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Research paper

Predictors for wellbeing and characteristics of mental health after stroke

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ABSTRACT

Background: Poor mental health after stroke is common and complex. We aimed to identify predictors of poor wellbeing and to examine the overlap of poor wellbeing, fatigue, and depression.

Method: Consecutive first-ever ischemic stroke-patients filled in questionnaires on wellbeing, fatigue, and depression at baseline and at one and six months. The World Health Organization 5-Item Wellbeing-Index (WHO-5), the Major Depression Inventory, and the Multidimensional Fatigue Inventory were used. Patients were genotyped according to serotonin-transporter gene polymorphisms. Multivariable logistic regression was used to identify potential predictors of poor wellbeing (WHO-5 score <50). Overlap between wellbeing, fatigue, and depression was examined using an Euler diagram.

Results: We included 919 patients. The prevalence of poor wellbeing was 279 (30.4%) six months after stroke. Living alone at stroke onset was the strongest predictor of poor wellbeing with a mutually adjusted odds ratio of 1.53 (95% confidence interval (CI): 1.03 to 2.28) at one month and 1.77 (CI: 1.13 to 2.76) at six months. Severe stroke at admission also predicted poor wellbeing at six months. Abnormal fatigue occurred in half and incorporated almost all patients with poor wellbeing. Less than 5% fulfilled the criteria for depression at any point and almost all of these patients had poor wellbeing and abnormal fatigue. Antidepressants were used by 292 (31.8%) during follow-up.

Limitations: Cognitive impairment was not measured and could interact with wellbeing post-stroke.

Conclusion: Living alone strongly predicted poor wellbeing after stroke. Satisfactory mental health-recovery seems to require psychosocial interventions when indicated in combination with antidepressant treatment.

1. Introduction

Many patients surviving a stroke suffer from mental and cognitive impairment (Jokinen-Salmela et al., 2015). Post-stroke depression (PSD) is common among stroke sequelae, reported to be present in approximately 30% of stroke survivors at any given time (Hackett and Pickles, 2014). PSD is associated with functional dependency as well as increased mortality and morbidity, highlighting the importance of identifying and treating the condition (S.A. et al., 1998). However, stroke patients may not meet the formal diagnostic criteria for depression but still face the challenges of poor wellbeing and a negative impact of depressive symptoms on their recovery process. Furthermore, patients' wellbeing may be low despite otherwise effective antidepressant treatment. A broader approach to mental health after stroke, including a focus on wellbeing, therefore seems reasonable. However, research in this field is sparse.

Different patient characteristics, such as physical disability and stroke severity, have been associated with PSD (Towfighi et al., 2017). PSD has also been associated with a well-described functional length polymorphism (5-HTTLPR) in the serotonin transporter gene causing different levels of gene transcription and thereby different levels of serotonin transporters (Mak et al., 2013). The associations between potential predictors, including serotonin transporter gene polymorphisms or any other genetic factors, and the broader concept of perceived wellbeing after stroke remain to be studied. Furthermore, little is known about the overlap and interactions of wellbeing, depression, and

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sequelae such as abnormal fatigue after stroke. Better understanding what predisposes to poor wellbeing after stroke will enable us to more efficiently identify patients at risk and potentially initiate relevant preventive and therapeutic strategies.

In the present study, we therefore aimed to study potential predictors of wellbeing, including specific genetic polymorphisms in the serotonin transporter gene, demographics, and several stroke-related risk factors. Furthermore, patient-reported wellbeing, abnormal fatigue, and depression, and the overlap between these entities will be visualized in order to examine mental health after stroke.

2. Methods

We included consecutive first-ever ischemic stroke patients admitted to the Acute Stroke Unit at Aarhus University Hospital, Denmark between October 2012 and July 2015 for genetic testing and six-month follow-up. Patients were included within seven days from symptom onset. The local ethics committee approved the study (study number M20110281), and all participants gave written informed consent.

2.1. Data collection

Wellbeing was registered using the World Health Organization 5-Item Wellbeing Index (WHO-5), a 5-item scale assessing the wellbeing of subjects as a measure of mental health (Topp et al., 2015). The WHO-5-score was dichotomized for logistic analysis with a poor outcome defined as a score <50, which is also the recommended cut-off score when screening for clinical depression (Topp et al., 2015). Depression was evaluated using the 10-item Major Depression Inventory (MDI) (Bech et al., 2001), and was defined as the presence of depressive symptoms according to the International Classification of Diseases, 10th Revision (ICD-10) corresponding to mild, moderate, or severe depression. Fatigue symptoms were registered using the 20-item Multidimensional Fatigue Inventory (MFI) (Smets et al., 1995). In accordance with previous studies, we used the 4-item "general fatigue" scale as an indicator for fatigue with a score >11 on the MFI being defined as abnormal (Cumming et al., 2016; Holzner et al., 2003).

All questionnaires were filled in at the hospital upon inclusion. During follow-up at one and six months, patients received, filled in, and returned the questionnaires by mail or filled in questionnaires at hospital visits. Patients were instructed to answer the questionnaires with regard to the presence of symptoms during the previous two weeks. The intention of the baseline questionnaires was to register symptoms prior to stroke onset.

Baseline data were obtained from The Danish Stroke Registry at inclusion to the study (Wildenschild et al., 2013). These data included age, sex, co-morbidities, smoking habits, and sociodemographic information as well as stroke severity, measured using the Scandinavian Stroke Scale (Multicenter trial of hemodilution in ischemic stroke–-background and study protocol. Scandinavian Stroke Study Group, 1985). Examining patient charts at six months, we extracted information on stroke sub-type according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (Adams et al., 1993) and lesion location according to the Oxfordshire classification (Bamford et al., 1991). Finally, patients filled in a questionnaire on the use of antidepressant medication.

2.2. Genotyping

For genotyping of the serotonin transporter (SERT), DNA was extracted from whole blood samples using standard procedures. Genotyping was performed on an ABI 3130 Prism Genetic Analyzer, and the fluorescent peaks were analyzed using Genemapper version 4.0 (Applied Biosystems, Foster City, CA). All genotypes were checked independently by two experienced investigators to reduce the risk of genotyping errors (Mortensen et al., 2018). We studied two polymorphisms: the length variation (short = S/long = L) in the serotonin-transporter-linked polymorphic region (5-HTTLPR) and a single-nucleotide (A/G) polymorphism (rs25531). The genotypes were grouped according to functional activity: SS, SL_G and L_GL_G (low expression), SL_A, L_GL_A (medium expression), and L_AL_A (high expression).

2.3. Statistical analysis

Data are presented using numbers and percentages, or median and interquartile range (IQR; Q1 and Q3) where relevant. Odds ratios (OR) with 95% confidence intervals (CI) are calculated using logistic regression models. Associations between potential predictors and poor wellbeing were analyzed using univariate and multivariable logistic regression mutually adjusting for the included predictor variables. Imputation using chained equations on missing test scores was performed for sensitivity analyses. In addition, we repeated the analyses after excluding patients with depression and patients treated with an antidepressant.

The overlap between poor wellbeing, depression, and fatigue was examined using an Euler diagram.

Data were analyzed using R version 3.4.4 (R Core Team, 2015) with RStudio (RStudio Team (2015)). Euler-diagrams were created using the "eulerr" package (Larsson, 2018), and imputation was done using the "mice" package (Buuren and Groothuis-Oudshoorn, 2011).

3. Results

A total of 919 first-ever ischemic stroke patients were included and genotyped. The median age was 68 years, and 565 (61.5%) were males. A total of 786 (85.5%) patients had mild to moderate stroke according to a Scandinavian Stroke Scale (SSS) score of 45 to 58. Baseline characteristics are presented in Table 1.

Poor wellbeing was present in 179 (20.9%) at baseline, in 211 (29.0%) at one month, and in 160 (24.7%) at six months. The overall prevalence was 279 (30.4%) during follow-up. Predictors of poor wellbeing at baseline and at one and six months are presented in Table 2. The strongest association with wellbeing was living alone, which predicted poor wellbeing at both one month (mutually adjusted OR: 1.53, 95%, confidence interval (CI): 1.03 to 2.28) and six months (mutually adjusted OR: 1.77, CI: 1.13 to 2.76). No independent predictors were observed at baseline. Smoking, vascular disease, female sex, and low Body Mass Index (BMI) were more frequent in patients with poor wellbeing at one and six months, although the associations were not statistically significant. At baseline, on the other hand, vascular disease and female sex were associated with a lower risk of poor wellbeing. At six months, severe stroke at stroke onset also predicted poor wellbeing. There was no apparent association between stroke subtype or lesion location and poor wellbeing at any point. Genotype distribution showed no deviation from the Hardy-Weinberg equilibrium for the tri-allelic 5-HTTLPR and rs25531 genotypes (χ^2-test, $p = 0.40$). Likewise, there was no association between poor wellbeing and the genotype expression groups at any point.

The mean WHO-5 score was 68.9 (SD 22.9) at baseline, 61.9 (23.3) at one month, and 66.0 (23.4) at six months. Abnormal fatigue was present in 328 (40.6%) at baseline, 394 (57.2%) at one month, and 288 (46.4%) at six months. Depression, defined as mild, moderate, or severe according to ICD-10 criteria on the MDI, was present in 18 (2.1%) at baseline, 42 (5.9%) at one month, and 33 (5.3%) at six months. At baseline, 51 (5.5%) patients were being treated with antidepressants. During the six months follow-up, 292 (31.8%) patients were being treated with antidepressants. Fig. 1 shows a diagram of symptom overlap with regard to poor wellbeing, abnormal fatigue, and depression at baseline and at one and six months. All depressed patients and most patients experiencing poor wellbeing had an abnormal fatigue score. The figure only includes patients completing all three questionnaires. Please see Table 2 for a complete overview of data included

Table 1
Predictors of poor wellbeing at BASELINE, and at one month and six months AFTER stroke.

	Baseline N = 856	Crude OR (95% CI)	Mutually adjusted OR (95% CI)	One month N = 728	Crude OR (95% CI)	Mutually adjusted OR (95% CI)	Six months N = 648	Crude OR (95% CI)	Mutually adjusted OR (95% CI)
SERT genotype expression group									
Low	207 (24%)	Ref.	Ref.	172 (24%)	Ref.	Ref.	155 (24%)	Ref.	Ref.
Medium	442 (52%)	1 (0.66 to 1.49)	0.98 (0.63 to 1.5)	378 (52%)	1.28 (0.85 to 1.94)	1.25 (0.81 to 1.96)	338 (52%)	1.52 (0.98 to 2.43)	1.54 (0.95 to 2.54)
High	207 (24%)	1.09 (0.68 to 1.76)	0.98 (0.59 to 1.63)	178 (24%)	1.34 (0.84 to 2.15)	1.43 (0.87 to 2.37)	155 (24%)	1 (0.58 to 1.74)	1.07 (0.59 to 1.93)
Age									
Per 10 years	856 (100%)	1.15 (1.02 to 1.3)	1.37 (1.18 to 1.61)	728 (100%)	0.91 (0.81 to 1.04)	0.84 (0.72 to 0.98)	648 (100%)	0.95 (0.83 to 1.09)	0.9 (0.76 to 1.07)
Sex									
Male	524 (61%)	Ref.	Ref.	452 (62%)	Ref.	Ref.	403 (62%)	Ref.	Ref.
Female	332 (39%)	0.65 (0.47 to 0.91)	0.52 (0.35 to 0.77)	276 (38%)	1.48 (1.07 to 2.05)	1.34 (0.92 to 1.96)	245 (38%)	1.34 (0.93 to 1.93)	1.22 (0.79 to 1.87)
Body Mass Index									
<18.5	15 (2%)	0.75 (0.25 to 2.79)	0.87 (0.25 to 3.62)	11 (2%)	2.29 (0.67 to 8.17)	1.58 (0.41 to 6.24)	10 (2%)	4.74 (1.3 to 19.26)	3.74 (0.87 to 17.19)
18.5 to 25.0	261 (30%)	Ref.	Ref.	215 (30%)	Ref.	Ref.	183 (28%)	Ref.	Ref.
>25.0 to 30.0	258 (30%)	1.01 (0.66 to 1.54)	1.00 (0.63 to 1.59)	229 (31%)	0.69 (0.46 to 1.04)	0.68 (0.44 to 1.06)	206 (32%)	1.15 (0.73 to 1.83)	1.19 (0.72 to 1.99)
type="Other" >30.0	183 (21%)	1.12 (0.7 to 1.79)	1.18 (0.7 to 1.98)	151 (21%)	0.64 (0.4 to 1.01)	0.52 (0.31 to 0.86)	137 (21%)	1.08 (0.65 to 1.81)	0.96 (0.54 to 1.69)
Unknown	139 (16%)	1.08 (0.66 to 1.82)	1.77 (0.91 to 3.63)	122 (17%)	0.68 (0.41 to 1.1)	0.46 (0.23 to 0.86)	112 (17%)	0.69 (0.37 to 1.23)	0.49 (0.22 to 1.02)
Smoking									
Never	273 (32%)	Ref.	Ref.	243 (33%)	Ref.	Ref.	219 (34%)	Ref.	Ref.
Former/occasional	270 (32%)	0.92 (0.59 to 1.42)	0.85 (0.53 to 1.37)	227 (31%)	1.1 (0.73 to 1.66)	1.23 (0.78 to 1.93)	206 (32%)	0.75 (0.47 to 1.19)	0.77 (0.46 to 1.27)
Regular	254 (30%)	0.61 (0.4 to 0.92)	0.64 (0.4 to 1.02)	206 (28%)	1.64 (1.09 to 2.47)	1.55 (0.98 to 2.44)	177 (27%)	1.61 (1.03 to 2.5)	1.64 (0.99 to 2.71)
Unknown	59 (7%)	0.69 (0.36 to 1.39)	2.42 (0.55 to 15.09)	52 (7%)	1.33 (0.67 to 2.52)	1.35 (0.33 to 4.78)	46 (7%)	0.89 (0.4 to 1.86)	1.94 (0.41 to 8.01)
Alcohol use									
≤ 14 (f)/21 (m) units/week	684 (80%)	Ref.	Ref.	587 (81%)	Ref.	Ref.	521 (80%)	Ref.	Ref.
> 14 (f)/21 (m) units/week	106 (12%)	0.67 (0.42 to 1.08)	0.63 (0.38 to 1.07)	83 (11%)	1.31 (0.8 to 2.13)	1.16 (0.67 to 1.97)	76 (12%)	1.09 (0.61 to 1.85)	1.05 (0.56 to 1.89)
Unknown	66 (8%)	0.59 (0.34 to 1.06)	0.51 (0.17 to 1.56)	58 (8%)	1.26 (0.69 to 2.21)	1.21 (0.4 to 3.46)	51 (8%)	0.84 (0.4 to 1.62)	0.85 (0.2 to 3.05)
Living arrangement									
With someone	542 (63%)	Ref.	Ref.	480 (66%)	Ref.	Ref.	435 (67%)	Ref.	Ref.
Alone	270 (32%)	0.75 (0.52 to 1.07)	0.85 (0.57 to 1.28)	210 (29%)	1.66 (1.17 to 2.36)	1.53 (1.03 to 2.28)	177 (27%)	1.89 (1.28 to 2.77)	1.77 (1.13 to 2.76)
Unknown	44 (5%)	0.55 (0.29 to 1.13)	1.13 (0.15 to 12.48)	37 (5%)	1.41 (0.67 to 2.83)	6.28 (0.3 to 255.4)	34 (5%)	0.95 (0.37 to 2.15)	3.36 (0.14 to 120.06)
Diabetes									
No	728 (85%)	Ref.	Ref.	623 (86%)	Ref.	Ref.	557 (86%)	Ref.	Ref.
Yes	85 (10%)	0.71 (0.43 to 1.22)	0.85 (0.49 to 1.54)	66 (9%)	1.46 (0.85 to 2.47)	1.39 (0.76 to 2.48)	56 (9%)	1.75 (0.97 to 3.1)	1.66 (0.85 to 3.18)
Unknown	43 (5%)	0.64 (0.33 to 1.33)	2.36 (0.2 to 146.14)	39 (5%)	1.14 (0.54 to 2.25)	0.84 (0.07 to 6.54)	35 (5%)	0.65 (0.24 to 1.5)	0.11 (0 to 2.55)
Hypertension									
No	369 (43%)	Ref.	Ref.	321 (44%)	Ref.	Ref.	279 (43%)	Ref.	Ref.

(*continued on next page*)

Table 1 (*continued*)

	Baseline N = 856	Crude OR (95% CI)	Mutually adjusted OR (95% CI)	One month N = 728	Crude OR (95% CI)	Mutually adjusted OR (95% CI)	Six months N = 648	Crude OR (95% CI)	Mutually adjusted OR (95% CI)
Yes	447 (52%)	0.72 (0.51 to 1.02)	0.67 (0.45 to 0.99)	371 (51%)	1.28 (0.92 to 1.79)	1.38 (0.95 to 2.01)	336 (52%)	1.27 (0.88 to 1.85)	1.28 (0.84 to 1.97)
Unknown	40 (5%)	0.5 (0.25 to 1.07)	0.2 (0 to 11.6)	36 (5%)	1.24 (0.56 to 2.57)	1.18 (0.01 to 54.36)	33 (5%)	0.76 (0.27 to 1.81)	0.64 (0 to 38.22)
Peripheral arterial disease									
No	769 (90%)	Ref.	Ref.	657 (90%)	Ref.	Ref.	582 (90%)	Ref.	Ref.
Yes	41 (5%)	0.91 (0.44 to 2.07)	1.03 (0.46 to 2.51)	31 (4%)	1.83 (0.86 to 3.79)	1.21 (0.51 to 2.81)	30 (5%)	1.3 (0.56 to 2.83)	0.83 (0.31 to 2.08)
Unknown	46 (5%)	0.65 (0.34 to 1.31)	1.13 (0.14 to 16.64)	40 (5%)	1.09 (0.52 to 2.13)	1.48 (0.12 to 12.18)	36 (6%)	0.73 (0.29 to 1.62)	1.4 (0.06 to 19.61)
Vascular diseases*									
No	577 (67%)	Ref.	Ref.	493 (68%)	Ref.	Ref.	431 (67%)	Ref.	Ref.
Yes	230 (27%)	0.55 (0.38 to 0.79)	0.39 (0.25 to 0.61)	193 (27%)	1.26 (0.88 to 1.8)	1.56 (1.00 to 2.42)	179 (28%)	1.29 (0.86 to 1.9)	1.35 (0.82 to 2.21)
Unknown	49 (6%)	0.53 (0.28 to 1.05)	0.51 (0.1 to 3.62)	42 (6%)	0.92 (0.43 to 1.83)	0.11 (0 to 1.45)	38 (6%)	0.73 (0.29 to 1.61)	1.44 (0.06 to 13.52)
SSS score									
45 to 58	583 (68%)	Ref.	Ref.	508 (70%)	Ref.	Ref.	463 (71%)	Ref.	Ref.
30 to 44	154 (18%)	0.83 (0.54 to 1.28)	0.69 (0.43 to 1.12)	124 (17%)	0.91 (0.58 to 1.4)	0.88 (0.52 to 1.45)	103 (16%)	1.08 (0.65 to 1.76)	1.07 (0.6 to 1.85)
15 to 29	62 (7%)	0.76 (0.42 to 1.45)	0.56 (0.27 to 1.2)	47 (6%)	1.7 (0.91 to 3.12)	1.97 (0.94 to 4.07)	39 (6%)	1.8 (0.88 to 3.53)	3.14 (1.36 to 7.16)
0 to 14	17 (2%)	1.13 (0.36 to 4.98)	0.6 (0.15 to 3.16)	13 (2%)	0.75 (0.17 to 2.5)	0.65 (0.11 to 2.88)	10 (2%)	2.14 (0.54 to 7.62)	4.35 (0.83 to 21.55)
Unknown	40 (5%)	0.57 (0.29 to 1.19)	0.61 (0.01 to 33.78)	36 (5%)	1.1 (0.51 to 2.24)	0.67 (0.01 to 30.92)	33 (5%)	0.71 (0.26 to 1.66)	0.76 (0 to 47.34)
Thrombolysis									
No	499 (58%)	Ref.	Ref.	409 (56%)	Ref.	Ref.	357 (55%)	Ref.	Ref.
Yes	290 (34%)	1.21 (0.84 to 1.75)	1.26 (0.83 to 1.93)	261 (36%)	0.73 (0.51 to 1.03)	0.71 (0.47 to 1.06)	239 (37%)	0.75 (0.5 to 1.1)	0.7 (0.44 to 1.09)
Unknown	67 (8%)	0.81 (0.46 to 1.5)	1.41 (0.34 to 8.66)	58 (8%)	1.27 (0.71 to 2.25)	2.2 (0.53 to 8.44)	52 (8%)	1.02 (0.51 to 1.92)	2.36 (0.54 to 9.56)
Thrombectomy									
No	741 (87%)	Ref.	Ref.	629 (86%)	Ref.	Ref.	560 (86%)	Ref.	Ref.
Yes	56 (7%)	1.59 (0.78 to 3.69)	1.87 (0.78 to 4.9)	50 (7%)	1.19 (0.63 to 2.18)	1.02 (0.44 to 2.25)	43 (7%)	0.92 (0.42 to 1.85)	0.74 (0.28 to 1.84)
Unknown	59 (7%)	0.71 (0.4 to 1.33)	0.67 (0.08 to 4.41)	49 (7%)	1.35 (0.71 to 2.46)	1.08 (0.18 to 6.81)	45 (7%)	0.98 (0.46 to 1.93)	1.34 (0.2 to 9.17)
Oxfordshire Classification (%)									
Total anterior circulation infarct	60 (7%)	Ref.	Ref.	42 (6%)	Ref.	Ref.	34 (5%)	Ref.	Ref.
Partial anterior circulation infarct	251 (29%)	0.65 (0.3 to 1.32)	0.47 (0.18 to 1.12)	211 (29%)	0.97 (0.48 to 2.04)	1.18 (0.48 to 3.02)	203 (31%)	0.86 (0.39 to 2.06)	1.48 (0.54 to 4.42)
Posterior circulation infarct	127 (15%)	0.68 (0.29 to 1.46)	0.54 (0.2 to 1.37)	107 (15%)	0.83 (0.38 to 1.85)	0.93 (0.36 to 2.5)	100 (15%)	1.08 (0.46 to 2.71)	2 (0.68 to 6.29)
Lacunar infarct	139 (16%)	0.7 (0.3 to 1.49)	0.5 (0.17 to 1.44)	122 (17%)	1.01 (0.48 to 2.2)	1.36 (0.47 to 4.07)	109 (17%)	1.01 (0.43 to 2.51)	2.12 (0.62 to 7.58)
Undetermined	19 (2%)	0.22 (0.07 to 0.68)	0.21 (0.05 to 0.76)	14 (2%)	1.24 (0.33 to 4.36)	1.15 (0.24 to 5.08)	11 (2%)	1.04 (0.2 to 4.57)	1.58 (0.22 to 9.31)
Unknown	260 (30%)	1.07 (0.48 to 2.2)	0.71 (0.16 to 3.4)	232 (32%)	0.81 (0.4 to 1.71)	2.24 (0.55 to 9.21)	191 (29%)	0.81 (0.36 to 1.95)	3.59 (0.74 to 17.7)
TOAST classification (%)									
Large-artery atherosclerosis	122 (14%)	Ref.	Ref.	104 (14%)	Ref.	Ref.	90 (14%)	Ref.	Ref.

(*continued on next page*)

Table 1 (*continued*)

	Baseline N = 856	Crude OR (95% CI)	Mutually adjusted OR (95% CI)	One month N = 728	Crude OR (95% CI)	Mutually adjusted OR (95% CI)	Six months N = 648	Crude OR (95% CI)	Mutually adjusted OR (95% CI)
Cardioembolism	137 (16%)	1.32 (0.75 to 2.36)	1.82 (0.95 to 3.53)	107 (15%)	0.8 (0.44 to 1.45)	0.66 (0.33 to 1.3)	109 (17%)	0.77 (0.41 to 1.44)	0.69 (0.33 to 1.43)
Small-vessel occlusion	117 (14%)	1.31 (0.72 to 2.4)	1.49 (0.65 to 3.41)	98 (13%)	0.9 (0.49 to 1.65)	0.64 (0.28 to 1.44)	88 (14%)	0.69 (0.35 to 1.34)	0.47 (0.18 to 1.2)
Other	29 (3%)	0.93 (0.39 to 2.43)	1.3 (0.47 to 3.78)	25 (3%)	2.08 (0.85 to 5.08)	2.14 (0.75 to 6.09)	24 (4%)	1.17 (0.43 to 2.99)	1.05 (0.33 to 3.17)
Undetermined	202 (24%)	1.21 (0.71 to 2.02)	1.41 (0.8 to 2.5)	174 (24%)	1.04 (0.62 to 1.77)	0.92 (0.52 to 1.64)	155 (24%)	0.78 (0.44 to 1.41)	0.67 (0.35 to 1.26)
Unknown	249 (29%)	1.91 (1.12 to 3.25)	1.58 (0.38 to 5.79)	220 (30%)	0.77 (0.46 to 1.29)	0.37 (0.11 to 1.27)	182 (28%)	0.64 (0.36 to 1.14)	0.24 (0.06 to 0.93)

* Vascular diseases include any or several of previous myocardial infarction, transitory ischemic attack, or diagnosed atrial fibrillation. F = female, M = male, SSS = Scandinavian Stroke Scale.

in the visualization.

At baseline, 63 (6.9%) did not complete the WHO-5, whereas 77 (8.4%) did not complete the MDI, and 112 (12.2%) missed the MFI. In total, 778 (84.7%) had complete questionnaires. After one month, 191 (20.8%) did not complete the questions related to WHO-5, 212 (23.1%) did not complete the MDI, and 230 (25%) did not complete the MFI. A total of 649 (70.6%) patients completed the WHO-5, the MDI, and the MFI after one month. At the last follow-up after six months, 271 (29.5%) were missing the WHO-5, 297 (32.3%) the MDI, and 298 (32.4%) the MFI. The number of patients who completed the wellbeing, depression, and fatigue scales was 578 (62.9%).

Sensitivity analyses of predictors for poor wellbeing using imputation on missing data showed similar results (data not shown). In sensitivity analyses excluding patients treated with antidepressants and in analyses excluding patients treated with antidepressants and patients with possible depression according to the MDI, vascular disease was associated with poor wellbeing at one month. Living alone, severe stroke, and smoking at stroke onset were all independently associated with poor wellbeing at six months (ONLINE SUPPLEMENT).

4. Discussion

We examined predictors of wellbeing and the degree of overlap between well-defined aspects of mental health after stroke in a middle-aged stroke cohort with stroke of mild to moderate grade. Living alone at stroke onset was the strongest predictor of poor wellbeing, but stroke severity at baseline also negatively affected reported wellbeing. In sensitivity analyses excluding depressed patients and patients treated with antidepressants, vascular disease and smoking also predicted poor wellbeing. All patients with depression and most patients with low wellbeing suffered from abnormal fatigue. Mental health problems were most pronounced at one month but were also present at baseline.

Previous studies examining predictors of depression after stroke report that physical disability, stroke severity, history of depression, and cognitive impairment are the most consistent predictors of poor wellbeing (Towfighi et al., 2017). The present study is, to the best of our knowledge, the first study to explore predictors, including SERT gene polymorphisms, of poor wellbeing after stroke. Living alone was the strongest predictor for low wellbeing one and six months after stroke. Previous studies report conflicting results on the association between living alone and PSD (Johnson et al., 2006). A recent study in males from the general population found that living alone was an independent predictor of all-cause mortality and cardiovascular mortality (Jensen et al., 2019). As a growing number of people are living alone, these results emphasize the importance of initiatives targeting psychosocial interventions.

We conducted analyses without patients with depression and patients treated with antidepressants. In these analyses, living alone remained the strongest predictor of poor wellbeing. This indicates that our results do not solely reflect an underlying association between depression and poor wellbeing. The sensitivity analyses further indicate that vascular disease and vascular risk factors, such as smoking at baseline, are predictors of poor wellbeing after stroke. Secondary prevention targeting vascular risk factors may thus further help prevent poor wellbeing and optimize the recovery process after stroke. It should be noted that we had no information on smoking status during follow-up, and smoking cessation after stroke may have affected wellbeing.

Examining the overlap between wellbeing, fatigue, and depression revealed that regardless of the absence of depression, patients may experience poor mental health and other symptoms such as fatigue which may affect their quality of life and potentially reduce their chance of optimal recovery. This is in line with the results from previous studies, indicating that abnormal fatigue may be present even in the face of well-treated depression (Andersen et al., 2012; Wu et al., 2015). Not all patients with depression are being treated effectively or sufficiently with antidepressants. The need for additional, targeted

Table 2
Test results and test completion at BASELINE, and at one month and six months AFTER stroke.

	Fatigue*	Depression*	Low wellbeing*	Complete cases	Non-complete cases
Baseline	318 (40.9%)	18 (2.3%)	166 (21.3%)	778 (84.7%)	141 (15.3%)
One month	364 (56.1%)	36 (5.5%)	186 (28.7%)	649 (70.6%)	270 (29.4%)
Six months	268 (46.4%)	31 (5.4%)	135 (23.4%)	578 (62.9%)	341 (37.1%)

* Data include patients with completed questionnaires only, corresponding to Fig. 1.

psychosocial intervention with a broader focus than depression must be considered in each patient. Consequently, a focus on all aspects of mental health is important in post-stroke care with such care ideally being provided via a multifaceted intervention.

We found that poor mental health, depression, and fatigue were most frequently present one month after stroke, but mental health problems were also present at baseline. The mean WHO-5 wellbeing score of 68.9 at baseline is comparable to that of the general Danish population (mean score 70) (Topp et al., 2015). Using ICD-10 criteria, previous studies have reported a prevalence of pre-stroke depression and fatigue among older adults similar to the figures reported here (Choi-Kwon et al., 2005; Lerdal et al., 2011; Sjöberg et al., 2017). The relatively high prevalence of mental health problems at baseline may, however, at least in part be caused by recall bias as patients were asked to report on pre-stroke symptoms immediately following a potentially life-changing event. Another possible explanation for the high prevalence of mental health problems could be pre-existing and "asymptomatic" chronic cerebrovascular lesions, e.g. white matter lesions and microbleeds, preceding the symptomatic stroke, which would increase the prevalence of mental health problems also before stroke onset. Identifying stroke patients from population-based studies where information on mental health has been registered prior to stroke onset could overcome the issue of recall bias in future studies.

5. Limitations

The relatively small number of participants limited our study, especially with respect to studying the association of wellbeing with the SERT genotype, but also other potential predictors such as stroke subtype where we had a high percentage of patients with an unknown Oxfordshire and TOAST classification. Patients for whom information on stroke subtype was available were consecutive, and the distribution of stroke sub-type in this group is likely to be representative of the entire cohort. The risk of a type II error is present, however, and could falsely infer the absence of otherwise relevant associations. A third polymorphism in the serotonin transporter gene, STin2 VNTR (variable

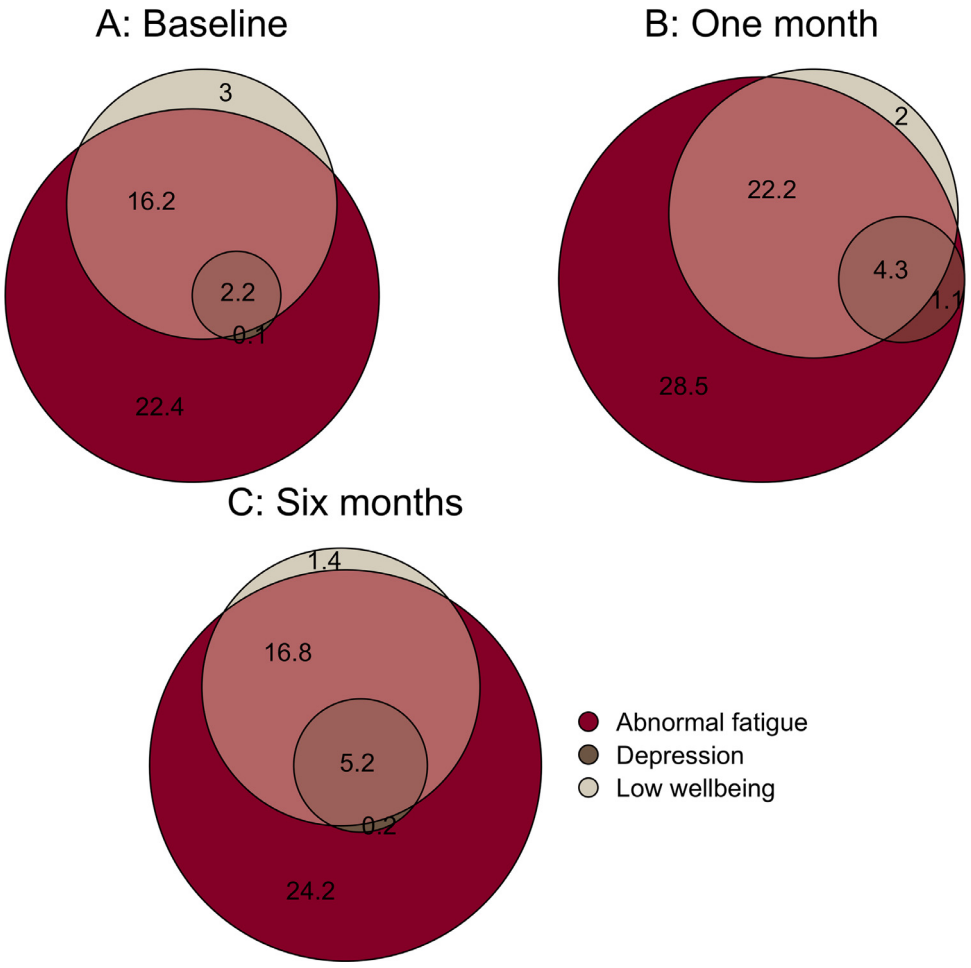

Fig. 1. Symptom overlap
Visualization of symptom overlap at baseline, and after one and six months. Includes patients with completed questionnaires only.

number of tandem repeats in intron 2), has been associated with PSD (Kohen et al., 2008). Significant adjustments to our laboratory set-up were required, if we were to analyze this polymorphism. Furthermore, no significant association between this polymorphism and PSD was found in the meta-analysis by Mak et al. (2013). Depression was not diagnosed using a diagnostic interview; however, the MDI can be used to generate an ICD-10 diagnosis of moderate to severe depression for research purpose and not only to estimate symptom severity (Bech et al., 2001). In the present study, we focused on patient-reported outcomes for which purpose the MDI is an appropriate tool. The WHO-5 may be used as a screening tool for depression, but it was chosen as a measure of subjective wellbeing as its positive wording reflects overall mental health (Topp et al., 2015). There was not complete follow-up on all patients, and not all patients filled in all questionnaires at each follow-up. Likely, patients with the most pronounced symptoms of depression, fatigue, and mood disorder were less prone to fill in and return the questionnaires. This would have led us to underestimate the presence of symptoms. Finally, we had no information on other aspects that could affect wellbeing after stroke such as functional outcome, cognitive impairment, pain, and the ability to return to work.

6. Conclusion

In conclusion, living alone most strongly predicted poor wellbeing after stroke. We found no association between serotonin transporter gene polymorphisms and wellbeing after stroke; however, larger scaled studies are warranted to study this association further. Despite a low prevalence of depression, abnormal fatigue and poor wellbeing were common. All depressed patients and most patients with poor wellbeing had abnormal fatigue. Mental health after stroke is complex, and our findings emphasize the importance of adopting a wide approach to the assessment and management as well as the need for applying a targeted psychosocial intervention. Antidepressant treatment is important when indicated, but it cannot stand alone.

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Declaration of Competing Interest

None

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.12.032.

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