

# No evidence for amyloid pathology as a key mediator of neurodegeneration post-stroke - a seven year follow-up study

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## Research article

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# Abstract

**Background:** Cognitive impairment (CI) with mixed vascular and neurodegenerative pathologies after stroke is common. The role of amyloid pathology in post-stroke CI is unclear. We hypothesize that amyloid deposition, measured with Flutemetamol ( $^{18}\text{F}$ -Flut) positron emission tomography (PET), is common in 7-year stroke survivors diagnosed with CI and, further, that quantitatively assessed  $^{18}\text{F}$ -Flut-PET uptake after seven years correlates with amyloid- $\beta$  peptide ( $\text{A}\beta_{42}$ ) levels in cerebrospinal fluid (CSF) at one year, and with measures of neurodegeneration and cognition at seven years post-stroke.

**Methods:** 208 patients with first-ever stroke or transient Ischemic Attack (TIA) without pre-existing CI were included during 2007 and 2008. At one- and seven-years post-stroke, cognitive status was assessed, and categorized into dementia, mild cognitive impairment or normal. Etiologic sub-classification was based on magnetic resonance imaging (MRI) findings, CSF biomarkers and clinical cognitive profile. At seven years, patients were offered  $^{18}\text{F}$ -Flut-PET, and amyloid-positivity was assessed visually and semi-quantitatively. The associations between  $^{18}\text{F}$ -Flut-PET standardized uptake value ratios (SUVr) and measures of neurodegeneration (medial temporal lobe atrophy (MTLA), global cortical atrophy (GCA)) and cognition (Mini-Mental State Exam (MMSE), Trail-making test A (TMT-A)) and CSF  $\text{A}\beta_{42}$  levels were assessed using linear regression.

**Results:** In total, 111 patients completed 7-year follow-up, and 26 patients agreed to PET imaging, of whom 13 had CSF biomarkers from one year. Thirteen out of 26 patients were diagnosed with CI seven years post-stroke, but only one had visually assessed amyloid positivity. CSF  $\text{A}\beta_{42}$  levels at one year, MTA grade, GCA scale, MMSE score or TMT-A at seven years did not correlate with  $^{18}\text{F}$ -Flut-PET SUVr in this cohort.

**Conclusions:** Amyloid binding was not common in 7-year stroke survivors diagnosed with CI. Quantitatively assessed, cortical amyloid deposition did not correlate with other measures related to neurodegeneration or cognition. Therefore amyloid pathology may not be a key mediator of neurodegeneration seven years post-stroke.

**Trial registration:** [Clinicaltrials.gov \(NCT00506818\)](https://clinicaltrials.gov/ct2/show/study/NCT00506818)

## Background

Post-stroke cognitive impairment (CI) is caused by both vascular and neurodegenerative changes (1), and as Alzheimer disease (AD) is accounting for 50-70 % of all dementia cases (2), the role of AD pathology are important to address in CI post-stroke . Due to an aging population and a decline in post-stroke mortality, strategies for timely diagnosis and disease prevention are urgently needed (3-6). Post-stroke cognitive impairment follows different trajectories, and risk scores based on clinical and neuroimaging variables are promising (7, 8), but do not include amyloid biomarkers. Amyloid positivity has been associated with more severe cognitive decline post-stroke in small studies (9, 10), and might be included in future prediction models and personalized management.

Known risk factors for dementia in the general population include neuroimaging variables such as  $\beta$ -amyloid deposition, medial temporal lobe atrophy (MTLA), and small vessel disease. The risk factors are additive, and there are several indications of mechanistic interactions (11, 12). Recent studies support the use of amyloid positron emission tomography (PET) in patients with uncertain diagnosis in a memory clinic setting (13-15), but studies are missing in the post-stroke population. Biomarkers of cortical amyloid deposition include cerebrospinal fluid (CSF) Amyloid- $\beta$  peptide ( $A\beta_{42}$ ) levels and amyloid-binding PET tracers. CSF  $A\beta_{42}$  levels are established biomarkers of Alzheimer's disease, and constitute the central biomarker for amyloid plaque formation (16).  $^{18}\text{F}$ -Flutemetamol ( $^{18}\text{F}$ -Flut) is increasingly used in dementia diagnostics, as it exhibits high affinity binding for fibrillary amyloid (17, 18). A negative  $^{18}\text{F}$ -Flut-PET examination indicates sparse or no fibrillar  $\beta$ amyloid, incompatible with a neuropathological diagnosis of AD (19).  $^{18}\text{F}$ -Flut-PET and CSF  $A\beta_{42}$  levels are inversely highly correlated (15, 20-22). In animal models, there has been a synergistic relationship between inflammation induced by stroke-related ischemia and  $\beta$ amyloid deposits (23-25), but this association has not been studied in humans (26, 27). Amyloid deposition increases with age (12), and theoretically might accelerate due to inflammation related to stroke. Quantitative assessment of amyloid PET allows a continuous approximation of amyloid plaques in different cortical regions, and might be more informative than binary visual assessments. MTLA and cortical atrophy are well described in both AD and pure cerebrovascular disease (28-30), but there is still no consensus regarding the contribution of amyloid pathology to post-stroke neurodegeneration and cognitive impairments (31-33). A recent study from Pendlebury et al shows that Apolipoprotein E  $\epsilon 4$  genotype, a known risk factor for AD linked to failure in amyloid clearance (34), is associated with increased risk of dementia after stroke (35). The Atherosclerosis Risk in Communities (ARIC)-PET Amyloid Imaging Study showed that an increasing number of midlife vascular risk factors were associated with amyloid deposition, consistent with a role of vascular disease in the development of AD (36).

The reported prevalence of visually assessed amyloid positivity range from 5 % of (a total of 38) MCI patients assessed six months post-stroke (37), to 40 % of (a total of 10) post-stroke dementia patients assessed from 0.5 to 4 years post-stroke (38). Of the seven studies identified (9, 10, 32, 33, 38, 39), 6 used the amyloid tracer Pittsburgh compound B, one used  $^{18}\text{F}$ -Flut-PET (37).

In the CAST (Cognition After STroke) study, dementia and mild cognitive impairment (MCI) were diagnosed and sub-classified according to proposed underlying etiology at one- and seven-years post-stroke (40, 41). In the present sub-study from the CAST cohort, all stroke survivors were offered  $^{18}\text{F}$ -Flut-PET at seven-year follow-up. To our knowledge, this is the first study on  $^{18}\text{F}$ -Flut-PET seven years post-stroke.

As stroke and AD share a common set of vascular risk factors, and amyloid depositions increases over time (42), we hypothesized that amyloid deposition is common in stroke survivors diagnosed with CI and, further, that quantitatively assessed  $^{18}\text{F}$ -Flut-PET uptake at seven years post-stroke correlates with CSF  $A\beta_{42}$  levels at one year, and with measures of neurodegeneration and cognition at seven years.

## Methods

## *Participants*

All patients with a first-ever stroke or TIA admitted to the stroke unit, at Bærum Hospital during 2007/2008 were invited to participate in the CAST study. Patients with subarachnoid hemorrhage, dementia, or MCI diagnosed before the stroke, patients who did not speak Norwegian and patients with a remaining life expectancy of less than one year estimated by the treating physician were excluded. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)(43) was administered to the patient's spouse, a first-degree relative or a close friend. A score of  $\geq 3.44$  on the IQCODE indicated pre-stroke cognitive decline, and the patient was excluded. From February 2014 to July 2016, surviving participants were invited to participate in the present follow-up study.

## *Examinations and Assessments*

At baseline, stroke etiology was classified according to the Trial of ORG 10172 (TOAST) classification (44), and patients underwent neuroimaging with computed tomography (CT) and/or magnetic resonance imaging (MRI).

In short, at baseline, at one and at seven-year post-stroke, vascular risk factors, and current medication were recorded. Fasting blood samples and an electrocardiography (ECG), were obtained, and body mass index (BMI) was calculated. Neurological impairment was assessed using the National Institutes of Health Stroke Scale (NIHSS) (45). Cognitive evaluation included the Mini Mental State Examination (MMSE) (46), the clock drawing test (47), the Trail making test part A and B (TMT-A and B) (48), and the 10-word memory test (49). Additional tests at seven year post-stroke were the Montreal Cognitive Assessment (MoCA) (50) and Controlled Oral Word Association Test (COWAT) (51). Global functional outcome was assessed by the modified Rankin Scale (mRS) (52) and personal activities of daily living (p-ADL) by the Barthel Activities of Daily Living Index (52).

Supplementary investigations at one and seven years included MRI of the brain, carotid ultrasound, and when possible, lumbar puncture was performed. Cerebrospinal fluid (CSF) was collected in polypropylene tubes and immediately transported to the local laboratory, in accordance with the manufacturers' instructions. Biomarkers for neurodegenerative disease (amyloid- $\beta$  peptide ( $A\beta_{42}$ ) levels, total tau (T-tau) and phosphorylated tau (P-tau)) were quantified with commercially available ELISAs (Fujirebio Europe, Gent, Belgium). The laboratory recommended a cut-off value of  $A\beta_{42} \leq 550\text{ng/L}$  for abnormality, modified from Sjögren et al (53).

## *Cerebral MRI*

At one- and seven-years follow-up, MRI scans were acquired on a Philips Intera system 1.5 tesla (Philips Medical Systems, Best, The Netherlands). The MRI study protocol consisted of 3D-T1, axial T2, 3D-FLAIR, DWI and SWI sequences

MRI investigations were evaluated for focal vascular lesions, medial temporal lobe atrophy (MTLA), white matter lesions (WML), and global cortical atrophy (GCA), by two radiologists, blinded to the clinical

information. Any discrepancies were resolved by consensus. MTLA was graded from 0 to 4; with MTLA grade 0 = no atrophy, MTLA 4 = highest degree of atrophy. MTLA 0–1 is considered normal (54). WML was rated using the visual rating scale proposed by Fazekas, scores ranging from 0 to 3 (55). GCA was rated using the visual rating scale known as Pasquier scale, ranging from 0 to 3 (56).

### *MRI Segmentations and Analyses*

Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite version 6.0.0 (<http://surfer.nmr.mgh.harvard.edu/>). This includes segmentation of the subcortical white-matter and deep gray-matter volumetric structures (57) and parcellation of the cortical surface (58). This labels cortical sulci and gyri, and thickness values are calculated in the regions of interest. All segmentations were manually inspected.

### *<sup>18</sup>F-Flutemetamol PET CT acquisition*

Seven years post-stroke, patients were examined with a Siemens Biograph40 mCT scanner (Siemens Healthineers, Erlangen, Germany). All patients received an intravenous injection of approximately 185 MBq <sup>18</sup>F-Flutemetamol (mean 188 MBq, range 165-218 MBq). Image acquisition started approximately 90 minutes after injection (mean 91 minutes, range 78 – 108) with a low dose CT followed by PET acquisition for 20 minutes (four frames of five minutes). 3D dynamic emission data were obtained with a resolution recovery algorithm with time of flight (TrueX with two iterations, 21 subsets and a Gaussian filter with FWHM of 2 mm, matrix size 400x400). Reconstructed images had a slice thickness of 2 mm and a voxel size of 2 x 2 x 2 mm<sup>3</sup>.

### *Qualitative classification of <sup>18</sup>F-Flutemetamol PET*

<sup>18</sup>F-Flut PET images were visually classified as positive (<sup>18</sup>F-Flut-PET (+)) or negative (<sup>18</sup>F-Flut-PET (-)) by at least two nuclear medicine physicians with experience in <sup>18</sup>F-Flut PET, and recorded in patients' medical records in line with standard clinical practice between 2015-2017. In addition one nuclear medicine physician with experience in <sup>18</sup>F-Flut PET repeated classification in 2019, and in case of discrepancy between the classifications, an additional expert was consulted. All image classifications were performed according to the validated electronic reader program (59) and as described previously (15).

### *Quantitative classification of <sup>18</sup>F-Flutemetamol PET*

Motion correction of the <sup>18</sup>F-Flut PET was performed using frame-by-frame rigid registration, then the frames were summed to a single time-frame image and rigidly registered to the anatomical MRI volume using a 6-parameter rigid registration as implemented in the Statistical Parametrical Mapping (SPM 12, Wellcome Trust Centre for Neuroimaging, UCL, UK) toolbox. <sup>18</sup>F-Flut-PET standardized uptake value ratios (SUVr) were obtained by normalization to the brainstem. Both the cerebellar cortex, pons and brainstem are widely used Flutemetamol reference regions, acquiring amyloid build plaques not until the fifth and final phase of amyloid deposition (60). Our choice of reference region was influenced by local tradition, a

feeling that the structural masks of the cerebellar cortex were less accurate, and a long series of publications utilizing the brainstem or pons as reference region. Prior to normalization, the brainstem mask was eroded by 1mm to avoid partial volume effects, inaccurate segmentation or co-registration.  $^{18}\text{F}$ -Flut-PET uptake was analyzed in five pre-selected cortical regions of interest (ROIs), as defined by Desikan et al. (61) and implemented in FreeSurfer as described above, known to hold substantial amyloid plaques in AD: the precuneus and posterior cingulate combined, anterior cingulate, prefrontal, inferior parietal, and lateral temporal cortex (62). The  $^{18}\text{F}$ -Flut-PET uptake for each region was averaged across the hemispheres. We further calculated a composite SUVR by averaging the uptake in the above-mentioned regions. SUVR were not calculated to categorize scans as positive or negative but used as continuous variables in correlation analyses.

### *Outcomes and Diagnosis of cognitive function*

At one and seven years post-stroke, the diagnoses of dementia and MCI were made in consensus meetings by two senior neurologists (B.F and B.T) and one senior geriatrician (A.R.Ø), using the criteria outlined by Winblad et al. (63) for MCI, and the International Classification of Diseases 10th revision (ICD-10) criteria (2) for dementia. Details of the novel method for sub-classification have previously been reported (41), with six potential subgroups; degenerative MCI or degenerative dementia, vascular MCI (MCI VaD) or vascular dementia (dementia VaD) or mixed degenerative and vascular MCI or dementia. The evaluations were based on the results from the medical history, cognitive assessments, the IQCODE and information regarding daily functioning. Sub-classification for proposed underlying etiology was based on MRI findings of vascular or degenerative brain changes, biomarkers in the CSF, the patient's vascular risk factors and clinical cognitive profile. Patients were classified with possible vascular disease when the radiological findings revealed WMLs without MTLA, while MTLA without WMLs was interpreted as degenerative etiology. Patients with combined pathologies were classified with mixed vascular and degenerative disease.

### *Statistics*

Categorical variables were compared with Pearson's chi-squared test and continuous variables with independent Student t-test. The relationship between death as dependent variable and age-adjusted CSF as independent variables were assessed with logistic regression analyses. Correlation analyses of  $^{18}\text{F}$ -Flut-PET SUVR and measures of neurodegeneration and cognition, were performed assessing the Pearson correlation coefficient in continuous variables (MTA, CSF  $\text{A}\beta_{42}$  levels, GCA, TMT-A), Spearman rho in ranked data (MMSE). Linear regression analyses were performed with  $^{18}\text{F}$ -Flut-PET SUVR as explanatory variable. Each regression model was adjusted for age. Statistical analyses were performed using SPSS Statistic version 23.

## **Results**

### *Study population*

Of the 208 patients included in 2007-2008, 111 completed seven years follow-up, of whom 26 patients agreed to PET imaging and 13 of these had CSF from 12 months. 12 out of the 26 patients who agreed to PET imaging were diagnosed with CI at seven years. In total, 80 patients died during the study period, and 17 were lost to follow-up for other reasons. A flow chart is presented in Figure 1. Characteristics and assessments at baseline and seven years for the complete study population are presented in Table 1. Characteristics and assessment at baseline, clinical cognitive profile and MRI findings at one year in stroke survivors by PET or no PET at seven years are presented in Table 2. Significantly more patients who agreed to PET had normal cognition and lower CSF T-tau at 12 months follow-up. There were no differences regarding age, stroke subtype or assessments at baseline, or MRI findings at one year.

### *Amyloid-binding in stroke survivors*

The main characteristics, MRI,  $^{18}\text{F}$ -Flut-PET, and cognitive assessment findings are summarized in Table 3 (see Additional file 1). Among the 26 patients who agreed to PET, five patients had no MRI at seven years, required in our quantitative assessment method. Four scans were visually classified  $^{18}\text{F}$ -Flut(+). 13 patients were diagnosed with CI (mixed or neurodegenerative disease) at seven years, one with a positive PET scan. Quantitative  $^{18}\text{F}$ -Flut-PET SUVr in different cortical regions is presented in table 4.

Comparing patients according to normal or CI at seven years, no difference in mean SUVr (SD) was observed (0.57 (0.08) vs 0.60 (0.18),  $p=0.54$ ). Eight patients changed from normal cognition at one year to CI at seven years, one of whom was amyloid positive. When comparing cognitive decline to stable cognition during follow-up, no difference in mean SUVr (SD) was observed (0.65 (0.24) vs 0.56 (0.07),  $p=0.16$ ). Three of four patients with visually positive PET had normal cognition at seven years.

Eighty patients died before follow-up, 33 with CSF from one year. Logistic regression assessing age-adjusted CSF  $\text{A}\beta_{42}$  levels and death, did not demonstrate any significant association (OR 1.0, 95%CI 0.99-1.0). Age-adjusted CSF T-tau was not significantly associated with death (OR 1.0, 95%CI 1.0-1.0)

### *Correlations*

$^{18}\text{F}$ -Flut-PET SUVr at seven years did not correlate with CSF  $\text{A}\beta_{42}$  levels at one year ( $r=0.12$ ;  $p=0.703$ ), MTLA ( $r=0.10$ ;  $p=0.670$ ), GCA ( $r=0.10$ ;  $p=0.652$ ) or MMSE ( $r=-0.32$ ;  $p=0.162$ ) at seven years, when adjusted for age. TMT-A at seven years was significantly correlated to  $^{18}\text{F}$ -Flut-PET SUVr ( $r=0.69$ ;  $p=0.00$ ), but exploring data revealed one outlier on the scatterplot, and after exclusion, there was no significant correlation. Associations between composite  $^{18}\text{F}$ -Flut-PET SUVr and CSF  $\text{A}\beta_{42}$  levels at one year are presented in Figure 2.

## **Discussion**

In this cohort, only one patient diagnosed with CI seven years post stroke was amyloid positive. Quantitatively assessed  $^{18}\text{F}$ -Flut-PET did not correlate with amyloid- $\beta$  peptide ( $\text{A}\beta_{42}$ ) levels in CSF at one year or MTLA, GCA, MMSE, or TMT-A at seven years.

Our findings with only one visually  $^{18}\text{F}$ -Flut(+) in post-stroke CI patients (8%) are in line with the results from the prospective DEDEMAS study (Determinants of Dementia After stroke), where only 2 out of 38 (5%) post-stroke MCI patients had positive amyloid scans. In the DEDEMAS study, neuropsychological testing was performed only six months after stroke, theoretically too early to capture amyloid deposition initiated by the stroke. As in our study, only a minor portion of patients completed the PET examination (38/178) (37).

Visual classification of  $^{18}\text{F}$ -Flut-PET is still the only validated method for clinical use, however quantification is beneficial to obtain a continuous measure of  $^{18}\text{F}$ -Flut-PET. One proposed cut-off for quantitatively assessed  $^{18}\text{F}$ -Flut-PET using CortexID, with pons as reference region, is SUVR 0.61 (64). All patients with visually positive PET in our study had composite SUVR > 0.61 in line with the cut-off, even though we applied a different software for quantification. Amyloid deposition increases with age (12), and in our cohort the oldest had the highest SUVR and were the only visually PET positive among participants with CI.

Roberts et al. studied the prevalence of PET amyloid-positivity in a non-demented cohort drawn from the general population. They found that amyloid positivity in persons with MCI ranged from 0% in the age group 50-59 to 16% in participants aged 80-89 years (12). Previous studies have reported a slightly higher prevalence between 10 and 30% in cognitively healthy-people (65, 66). The frequency of amyloid positivity in our cohort is consistent with the observations from the general population, so no evident stroke-related inflammation with amyloid deposition is observed in our cases. Two cases had larger strokes with NIHSS  $\geq 4$  at discharge, both without amyloid positivity after seven years.

When assessing PET semi- quantitatively, PET SUVR did not differ substantially between cases, and there was no significant difference when comparing those with or without CI, or when comparing those who experienced cognitive decline or stable cognition during follow-up. As our patients were imaged in regular clinical routine, with variable start in image acquisition, we acknowledge that this may affect the SUVR.

Three patients were diagnosed with MCI AD in consensus, none with amyloid positivity. This is in line with a previous study from the CAST cohort, where we found a correlation between pathological cerebrospinal fluid (CSF) concentrations of microtubule-associated protein tau (T-tau) one year post-stroke and brain atrophy, indicating that tau-linked neurodegeneration might be more important than amyloid post-stroke (67). Recent studies suggest that changes in the blood-brain barrier (BBB) and BBB-mediated neurodegeneration, plays an essential role in cognitive dysfunction independent of  $\text{A}\beta$  biomarkers (68, 69).

In the study by Roberts et al., more amyloid-positive participants died compared to amyloid negative during the four year follow-up period, 13% vs 4.6% respectively (12). Death before follow-up might bias our findings, but when assessing the relation between CSF biomarkers at one year and prospective

mortality using logistic regression analysis, CSF A $\beta$ 42 at one year was not associated with death in our cohort.

As shown in Figure 2, surprisingly, CSF A $\beta$ 42 at one year did not correlate with PET SUVR at seven years. Three patients had pathological levels of CSF A $\beta$ 42 at one year, all without amyloid positivity at seven years. Contrary to CSF T-tau, CSF A $\beta$ 42 levels remain unchanged after stroke when followed for six months (72). One possible explanation could be that stroke decreases the ability to amyloid clearance, maybe due to changes in the BBB (73), with normalization after some years. Garcia-Alloza et al. (74) demonstrated A $\beta$  formation in a mice model as a transient phenomenon induced by a stroke, most likely through interference with amyloid clearance pathways. One study with repeated amyloid PET in 21 patients, one and 18 month post-stroke, found a significant reduction in amyloid accumulation in the infarct region, probably caused by a breakdown of BBB in the acute phase, with a leak of the radioactive ligand with “false” high SUVR (32). The optimal timing for A $\beta$  assessment post-stroke is not known but is essential for the development of future prediction models and individualized management. Due to small numbers, our observations must be confirmed in larger samples and interpreted with caution.

Our study has several limitations. First our limited sample size, as only 56 patients agreed to lumbar puncture at one year and 26 to PET after seven years. Patients on anticoagulation therapy or unable to consent, were excluded from lumbar puncture due to ethical considerations. This might bias our findings. After seven years, due to time consuming examinations and long travel distances between hospitals, only highly motivated patients, and more with normal cognition at one year, agreed to PET, making our findings less generalizable. The strength in our study is the long-term follow-up with the same team of nurses and physicians, and measurement of amyloid at two time points. As far as we know, this is the first study to offer PET examination seven years post-stroke, and by that adding important knowledge to amyloid evaluation post-stroke.

## Conclusions

In conclusion, amyloid binding was not common in our cohort of stroke survivors diagnosed with CI. Assessed quantitatively, amyloid load correlates neither with other measures related to neurodegeneration nor with CSF A $\beta$ 42 at one year in this cohort. Therefore, amyloid pathology may not be a key mediator of neurodegeneration seven years post-stroke. Validations of our findings in larger studies are needed.

## List Of Abbreviations

AD	Alzheimer’s disease
BMI	body mass index
CAST	Cognition After STroke
CI	Cognitive impairment

COWA	Controlled Oral Word Association Test
CSF A $\beta$ <sub>42</sub>	Amyloid- $\beta$ peptide-42
CSF	Cerebrospinal fluid
CT	Computer tomography
ECG	ECG
GCA	Global cortical atrophy
IQCODE	Informant Questionnaire on Cognitive Decline in the elderly
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
MTLA	Medial temporal lobe atrophy
NIHSS	National Institutes of Health Stroke Scale
OCSP	Oxfordshire Community Stroke Project classification
p-ADL	Barthel Activities of Daily Living Index
PET	Positron emission tomography
P-tau	Phosphorylated microtubule-associated protein tau
RCT	Randomized controlled trial
SUVr	standardized uptake value ratios
TIA	Transitory ischemic attack
TOAST	The Trial of Org 10,172 in Acute Stroke Treatment
TMT A	Trail Making Test A
TMT B	Trail Making Test B

T-tau                    Microtubule-associated protein tau

VaD                     Vascular

<sup>18</sup>F-Flut                <sup>18</sup>F-Flutemetamol

## Declarations

### Ethics approval and consent to participate

The study was approved by the Regional Committee for Medical and Health Research Ethics South East and by the Data Protection Authorities (2013/1829). Written informed consent was obtained from all patients; if the patient was cognitively impaired, relatives also gave their written assent. Patients unable to give consent were excluded from lumbar puncture in line with recommendations from REK.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

### Competing interests

Hege Ihle-Hansen is a member of the editorial board in BMC neurology.

### Funding

Not applicable.

### Authors' contributions

BF, BT, ARØ, HeIH, TBW and GH researched literature and conceived the study. HeIH, BF, BT and GH were involved in the protocol development and gaining ethical approval. HåIH, HeIH and GH were involved in patient recruitment. PS, EGM and MB analyzed the patients PET and MRI. GH wrote the first draft of the manuscript. Revision of manuscript for important intellectual content: STP. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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## Tables

**Table 1.** Baseline characteristics (n = 208) and assessments in survivors at seven years (n = 111)

	Baseline	7 year follow-up
Male (%)	105 (51)	61 (55)
Mean age, years (SD)	72.0 (12.2)	75.2 (11.2)
Less than 9 years of education (%)	50 (24)	
<b>Stroke subtype (%)</b>		
Cerebral infarction	164 (79)	
TIA	28 (14)	
Cerebral hemorrhage	16 (7)	
<b>Risk factors (%)</b>		
Hypertension*	123 (59)	
Hyperlipidemia	117 (56)	
Diabetes	23 (11)	
Cigarette smoking (present)	18 (18)	
Coronary heart disease	45 (22)	
Atrial fibrillation	65 (31)	
Daily alcohol use	20 (24)	
BMI>25	119 (57)	
<b>TOAST classification (%)</b>		
Large-vessel disease	21 (10)	
Cardio-embolic disease	60 (29)	
Small-vessel disease	64 (31)	
Stroke of undetermined etiology	63 (30)	
<b><u>Assessments. Mean (SD) (n)</u></b>		
NIHSS	2.44 (4.6)	1.02 (2.3) (109)
BI	17.5 (5.1)	18.7 (3.7) (109)
mRS	1.5 (1.4)	1.4 (1.3) (109)
IQCODE	3.1 (0.2) (n=208)	
MMSE	26.0 (4.5) (n=195)	25.8 (5.9) (n=109)
TMT-A	73.7 (66.7) (n=177)	55.7 (39.6) (n=101)
TMT-B	152.8 (89.8) (n=152)	126.4 (67.7) (n=82)
10-Word test immediate recall	17.9 (2.9) (n=170)	22.5 (8) (n=106)
10-Word test, delayed recall	4.3 (2.5) (n=184)	4.7 (3) (n=105)

TIA= Transient Ischemic Attack; Hyperlipidemia = total cholesterol > 5mmol/L or LDL >3 mmol/L; LDL = Low Density Lipoprotein; Diabetes = an established diagnosis or Haemoglobin A1C (HbA1c)  $\geq$ 7.0; Coronary Heart Disease=previous myocardial infarction or present angina pectoris; BMI=Body mass index; TOAST = the trial of org 10172 in acute stroke treatment classification; NIHSS=National Institute of Health Stroke Scale; BI=Barthel Activities of Daily Living Index; mRS=modified Rankin scale; IQCODE = the informant questionnaire on cognitive decline in the elderly. MMSE=Mini Mental State Examination; SD=standard deviation.\* Hypertension= use of BP lowering drugs at baseline.

**Table 2.** Characteristics at baseline, clinical cognitive profile and MRI findings at one year in stroke survivors by PET or no PET at seven years.

	PET	NO PET	P value
N	26	85	
Male (%)	18 (69)	43 (51)	0.227
Mean age, years (SD)	72.9 (7.0)	75.9 (11.8)	0.239
Less than 9 years of education (%)	4 (15)	18 (21)	0.776
Living alone (%)	4 (15)	24 (28)	0.288
<b>Stroke subtype (%)</b>			0.926
Cerebral infarction	20 (77)	66 (78)	
TIA	4 (15)	11 (13)	
Cerebral hemorrhage	2 (8)	8 (9)	
<b>TOAST classification (%)</b>			0.724
Large-vessel disease	2 (8)	12 (14)	
Cardio-embolic disease	8 (31)	19 (22)	
Small-vessel disease	9 (35)	29 (34)	
Stroke of undetermined etiology	7 (27)	25 (30)	
<b>Assessments. Mean (SD) (n)</b>			
NIHSS	1.12 (2.1)(26)	1.99 (3.6)(85)	0.247
mRS	1.0 (1.2)(26)	1.26 (1.2)(85)	0.266
IQCODE	3.0 (0.1)(26)	3.1 (0.2)(85)	0.641
MMSE	27.8 (2.1)(26)	26.5 (4.0)(82)	0.113
<b>Clinical profile 12 months</b>			
Dementia	1 (26)	13 (84)	0.223
MCI	6 (26)	31 (84)	0.286
Normal cognition	19 (26)	40 (84)	0.040
<b>MRI 12 months. Mean (SD) (n)</b>			
MTLA grade	0.79 (0.8)(24)	1.18 (1.2)(77)	0.135
Fazekas score	1.52 (0.8)(25)	1.86 (0.9)(76)	0.095
Global Cortical Atrophy	1.28 (0.7)(25)	1.48 (0.6)(75)	0.177
CSF (A $\beta$ )-42 (ng/L) 12 months (n)	840 (250) (13)	861(302) (41)	0.824
CSF total tau (ng/L) 12 months (n)	270 (101)(13)	387(192) (41)	0.040

TIA= Transient Ischemic Attack; TOAST = the trial of org 10172 in acute stroke treatment classification; NIHSS=National Institute of Health Stroke Scale; BI=Barthel Activities of Daily Living Index; mRS=modified Rankin scale; IQCODE = the informant questionnaire on cognitive decline in the elderly; MMSE=Mini Mental State Examination; SD=standard deviation;MCI=mild cognitive impairment; MTLA=medial temporal lobe atrophy. CSF (A $\beta$ )-42=cerebrospinal fluid amyloid- $\beta$  peptide

Clinical characteristics, imaging features and CSF A $\beta$ -42 of patients with PET examination

Age/ Gender	Stroke types/ Infract location/ NIHSS discharge	Cognitive evaluation		MTA	GCA	MSSE	TMT- A	Amyloid	Binding Year 7	CSF (Aβ)-42 (ng/L)
		Year 1	Year 7	Year 7	Year 7	Year 7	Year 7	Visual assessment  18F- Flut(+)	Semi- quantitative assessment  Composite SUVR, max	Year 1
59 f	Cortical, left	Dementia	Normal	-	-	27	68	No	*	402
69 m	side, NIHSS 4	VaD	MCI	-	-	29	71	No	*	-
70 m	Lacunar, left	Normal	VaD	3.5	2	28	44	Yes	0.65, 0.82	-
73 m	side, NIHSS 0	Normal	Normal	-	-	30	37	No	*	-
73 f	Lacunar,	Normal	Normal	3.0	2	27	72	No	0.50, 0.65	-
63 m	posterior,	MCI mix	MCI	1.0	1	26	61	No	0.57, 0.76	1084
58 m	NIHSS 0	MCI mix	mix	1.5	1	27	32	No	0.54, 0.71	402
63 m	Lacunar, right	Normal	MCI	2.5	1	29	30	No	0.55, 0.69	985
68 m	side, NIHSS 0	Normal	VaD	0.5	1	30	41	Yes	0.74, 0.85	-
73 m	TIA, right	Normal	MCI	-	-	29	48	Yes	*	-
65 m	side, NIHSS 0	Normal	VaD	1.0	2	29	35	No	0.54, 0.71	804
78 f	Cortical, right	Normal	Normal	3.5	2	27	93	Yes	1.13, 1.24	-
71 m	side, NIHSS	Normal	Normal	2.0	1	28	29	No	0.55, 0.72	1171
74 m	10	Normal	Normal	-	-	28	37	No	*	-
58 m	Cortical, right	Normal	MCI	1.1	1	27	31	No	0.53, 0.71	848
50 m	side, NIHSS 2	Normal	mix	0.5	1	28	24	No	0.57, 0.73	1175
61 m	Lacunar,	Normal	MCI	1.5	2	26	50	No	0.63, 0.79	-
66 f	posterior,	Normal	mix	1.0	1	27	43	No	0.58, 0.71	484
62 f	NIHSS 0	MCI mix	MCI	1.0	1	29	28	No	0.52, 0.70	-
64 f	Cortical, left	Normal	VaD	1.5	1	30	39	No	0.49, 0.64	761
72 m	side, NIHSS 0	Normal	MCI	0.5	2	29	30	No	0.51, 0.69	963
65 m	Undetermined,	MCI mix	AD	1.5	1	30	31	No	0.54, 0.72	825
52 f	left side,	Normal	MCI	1.0	1	29	26	No	0.50, 0.58	-
65 m	NIHSS 2	Normal	mix	1.5	1	28	30	No	0.53, 0.71	-
59 m	TIA, left side,	MCI mix	Normal	1.0	1	28	33	No	0.59, 0.77	901
70 f	NIHSS 0	Normal	MCI	2.0	1	27	45	No	0.54, 0.70	-
	Lacunar,	MCI mix	VaD							
	posterior,		MCI							
	NIHSS 1		mix							
	TIA, right		Normal							
	side, NIHSS 1		Normal							
	Cortical, left		Normal							
	side, NIHSS 0		Normal							
	Subcortical H,		Normal							
	left side,		MCI							
	NIHSS 1		AD							
	TIA left side,		Normal							
	NIHSS 0		MCI							
	Lacunar,		AD							
	posterior,									
	NIHSS 0									
	Lacunar, left									
	side, NIHSS 2									
	Cortical, left									
	side, NIHSS 1									

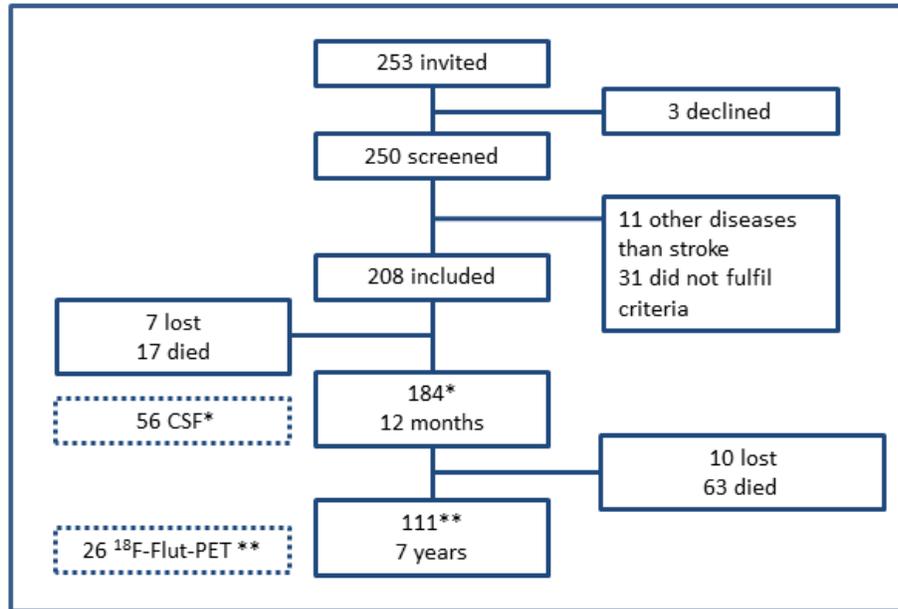
TIA, left side, NIHSS 0			
Lacunar, right side, NIHSS 1			
Lacunar, left side, NIHSS 0			
Subcortical H, right side, NIHSS2			
TIA, left side, NIHSS 0			
Lacunar, right side, NIHSS 2			
Cortical, left side, NIHSS 0			

ssing; m=male; f=female; lacunar infarcts; subcortical small (<15 mm) infarcts in the distal distribution of deep ing vessels; cortical infracts affects regions of the cerebral cortex; TIA=Transient Ischemic Attack; National Institute of Health Stroke Scale; H=hemorrhage; MCI=mild cognitive impairment; mix=mixed disease; scular disease; AD= neurodegenerative disease; MTA= medial temporal atrophy; GCA=global cortical atrophy; Mini Mental State Examination ;TMT-A= trail making test A; (Aβ)-42= cerebrospinal fluid (CSF) amyloid-β

**Table 4:** Quantitative <sup>18</sup>F-Flutemetamol PET SUVr in different cortical regions

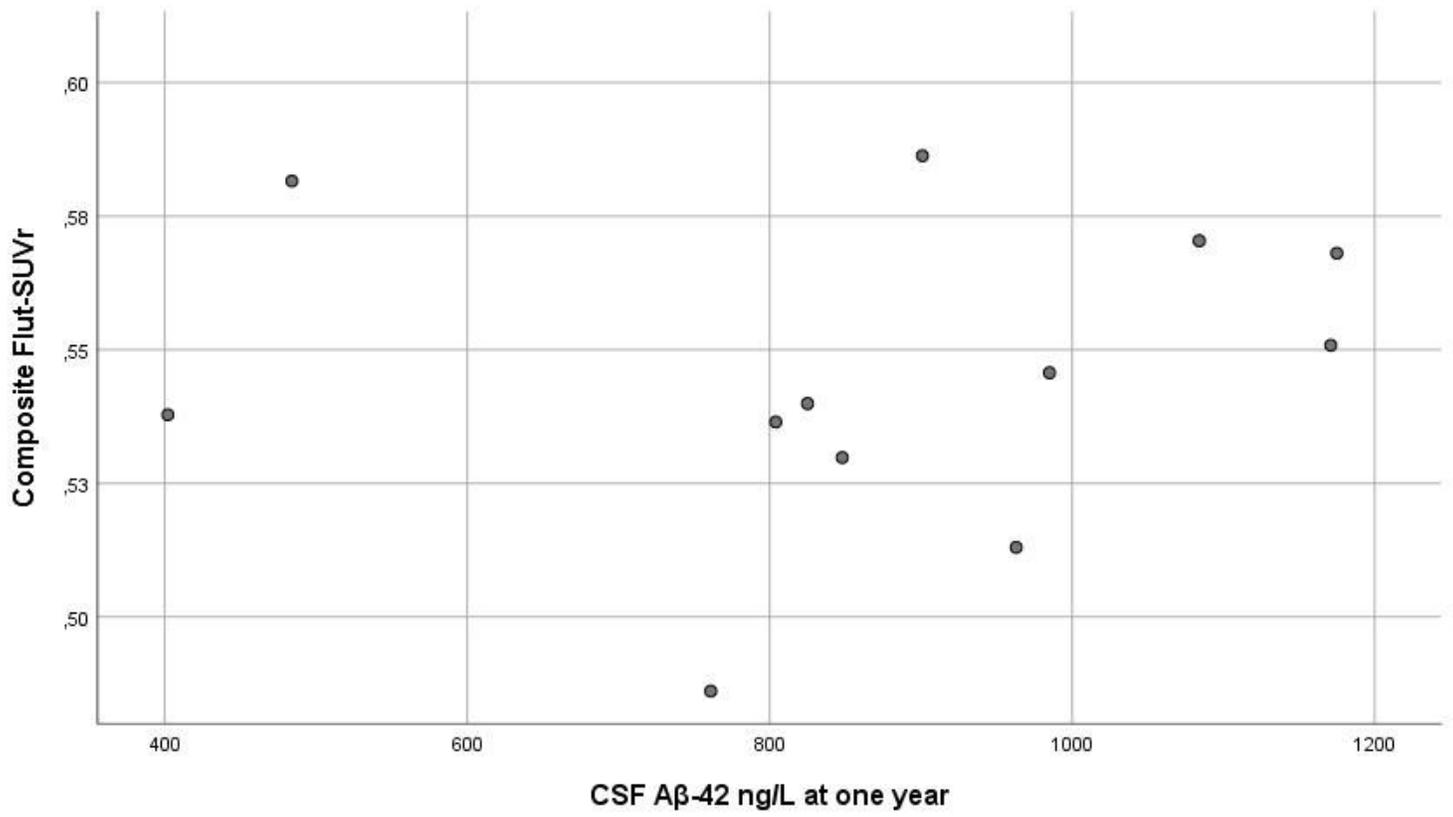
Cases	precuneus and posterior cingulate combined	anterior cingulate	prefrontal	inferior parietal	lateral temporal	Composite SUVr
1	-	-	-	-	-	
2	-	-	-	-	-	
3	0.82	0.70	0.60	0.64	0.55	0.65
4	-	-	-	-	-	
5	0.48	0.47	0.46	0.46	0.44	0.50
6	0.55	0.56	0.52	0.51	0.51	0.57
7	0.54	0.48	0.48	0.48	0.48	0.54
8	0.54	0.52	0.50	0.51	0.49	0.55
9	0.85	0.68	0.68	0.75	0.65	0.74
10	-	-	-	-	-	
11	0.52	0.51	0.49	0.49	0.48	0.54
12	1.24	1.21	1.21	1.14	1.16	1.13
13	0.54	0.49	0.50	0.51	0.49	0.55
14	-	-	-	-	-	
15	0.51	0.48	0.47	0.49	0.47	0.53
16	0.57	0.54	0.51	0.53	0.50	0.57
17	0.64	0.64	0.56	0.59	0.57	0.63
18	0.59	0.63	0.57	0.53	0.51	0.58
19	0.51	0.50	0.46	0.47	0.46	0.52
20	0.48	0.45	0.44	0.45	0.43	0.49
21	0.50	0.48	0.46	0.46	0.46	0.51
22	0.51	0.47	0.48	0.49	0.50	0.54
23	0.49	0.49	0.48	0.48	0.47	0.50
24	0.51	0.50	0.47	0.46	0.48	0.53
25	0.56	0.53	0.57	0.50	0.53	0.59
26	0.54	0.54	0.51	0.48	0.50	0.54

## Figures



**Figure 1**

Flow chart



**Figure 2**

Associations between composite 18F-Flut-PET SUVr and CSF Aβ<sub>42</sub> levels at one year