significantly between patients with and without prevalent depression according to HDRS-17 score result (Table 2).

We furthermore found that eight of eleven (72%) patients with and eight of 45 (18%) patients without a score-based diagnosis of depression also expressed an unmet need with regard to help with emotional problems (defined as confusion/depression/crying) after the stroke (p-value <0.001) (Table 1).

For 34 of our 56 patients, information on whether prior anti-depressant medication had been prescribed was available. Altogether eleven of these 34 patients had a history of prior treatment with anti-depressants mostly starting during the stay in the acute or rehabilitation hospital due to the acute presence of symptoms (such as crying/loss of interest) for depression (Table 3).

Interestingly, five of eleven patients with anti-depressant medication in our study still were classified as depressed according to their current HDRS-17 result and four of these five patients did not recall to have previously been screened for depression (Table 3). Altogether the recalled screening rate reported in patients with a history of prior anti-depressant treatment did not differ from the overall recalled screening rate for depression (36%) (Table 3).

Association Between Depression, Current Social Situation, Medication Adherence and Quality of Life

With regard to their current situation, patients with depression reported significantly lower social contacts and a worse

Table 1 Overview of Recalled Screening, Quality of Life, Social Care and Unmet Emotional Long-Term Needs After Stroke are Depicted in Patients with and Without Prevalent Depression

Hamilton Depression Scale	Depression No (n=45) (Cutoff < 9)	Depression Yes (n=11)	p-values	Benjamini Hochberg Critical Value (I/Number of Tests) *Q(fdr)	Rank (Order of p-values)
Primary research question: association of recalled prior screening and unmet need for help with emotional problems with prevalent depression					
Screening for depression yes (n)	19 (43% of all non-depressed) (n=44)	1 (9% of all depressed)	0.036	0.039	7
Unmet need with emotional problems	8 (18% of all non-depressed)	8 (72% of all depressed)	<0.001	0.006	1
Secondary research questions: associations between depression and current complications/need for further care					
Recommendation for mediation into further socio-economic counselling	2 (5% of all non-depressed)	4 (36% of all depressed)	0.002	0.011	2
Nikolaus-score: socio-economic situation (median (min-max/IQR))	2 (0–3/1)	1 (0–3/1)	0.010	0.017	3
Nikolaus-score: social-contact (median (min-max/IQR))	5 (1–6/1)	4 (2–6/2)	0.014	0.022	4
Recommendation to apply for further socio-economic care and benefits	2 (5% of all non-depressed)	3 (27% of all depressed)	0.017	0.028	5
Nikolaus-score: housing situation (median (min-max/IQR))	9 (3–11/3)	8 (5–11/2)	0.029	0.033	6
EQ-5D-5L (visual analogue scale) (median (min-max/IQR))	70 (30–100/28)	62 (40–85/26)	0.142	0.044	8
EQ-5D-5L–Index (median (min-max /IQR))	0.81 (0.06–1/0.3)	0.84 (0.23–1/0.53 (n=10))	0.276	0.05	9

Notes: Depicted are associations between recalled prior screening and prevalent depression measured by the HDRS-17 and between depression and its potential complications. P-values are corresponding to Mann–Whitney-U or chi-square test where appropriate. P-values were controlled for multiple testing using the Benjamini-Hochberg procedure. The false discovery rate (FDR) was set to 0.05. With regard to the socio-economic situation as well as with regard to unmet need with emotional problems and recommendations to apply for further social-economic counselling and benefits p-values were smaller than the critical value calculated by Benjamini-Hochberg.

socio-economic and housing situation than patients without depression (Table 1). The socio-economic situation in our study was evaluated by an experienced social worker who recommended further mediation, counselling or application for benefits if necessary. To better understand whether differences in the socio-economic situation also reflected differences in the need for further intervention, in a next step we compared the rate of recommendations for counselling and applications for benefits in depressed and non-depressed patients. We found significantly higher recommendation rates for further intervention in patients with depression (Table 1).

These results remained significant even after correction for multiple testing (Table 1). However, we observed no association between depression and overall level of quality of life in this group comparison. Despite of this post-hoc analyses for correlation between HDRS-17 values with the visual analogue scale of the EQ-5D-5L showed a significant association (r^2=−0.382, p =0.004).

Furthermore, also correlations between the assessments used to determine the social situation and the HDRS-17 results were significant (Supplementary Table 1).

Performance of Single Items of the HDRS-17 for Diagnosis of Depression After Stroke

Lower rates of recalled out-patient screening in patients with prevalent depression might be attributed to regular screening using the standard tools is too time-consuming

Table 2 Patient Characteristics That are Potentially Associated with Depression

	Depression No (n=45) (HDRS-17 Cutoff < 9)	Depression Yes (n=11)	p-values
Sex (Male, n (%))	29 (64% of all non-depressed)	4 (36% of all depressed)	0.09
Thrombocyte inhibition yes (n)	34 (75% of all non-depressed)	6 (54% of all depressed)	0.18
Years in education (median (min-max/IQR)/mean (SD/95% CI)	14 (8–23/5)/14 (3/13–15)	15 (10–23/5)/ 16 (4/13–18)	0.34
Statins yes (n)	36 (80% of all non-depressed)	8 (73% of all depressed)	0.44
Modified Rankin (3 months after stroke median (min-max/IQR))	2 (0–4/2) (n=43)	2 (1–5/3)	0.46
Anticoagulation yes (n)	14 (31% of all non-depressed)	4 (36% of all depressed)	0.74
Age (median(min-max/IQR)/mean (SD/95% CI))	73 (42–86/15)/ 70 (10/66–73)	66 (63–86/7)/ 69 (8/64–75)	0.70
Cognition (MoCA Score) (median (min-max)/IQR)	24 (6–30/5)	27 (17–29/8)	0.23

Notes: Factors potentially influencing the associations of prior screening with depression and/or the association of depression with the development of complications. Depicted are differences in potential confounders or mediators of the association between depression and prior screening for depression or depression and its complications. P-values are corresponding to Mann–Whitney U, *t*-test or chi-square test where appropriate. For score data, median as well as minimum and maximum values and the interquartile range are indicated. For continuous variables (age and years in education) additionally the means, standard deviations and 95% confidence intervals are reported.

Table 3 Overview of Intake of Antidepressant Medication After Stroke

		No Evidence for Prior Post-Stroke Antidepressant Medication	Evidence for Prior Post-Stroke Antidepressant Medication	Sum
No prior screening reported	Depression according to HDRS-17	4	4	8
	No Depression according to HDRS-17	13	3	16
Prior screening reported	Depression according to HDRS-17	0	1	1
	No Depression according to HDRS-17	6	3	9
Sum		23	11	34

Notes: Reported are the numbers for patients with and without prior anti-depressant medication and their distribution across the groups with and without prevalent depression and prior screening for depression.

for general practitioners. Therefore, we aspired to exploratively test how a reduced version of the Hamilton depression scale using only two items in a dichotomous manner would perform compared to the full 17-item version of the Hamilton scale. When comparing single items of the HDRS-17 (dichotomized in healthy or pathological irrespective of the strength of the items) differences between depressed and non-depressed stroke patients (Figure 1) were highest for loss of interest in work and other activities (Item 7), feelings of guilt (Item 2) and depressive mood (Item 1) (Figure 1).

Items 1 and 7 of the HDRS-17 also represent the two criteria that are necessary for a diagnosis of depression according to the DSM-5 (depressive mood/loss of interest or pleasure in work and other activities), so in a next step, we strove to see how these items would compare to the overall score with regard to sensitivity and specificity of detecting depression. For a combination of item 1 and item 7, the sensitivity for detecting depressed patients was at 100%. In other words, all patients who were diagnosed as depressed according to the 17-item version of the HDRS-17, could also be detected by a two-item screening. The

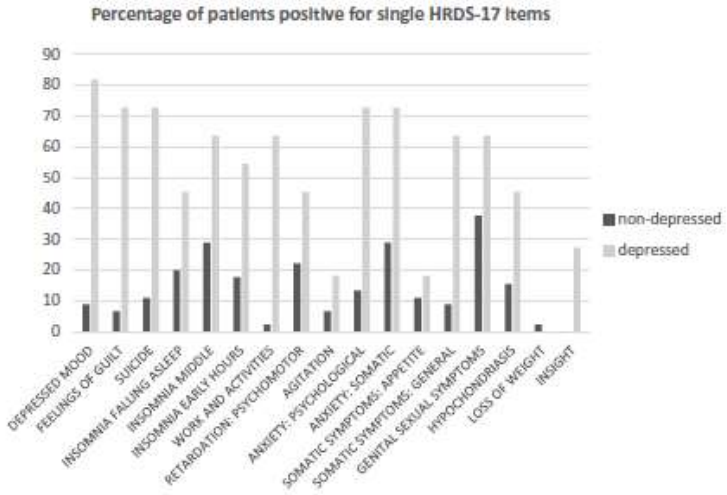

Figure 1 HDRS 17-items.
Notes: Impairments in patients with and without post-stroke depression. Shown are the percentages of depressed vs non-depressed patients who are positive for the single items.

specificity for using only two questions was 0.91 when compared with the overall HDRS-17 (Table 4).

For item 8 (asking about "feelings of anxiety and depression") of the PSC, the sensitivity and specificity for detecting depression in comparison to the HDRS-17 was lower than for the two-item screenings (0.91 and 0.71, respectively). However, when comparing the single items, the sensitivity for detecting depression was highest for item 8 of the PSC (91%), compared to 82% and 64% of the single items 1 and 7 of the HDRS-17.

Among the single items of the HDRS-17 for which the strength of the rating also was highly correlated (Table 5) with overall score results, again were "interest in work and other activities" (Item 7 of the HDRS-17), depressive mood (Item 1) and their combination.

Discussion

With low-recalled screening rates we observed a high rate of manifest depression 2 to 3 years after stroke onset. Patients with depression further reported experiencing a poor social situation and less emotional support, which might increase the risk for developing additional medical complications such as cardiovascular disease, metabolic syndrome or chronic pain.[8] Furthermore, social counselling and application for benefits were recommended more frequently in patients with depression. The lower rate of

Table 4 Negative and Positive Predictive Value, Sensitivity and Specificity for a Combination of Two and Single Items in Detecting Depression

	Negative Predictive Value	Positive Predictive Value	Sensitivity	Specificity	p-value
Depressed mood (item 1) and interest in work (item 7) (if one pos., whole item pos.)	1	0.73	1	91	<0.001
Item 7 work	0.92	0.88	64	97	<0.001
Item 1 depressed mood	0.95	0.69	82	91	<0.001
PSC item 8 (feelings of anxiety or depression)	0.97	0.43	91	71	<0.001

Notes: Positive and negative predictive values, of HDRS-17 items work, feelings of guilt, depressed mood and combined items. P-values indicate results of the Fisher's exact test confirming the dependence of the results of the 2 vs 17 item screening.

Table 5 Correlations Between Overall HDRS-17 Value and Ratings for Single Items of the Score

	Correlation with HDRS-17 (Spearman's Rho)
Item 1: depressed mood	0.567 (p-value<0.001)
Item 7: interest in work/activities	0.566 (p-value <0.001)
Item 10: anxiety psychological	0.634 (p-value<0.001)
Item 11: anxiety somatic including symptoms such as increased heart rate and breathing, diarrhea, headache	0.537 (p-value <0.001)
Items 1+7	0.669 (p-value <0.001)

Notes: Correlations between overall HDRS-17 value and single items of the score. Shown are items that were most highly correlated with the overall score-result.

recalled screening, the higher rates of expressed unmet need with regard to emotional problems and the undersupply of social care may indicate that in patients with depression social problems and emotional needs currently were not adequately addressed during aftercare for stroke. Since some of the patients who did not recall screening already had received prior anti-depressant medication mostly initiated during the hospital stay, a lack of adequate care in the out-patient setting could indicate that further treatment recommendations for patients with depression were not adequately followed up after the transfer to the out-patient setting. However, this remains speculative, since we had only limited information on the antidepressant medication used and no information on the circumstances of prescription or whether and which recommendations for out-patient treatment were given specifically. Future studies should investigate this issue in more detail considering that anti-depressant drugs might also be prescribed prophylactically or for the treatment of post–stroke pain.[12] Furthermore, response rates to antidepressant treatment can change over time. Therefore, continuous screening for disease symptoms may be essential to improve out-patient treatment and adequately address emotional needs. Simplified screening methods for out-patient depression after stroke might support general practitioners to monitor the disease in a time-effective fashion. Our data suggest that loss of interest in work and other activities (Item 7 of the HDRS-17) in combination with depressed mood (Item 1) in our study displayed the same sensitivity as the 17-item HDRS-17 for detecting depression in our sample.

Previous work found two-question-screenings for depression to be similarly accurate as more extensive instruments[13] and mail-delivered short versions to be similar to long versions of self-assessment tools (Beck depression inventory) after stroke.[14] The Beck depression inventory (self-assessment) and the HDRS-17 (interviewer-based face to face assessment) moreover have been evaluated to be similarly useful in the detection of depression.[15] Interviewer-based ratings and diagnoses, however, compares favorably to real-life situations when patients visit their general practitioner in out-patient aftercare. For this type of interview, studies confirming the efficiency of using reduced score versions of face-to-face assessments such as the HDRS-17 during the post-stroke aftercare have been lacking so far. Previous studies using a 9 item version of the Hamilton depression inventory indicate that these versions also displayed high internal consistency and test –retest reliability.[16] However, they were never established in clinical routine. Other two-item versions of screening tools for depression such as the PHQ-2 have been tested successfully for depression but were not validated in stroke patients.[9] Our small study was not powered for a detailed analysis of the precision of a two-item score. However, an exploratory comparison of the full versus the two-item version, data collected in our study indicated that using verbal screening including two items in a dichotomous manner in our study would have left no patient with depression undetected.

Limitations of our study include first of all the small size of our exploratory study. Due to this, we can only draw limited conclusions. Larger long-term studies following the intake and effects of antidepressant medication are needed to confirm our findings. However, the patients were well characterized with the exception that information on prior anti-depressant medication intake was only available for 34 of 57 and for nine of eleven patients that were classified as depressed according to the HDRS-17. Data collected in smaller studies can be prone to different forms of bias and data on screening in our study were self-reported and collected retrospectively. Therefore, we cannot exclude a recall bias with regard to the screening for depression. Such a bias may distort our results as patients with depression tend to have cognitive impairments as well.[17] However, in our study, we did not see differences in people with and without depression with regard to cognitive impairment and results remained significant also after adjusting for confounding factors including cognition. Furthermore, although we offered transportation we cannot exclude a selection bias concerning patients unable to attend our study center.

Even though we controlled for a wide panel of potential confounders we did not control for stroke lesion.

However, the type of lesion induced by the stroke may explain some of the variability associated with depression, but – especially since differences with regard to cognition did not seem to be an issue – is unlikely to affect recalled screening or the quality of medical support with regard to emotional problems. Therefore, the type of lesion should not confound our results with regard to the association between recalled screening and depression.

Due to the cross-sectional design of our study, we have only limited information on the status of depression and unmet need at stroke onset. Therefore, we cannot be certain whether the outcomes such as unmet need for support with emotional problems or lower social-support represent consequences of the depression or should be considered risk factors in the development of the disease. In any case, social loneliness has previously been reported to provide a link between depression and organic disease.[8] Also, the fact that further socio-economic counselling and care in our study was recommended at significantly higher rates in patients with depression underlines the need for detection of depression in long-term stroke aftercare to identify vulnerable patients that may not be able to organize optimal care for themselves.

Finally, the results from the two-item screening are not independent from the overall results of the HDRS-17. Consequently, the high sensitivity rate for detecting depression using the two-item version of the HDRS-17 needs to be interpreted with great care.

In conclusion, we found that a minority of patients recalled to have been screened for post-stroke depression. In patients with depression a lower rate of recalled screening, a worse social situation and more unmet need with emotional problems were observed. Patients with post-stroke depression further were more often recommended to apply for social support and benefits, indicating that available resources were not being used to the extend they were needed to ensure optimal stroke aftercare. Undersupply of care in patients with post-stroke depression might induce a vicious circle increasing the risk for additional medical complications leading to increased mortality and disability.[2,5] Results of our exploratory analysis further question whether using only two items of the HDRS-17 scale may be sufficient for detecting patients at risk for post-stroke depression when time does not allow for more detailed assessment of all patients. This finding could be important, since previous studies have demonstrated that unassisted judgments of general practitioners for depression in their patients lack sensitivity.[18] Our findings warrant larger, prospective, multicenter studies exploring in more detail the effect of a better treatment and a more efficient screening for post-stroke depression in improving medical and social outcomes in the long-term course of stroke.

Ethics and Informed Consent

All participants provided written informed consent and the study received full ethics committee and data protection approval by the institutional review board of Charité – Universitätsmedizin Berlin (reference EA1/183/14), and was registered on clinicaltrials.gov (NCT02320994).

Data Sharing Statement

Data are available based upon reasonable request from the corresponding author and the PI of the MAS study: Andreas Meisel: andreas.meisel@charite.de and Inken Padberg: inken.padberg@charite.de.

Acknowledgments

We thank Susanne Zöllner for help with data acquisition within the MAS-1 study and Dike Remstedt for help with data acquisition as well as for critically reviewing the English language and the wording of the manuscript.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Funding

We acknowledge support from the German Research Foundation (DFG) and the Open Access Publication Fund of Charité – Universitätsmedizin Berlin. These sponsors had no involvement in any of the stages from study design to submission of the paper for publication.

Disclosure

The authors report no conflicts of interest in this work.

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7 CV

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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9 Danksagung

Ich danke meinen Betreuern Andreas Meisel und Bob Siegerink für Ihre Unterstützung, sowie, meinen Kollegen, insbesondere Dr. Ira Napierkowski, Petra Knispel, Benjamin Hotter und Sophie Lehnerer für moralische Unterstützung und eine gute Zusammenarbeit.