Master's thesis

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Examining the Characteristics of the Participants Included in the Nor-COAST MRI Sub Study

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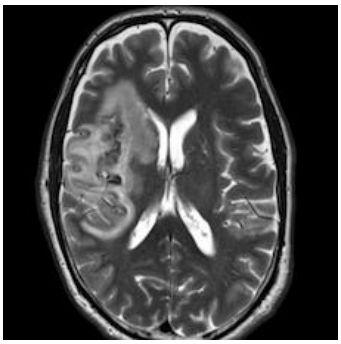

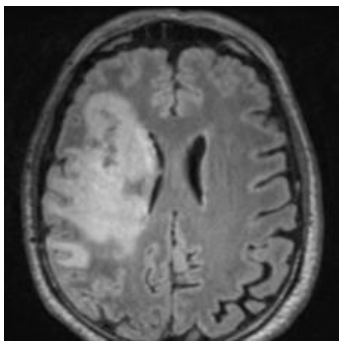

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Abstract

The research field of stroke and post-stroke dementia (PSD) is regularly faced with challenges of recruitment to its studies. A subset of patients is frequently excluded from studies, and this may potentially affect the external validity of the findings. There is currently a large prospective observational multicentre study on post-stroke cognitive impairment (CI) taking place in Norway (Norwegian Cognitive Impairment After Stroke (Nor-COAST)). Current study aims to analyse the generalisability of the findings from the St Olav branch of the Nor-COAST study, through examining what characterises the group who underwent a study-specific MRI-protocol, and those who did not. Current study will assess potential differences in age, in clinical aspects, such as CI and stroke severity, and in brain health aspects, such as the presence of microbleeds and white matter hyperintensities (WMH). This will be done through the use of baseline characteristics derived from the Nor-COAST dataset, and the analysis of brain-scan image descriptions made by neuroradiologists. From the total of 401 participants, 217 (54.1%) underwent a study-specific MRI, whereas the rest only had a brain CT scan or a much shorter MRI protocol. It was found that there was little difference between the groups, except for haemorrhagic stroke being associated with being excluded from the MRI study. The presence of WMH or having had a prior stroke were found associated with sub study participation. This indicates that the results from the study-specific MRI scans can be generalised to most of the St Olav branch of the Nor-COAST study, except those with haemorrhagic strokes. This shortcoming may put a limitation also on the overall generalisability qualities of Nor-COAST. Lastly, these results indicate that it is indeed possible to conduct stroke research without extensive inclusion bias, although much research has found the opposite to be standard.

ACKNOWLEDGEMENTS

I would like to express my very great appreciation to my two supervisors, Mona K. Beyer and Ingvild Saltvedt, for their guidance, support, and critical comments - your help has been of immense value both to the thesis and to my future work. Special thanks should also be given to Stian Lydersen for his help in ensuring the statistical analyses were sound. I would also like to thank Till Schellhorn for his beautiful brain scan images.

Finally, I wish to thank Sigrún, Ni Muser, and my family, for their support, encouragement, and great coffee.

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Abbreviations	
PSD	Post Stroke Dementia
CI	Cognitive Impairment
MCI	Mild Cognitive Impairment
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
DWI	Diffusion-Weighted Imaging
ADC	Apparent Diffusion Coefficient
PWI	Perfusion-Weighted Imaging
FLAIR	FLuid-Attenuated Inversion-Recovery
SWI	Susceptibility-Weighted Imaging
MRA	Magnetic Resonance Angiography
WMH	White Matter Hyperintensities
Nor-COAST	NORwegian COgnitive impairment After Stroke
NC-p	Nor-COAST protocol
Non-NC-p	Not Nor-COAST protocol
GDS	Global Deterioration Scale for assessment of global cognition function
CCI	Charlson Comorbidity Index
mRs	Modified Rankin scale
NIHSS	National Institutes of Health Stroke Scale

Introduction

Background:

Stroke is the most common life-threatening neurological disease, the second leading cause of death, and the third most common cause of disability, worldwide (Feigin et al., 2016). Improvements in stroke treatment and better treatment of modifiable cardiovascular risk factors has led to a decline in the prevalence, incidence, and mortality rate, but has also thus increased the number of survivors struggling with the aftermath (Feigin, Norrving, & Mensah, 2017). Suffering from a stroke significantly increases the probability of developing other diseases, such as dementia, and the number of stroke survivors with disabilities will therefore increase (Feigin, et al., 2014).

There is a significant association between stroke and dementia. Around 10% of first time stroke patients suffer from dementia prior to the stroke, around 10% develop post stroke dementia (PSD) within the first year after a first-ever stroke, and around 30% develop PSD after recurrent strokes (Pendlebury, & Rothwell, 2009). With an ageing world population, the prevalence of dementia is estimated to increase and around 600 million people will live with this disease by the year 2050 (Wortmann, 2012). The increase in both stroke and dementia cases will put a growing strain on the world's health systems and on the quality of life for a considerable proportion of the world's population. Research on the prevention of dementia after stroke is therefore crucial in lowering these numbers and creating a better future.

Any kind of brain pathology leaves the brain more vulnerable to later disease or events, such as stroke, dementia, and CI. Vascular pathology increases the risk of dementia (Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005), and modifiable vascular risk factors, such as obesity, hypertension, little physical activity etc., contribute to impaired brain health, with MRI measures of subclinical brain infarcts, cerebral microbleeds, and WMH as prominent signs of injury (Gardener, Wright, Rundek, & Sacco, 2015). Patient post-stroke outcome depends on many factors, but can limit independence and activities of daily living, and impact subjective well-being (Zahuranec, Skolarus, Feng, Freedman, & Burke, 2017). Pre-stroke factors found to be associated with worse patient outcome include CI (Moulin, & Leys, 2017), functional impairment (Askim, Bernhardt, Salvesen, & Indredavik, 2014), and comorbidities, such as congestive heart failure, chronic kidney disease, atrial fibrillation, Parkinson's disease etc. (Mohamed, Bhattacharya, Shankar, Chaturvedi, & Madhavan, 2015; Schmidt, Jacobsen, Johnsen, Bøtker, & Sørensen, 2014). Old age (Sun, Tan, & Yu, 2014), prior stroke (Hankey, 2014; Pendlebury, & Rothwell, 2009) and lacunes (Caplan, 2015; Makin, Turpin, Dennis, &

Wardlaw, 2013) are also associated with worse patient outcomes. Factors of the stroke itself found to worsen patient outcome include more severe strokes (Bhaskar et al., 2017; Chaudhari et al., 2014), posterior circulation infarcts (Kim et al., 2017; Savitz, & Caplan, 2005), and haemorrhagic stroke rather than ischemic stroke (Moulin et al.,2016; Murao, Rossi, & Cordonnier, 2013). The location of the stroke can also determine outcome (Kalaria, Akinyemi, & Ihara, 2016). Multiple stroke lesions are shown to cause dementia, irrespective of location, and multi-infarct is the most common form of vascular dementia (McKay, & Counts, 2017). Lesions in the left hemisphere (Pendlebury, & Rothwell, 2009) and deep vein thrombosis in the brain (Bustamante et al., 2016) have also been shown to be associated with worse post-stroke outcome. The same association has been found with longer time spent in hospital after the stroke (Huang, et al., 2013).

Stroke and PSD diagnosis:

The clinical diagnosis of cerebral infarction is based on The World Health Organization (WHO) criteria. WHO defines stroke as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin" (WHO MONICA Project Principal Investigators, 1988). Stroke is characterised by a sudden loss of neurological function due to an intracranial ischemia caused by a blood clot blocking the blood supply to the brain, or haemorrhage, caused by the breakage of a blood vessel leading to bleeding in to the brain. Initial stroke diagnosis is based on clinical symptoms. Symptoms depend on what area of the brain that is affected, but may include sudden numbness of the face or a limb, confusion, language problems, problems with vision, troubles walking, severe headache, and unconsciousness (Yew & Cheng, 2015).

The diagnosis of PSD can be made after three to six months when the patient has stabilised from the stroke, and is based on diagnostic criteria as for example the DSM IV criteria. PSD is a consequence of insufficient blood supply to the brain, leaving brain cells of the affected area to die. Symptoms of PSD depends on the part of the brain that is affected by the stroke, but more than one cognitive domain, such as memory, executive function, or attention, must be impaired for it to be diagnosed as PSD. Other symptoms may include different cognitive- and functional impairment, balance problems, language deficits, mood changes, and urinary incontinence. Diagnosis is based on interviews with the patient and caregivers, clinical examination, neuropsychological test, family history, and brain imaging scans (García & García, 2015). Brain image scans can also reveal underlying Alzheimer's

disease (AD) that often can be asymptomatic. AD patients commonly have a reduced brain reserve, and are thus at higher risk of having both a stroke and suffering from PSD (Mok et al., 2017).

The introduction of dedicated stroke units has been considered a breakthrough in the treatment of stroke patients, and has shown to improve outcomes of both mortality and function (Stroke Unit Trialists' Collaboration, 2013). During the last years, clinical therapies for acute ischemic stroke predominantly revolve around thrombolysis; a vascular recanalization. This therapy however has a narrow time window of administration, and can lead to blood coagulation abnormalities and intracranial haemorrhage, thus leaving it available to only a subset of stroke sufferers (Powers, et al., 2018). In the search of other therapy strategies, the research field on stroke was for long mostly concerned around neuroprotective approaches during the acute phase of a stroke, but most of the clinical studies failed to succeed. Many studies were criticized for having methodological issues, such as inclusion biases, and it was generally though that this was the reason for the failure. It is however plausible that neuroprotective approaches may indeed not be the right way to go, and the field is thus experiencing a paradigm shift, with the studies now mostly turning towards other mechanisms, such as comorbidities, regeneration, and plasticity. For instance, the impact of immune cells on the damaged tissue after stroke, and post-stroke comorbidities has gained much interest (Roth, & Liesz, 2016).

<u>The use of imaging techniques in stroke patients:</u>

The first course of action in the examination of the aetiology of a stroke is typically non-contrast computed tomography (CT) scan to rule out haemorrhage or large ischemic strokes, in order to administer thrombolysis as soon as possible. Following the acute state, many patients will then undergo a magnetic resonance imaging (MRI) protocol that more thoroughly investigate overall brain health, and progression and outcome of the affected brain parenchyma (Audebert & Fiebach, 2015). Imaging techniques can distinguish between haemorrhagic and ischemic stroke, identify the location and the extent of a blood clot, evaluate the extent of damaged tissue, recognise hypoperfused tissue at risk of infarction (penumbra) and identify the aetiology of the stroke. This allows for early and accurate detection of the stroke and consequently early and accurate treatment, and is one of the reasons for the reduction in stroke mortality. Diffusion-weighted imaging (DWI) can detect ischaemia within minutes after arterial occlusion, and can together with an apparent diffusion coefficient (ADC), with T2-weighted images distinguish acute, subacute, and older strokes. The standard MRI protocol for the assessment of stroke also includes perfusion-weighted imaging (PWI), fluid-attenuated inversion-recovery imaging

(FLAIR), T2-weighted gradient echo imaging with susceptibility-weighted imaging (SWI), and MR angiography (MRA), and takes about 20 minutes to run (Roldan-Valadez & Lopez-Mejia, 2014; Vymazal, Rulseh, Keller, & Janouskova, 2012). Figure 1 depicts examples of brain scan images using some of these MRI sequences; T2, DWI, T2-FLAIR, and SWI.

Figure 1: Examples of brain scan images of the same acute right hemisphere infarction, using different MRI sequences

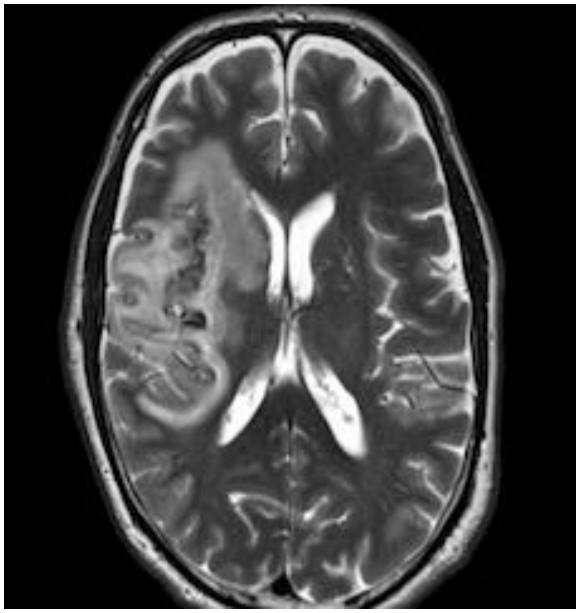


Photo 1: Acute infarction, as seen in an axial T2 image.

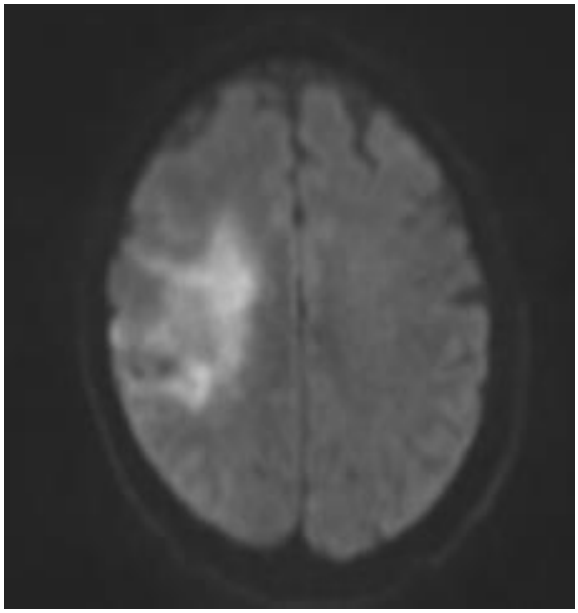


Photo 2: Acute infarction, as seen on DWI.

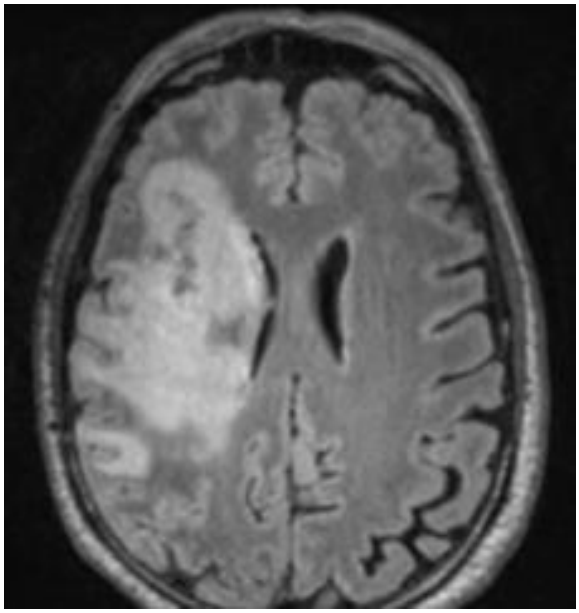


Photo 3: Oedema, as seen on axial T2-FLAIR scan.

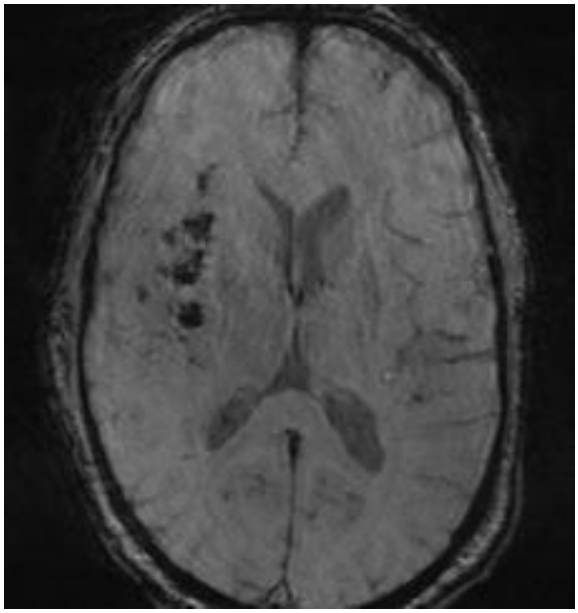


Photo 4: The infarction haemorrhage, as seen on SWI.

Figure 1: Images of the same middle cerebral artery acute infarction of the right hemisphere, shown with different MRI sequences; T2. DWI, T2-FLAIR, and SWI.

Although the diagnosis for PSD is initially made through clinical assessment, the use of imaging techniques, such as with different CT and MRI sequences, allows examination of the aftermath of the stroke and unfold pathological changes in the brain. The MRI can be used to uncover focal atrophy of the brain, such as hippocampal atrophy in AD, or atrophy associated with neurodegeneration in general, through the use of 3DT1 or 3D FLAIR (Helsedirektoratet, 2017, https://www.magicapp.org/app#/guideline/2273). It can also be used to classify vascular pathology. Common imaging findings include microbleeds, WMH (Grysiewicz, & Gorelick, 2012), and lacunes (Caplan, 2015).

Microbleeds are seen as hypointense punctuations on T2 and SWI sequences (Shibuya, Leite, & Lucato, 2017). It is suggested that microbleeds most likely represents blood leakage from microvasculopathies, as seen through deposits of blood-breakdown products, such as ferromagnetic hemosiderin iron (Charidimou, et al., 2018; Janaway, et al., 2014). The mechanisms underlying these lesions are however still not fully understood, but exacerbating factors include hypertension, cerebral amyloid angiopathy (CAA) (Pasi et al, 2018), and aging, in part due to inflammation (Sumbria, et al., 2018).

WMH are typically detected on FLAIR sequences, but both the pathophysiology and aetiology is not fully understood. Axonal loss and demyelination (Prins & Scheltens, 2015), altered cerebrovascular autoregulation and blood-brain barrier dysfunction (Simpson, et al., 2007), inflammation and CAA (Gouw, et al., 2011) are among suggested possible factors. WMH of vascular origin are hyperintense on T2 and FLAIR and show decreased attenuation on CT (Shibuya, Leite, & Lucato, 2017).

Although not fully understood, lacunes are suggested to be the results of subcortical infarctions occurring in the area around the perforating arteries (white matter, basal ganglia, thalamus etc.). They are usually small, around 20 mm across, and can be seen as hyperintense on DWI, T2, and FLAIR, and hypointense on ADC maps. Lacunes of vascular origin usually reside in the same area but are smaller (up to 15 mm across) (Shi, & Wardlaw, 2016; Shibuya, Leite, & Lucato, 2017).

Figure 2 depicts examples of brain scan images of microbleeds, WMH, and lacunes, using different MRI-sequences. Photo 2 of figure 2 depicts WMH of 3 on Fazekas scale. The scale classifies the white matter into periventricular white matter and deep white matter, with the grade depending on the size and the confluence of lesions. The scale ranges from 0 to 3, with 3 being the most severe, indicating irregular periventricular signal extending into the deep

white matter for the periventricular white matter division, and large confluent areas for the deep white matter division (Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987).

Figure 2: Examples of brain scan images of microbleeds, WMH, and lacunes, using different MRI sequences.

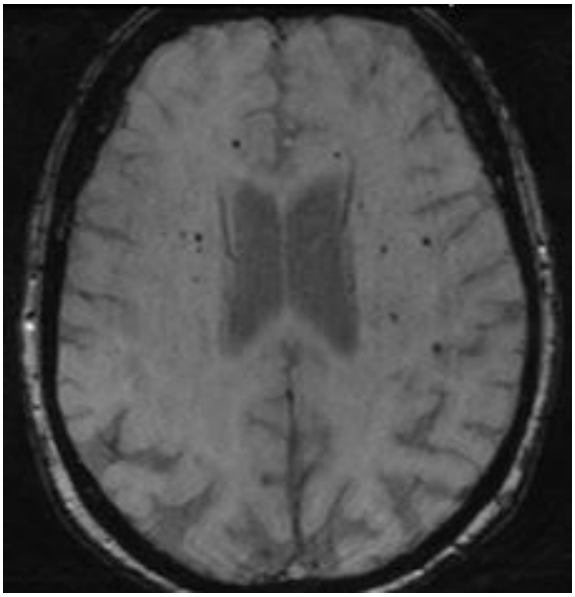


Photo 2: Multiple microbleeds in both hemispheres, as seen on SWI.

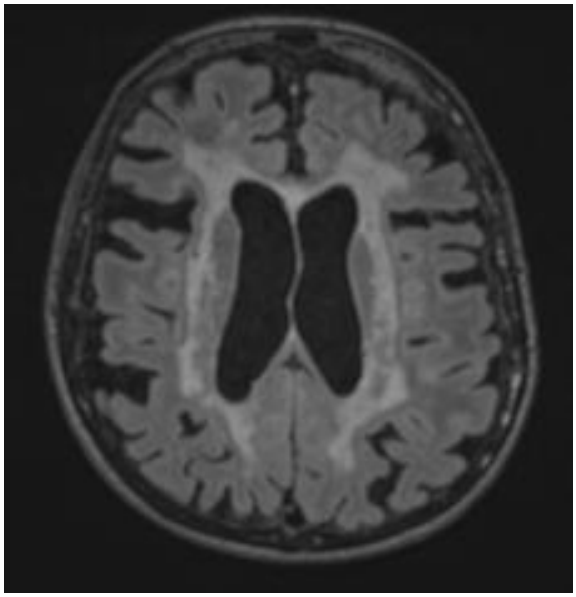


Photo 2: WMH severity of 3 of the Fazeka scale, as seen on axial T2-FLAIR.

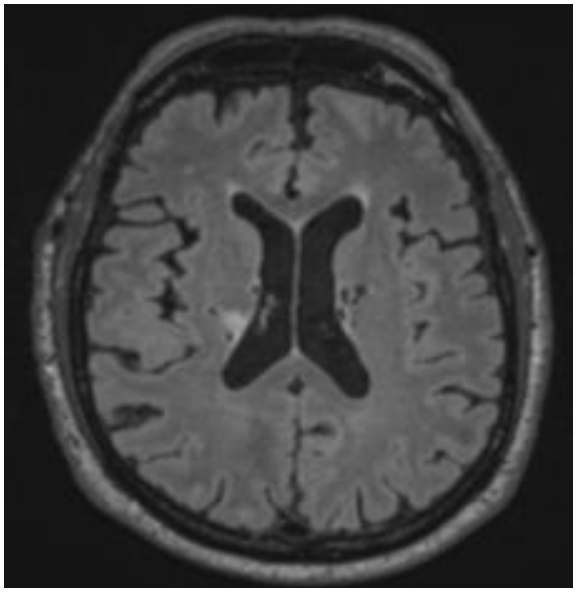


Photo 3: Multiple lacunes surrounding the ventricles, as seen on axial T2-FLAIR.

Figure 2: Images depicting microbleeds (photo 1), WMH (photo 2), and lacunes (photo 3), using different MRI-sequences; SWI and T2-FLAIR.

The selection of study participants:

Clinical research on dementia and other related neurological conditions, such as Alzheimer's disease face several distinctive methodological challenges, with the field lacking a 'gold standard' of what are the best practices. The challenges the field faces include sample selection biases, diagnostic criteria uncertainty, time-varying measurements, and the handling of complex and multidimensional data, among others, all having the potential to compromise the translational potential of the findings (Weuve et al., 2015). Several specific issues concerning the methods commonly used for research on stroke-related dementia today has been revealed, together with the effects of selection bias on results obtained from cognitive tests (Pendlebury, et al., 2015a). Pendlebury et al. found that patients over the age of 80, or with pre-existing functional impairments, dysphasia, or other comorbid diseases, tend both to have a higher risk of suffering from PSD, and to be excluded from studies due to practical reasons. Those over the age of 80 have a higher tendency to suffer from pre-stroke dementia, and many die before they can even be included in a study. Not only the recruitment, but also the retention of elderly participants over the course of a study can be problematic, especially for those aged 85 and over (Davis et al., 2014). This difficulty can be due to a multitude of reasons, such as transportation problems, poor health (Shearer, Fleury, & Beleya, 2010), medical issues, caregiver burden (Saunders, Greaney, Lees, & Clark, 2003), and sensory impairments and CIs (Mody et al., 2008). Increasing age, cognitive decline and poor health have been found to be associated with dropouts particularly from longitudinal studies (Chatfield, Brayne, & Matthews, 2005). Persons who live alone, have lower socio-economic status, are less educated, are women, and those who are unmarried also have a higher tendency to drop out. Practical reasons, such as the study being too time-consuming or too frequent and thus exhausting for the patient, may also be of importance (Bhamra, Tinker, Mein, Ashcroft, & Askham, 2008).

The severity of the stroke may also lead to reasons for not participating in studies, for example those with less serious strokes tend to leave the hospital before one can ask them to participate, and those with more severe types may be too sick to undergo exhausting testing. In a comprehensive review, Pendlebury (2012) showed that there is an inclusion bias in whether the study is population-based or hospital-based, and that the rates of dementia within the first year is the lowest in first-ever stroke in population-based studies, and the highest in major or recurrent stroke in hospital-based studies. Dementia rates were found to be twice as high in hospital-based studies, most likely due to the fact that these patients are more likely to be older and have more serious strokes (Pendlebury, 2015b).

Some of the assessment tools used for PSD diagnosis may not be sensitive to some issues commonly related to older age, such as visual impairments (Killen et al., 2013) and motor- and language difficulties (Wall, Isaacs, Copland, & Cumming, 2015), thus potentially lead to an either over- or underestimating of the degree of cognitive decline or dementia, if not tested for (Killen et al., 2013). If any of these impairments are discovered, the clinicians are forced to use different assessment tools that do not depend on vision, or motor capabilities, thus creating a discrepancy in diagnosis between different individuals (Coull, Silver, Bull, Giles, & Rothwell, 2004). A systematic review revealed that the most common excluding factors in stroke research were, in ascending order based on prevalence; CIs, communication issues, endurance problems, sensory loss, psychiatric illness and motor limitations. Since many stroke survivors are excluded as they are unable to complete the diagnostic tasks, it may lead to an under-representation of several stroke sub-groups and thus change the generalisability of a study (Wall et al., 2015).

Recruiting a large enough sample size is crucial for ensuring high statistical power as it minimises random error and can detect results of smaller effect sizes (Button et al., 2013). When there is low statistical power, the likelihood of significant findings actually reflecting a true effect is also affected. Having a large sample size may however be costly or unethical (Das, Mitra, & Mandal, 2016), and smaller sample sizes are common in most research fields, such as in the neurosciences (Button et al., 2013) and in randomised trials studies in medical research, with one review revealing a sample size median of 52 over 519 studies (Chan & Altman, 2005).

Taking all the methodological challenges together, the results obtained from these studies therefore exclude a substantial proportion of stroke patients, with the effect that the results may not be generalizable to all who suffer a stroke. It also results in an underestimation of patients suffering from dementia following stroke (Pendlebury, et al., 2015b). It is important to know whom the results of the study can be generalised to for both the applications and implications of the study. Being aware of possible biases is crucial to hold both internal and external validity of the study (Tripepi, Jager, Dekker, & Zoccali, 2010). Internal validity is ensured through thoughtful study design and data collection, and the use of appropriate statistical analyses, whereas external validity depends on statistical inference, but also the researchers' ability to judge what facts of the study are relevant for further conclusion (Kukull & Ganguli, 2012).

There is currently a large prospective observational multicentre study on post-stroke CI taking place in Norway (Norwegian Cognitive Impairment After Stroke (Nor-COAST)). The Nor-COAST study aims to describe incidence, and to identify predictors for the development

of PSD and mild cognitive impairment (MCI) after suffering a stroke. A master thesis examining the generalisability of the results from this study was conducted, comparing the group to a Norwegian Stroke Registry (NHR) population. The report found that the two populations were not significantly different, except for the Nor-COAST study population having a lower mean score of stroke severity, more 'mild strokes' and less 'severe strokes', and less haemorrhagic strokes than the NHR population (Kuvås, 2018).

Aim of the current study:

The overall aim of the present study is to analyse whether or not the patients participating in the MRI sub-study of St Olav branch of Nor-COAST are representative for the Nor-COAST population as a whole.

We hypothesise that those who did not provide study-specific MRI-protocol data were younger or older than those who did, due to either being admitted to a different unit of the hospital, or being too frail, respectively. We also hypothesise that those who did not provide study-specific MRI data had more comorbidity, and were more cognitively and functionally impaired. Lastly, we hypothesise that those who had more brain pathology such as the presence of haemorrhage and pre-stroke pathology, showed a higher tendency to not go through study-specific MRI-protocol.

The objective of current research is thus to analyse what characterises those in the St Olav branch of the Nor-COAST study who underwent a complete study-specific MRI scan protocol (NC-p), and those who did not (non-NC-p). More specifically we will investigate;

- How does the age of the patient affect study-specific MRI scan participation?
- Do clinical aspects, such as stroke severity and comorbidities, affect participation?
- Do brain health aspects, such as microbleeds, WMH, and prior stroke affect study-specific MRI scan participation?

Method

The Nor-COAST study

Design:

The Nor-COAST study has been financed by The National Health Association. The overall aim of this study is to study post-stroke cognitive impairment (PS-CI). Nor-COAST recruited participants from stroke units and neurology units at five hospitals in Norway; St. Olav hospital, Haukeland hospital, Oslo university hospital, Ullevål and Vestre Viken hospital, Bærum hospital, and Ålesund hospital. Data collection was obtained at baseline, during the hospital stay, 3 and 18 months after the stroke, and included evaluation of cognition, lifestyle, physical activity, blood samples, activity monitoring, pharmacological and non-pharmacological secondary prevention, and cerebral MRI. Baseline characteristics from all participant were collected through interviews with the participant or next of kin, or through medical records. The study has five work-packages (WPs):

- WP1 – study incidence, prevalence and trajectory of PS-CI
- WP2 – study pathogenetic mechanisms by a) study neuroimaging at baseline and follow up, and b) study biomarkers
- WP3 – study predictors for PS-CI
- WP4 – study importance of physical activity for PS-CI
- WP5 – study if secondary prevention is of importance for development of PS-CI

The current master-thesis is part of WP2 a).

Participants:

818 participants were included in the Nor-COAST study. Inclusion criteria included; 1) suffering an acute stroke diagnosed according to World Health Organisation (WHO) criteria (WHO MONICA Project Principal Investigators, 1988), and hospitalised within one week after onset of symptoms, 2) aged 18 or over, 3) able to communicate in Norwegian, 4) if not able to communicate due to a medical condition, a caregiver or next of kin must be available, 5) must give informed consent, or be done by a caregiver or next of kin if participant is unable to consent. Exclusion criteria included; 1) not treated in participating stroke unit, 2) symptoms are explained by other disorders than ischemic infarcts or intra-cerebral haemorrhages.

The current study

Design:

Current study is a sub study of the Nor-COAST study. Data collected from participants recruited from the stroke unit and the neurology unit at St Olav hospital were used, with a

collection of baseline characteristics and brain-scan image descriptions made by neuroradiologists describing the extent of the stroke and brain pathology.

Participants:

401 participants were recruited from St. Olav hospital. Inclusion criteria for MRI participation included; 1) being of good enough health and be able to do an MRI scan whilst in hospital, or within two weeks after the acute stroke, 2) having no contraindications for MRI scanning, 3) having given informed consent to MRI.

Data collection:

The study specific MRI protocol included axial T2 weighted imaging, DWI, sagittal 3D-T1 weighted imaging (ADNI), sagittal 3D FLAIR, and axial susceptibility weighted imaging (SWI).

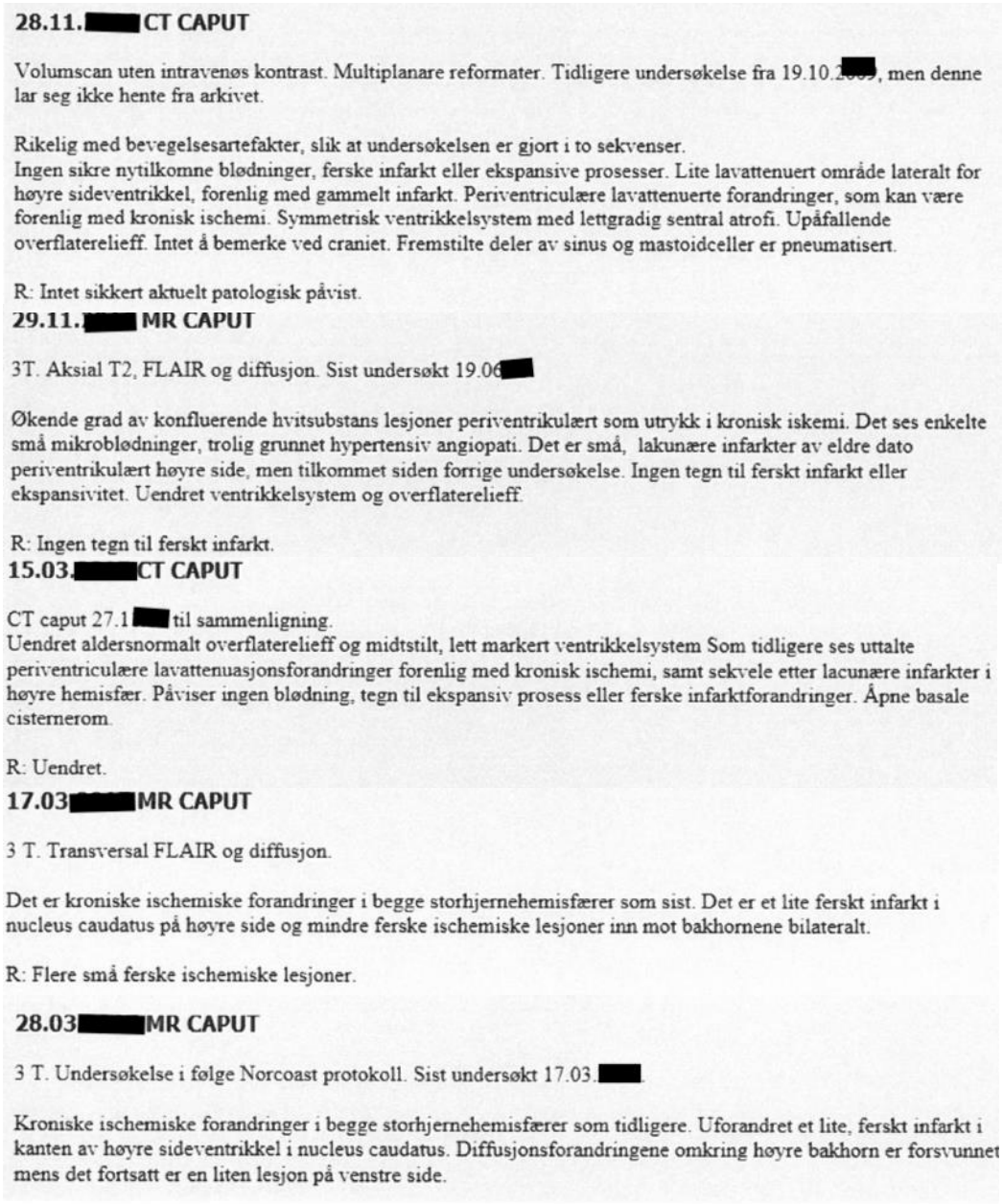
The collection of data was completed by a single student observer, and was achieved in two steps; 1) brain image variables were registered through analysis of reports of brain-scan images done as part of clinical routine by neuroradiologists, and 2) clinical variables were gathered involving baseline characteristics that had been assessed as part of the Nor-COAST dataset. In addition, time from stroke to the last MRI scan, and if the patient had had multiple MRIs during the hospital stay was registered.

All the data obtained from the brain scan reports was used, even though some were only descriptions of CT scans or non-NC-p MRI. Some of the participants had multiple bands of scans, where multiple scans done within a few weeks were registered as a single band. Multiple bands of scans thus represent multiple visits to the hospital and most probably different cerebral events. If the participant had multiple bands of scans from multiple incidents, either the newest band was used, or if the newest band contained no description of an infarct, the next band in line containing an infarct was used. If none of the bands contained descriptions of an infarct, the newest band of scans was used. If there were discrepancies in the data, such as of different infarcts, the newest scan results were used for registration.

When there was inconsistency in the data between different neuroradiologists, the most prominent or clear statement was chosen. An example of this was a case where three out of four different neuroradiologists, from four different brain scans of the same participant within one band of scans, described a stroke in the left hemisphere, whereas the last one described the same in the right hemisphere. The stroke was registered to be in the left hemisphere.

Data collection of the brain image variables was achieved blindly, as the clinical variables were at that time unknown to the observers.

Figure 1: Example of Brain Image Data



28.11.[redacted] CT CAPUT

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Rikelig med bevegelsesartefakter, slik at undersøkelsen er gjort i to sekvenser.
Ingen sikre nytilkomne blødninger, ferske infarkt eller ekspansive prosesser. Lite lavattenuert område lateralt for høyre sideventrikkel, forenlig med gammelt infarkt. Periventriculære lavattenuerte forandringer, som kan være forenlig med kronisk ischemi. Symmetrisk ventrikkelsystem med lettgradig sentral atrofi. Upåfallende overflaterelieff. Intet å bemerke ved craniet. Fremstilte deler av sinus og mastoidceller er pneumatisert.

R: Intet sikkert aktuelt patologisk påvist.

29.11.[redacted] MR CAPUT

3T. Aksial T2, FLAIR og diffusjon. Sist undersøkt 19.06[redacted]

Økende grad av konfluerende hvitsubstans lesjoner periventrikulært som utrykk i kronisk iskemi. Det ses enkelte små mikroblødninger, trolig grunnet hypertensiv angiopati. Det er små, lakunære infarkter av eldre dato periventrikulært høyre side, men tilkommet siden forrige undersøkelse. Ingen tegn til ferskt infarkt eller ekspansivitet. Uendret ventrikkelsystem og overflaterelieff.

R: Ingen tegn til ferskt infarkt.

15.03.[redacted] CT CAPUT

CT caput 27.1[redacted] til sammenligning.
Uendret aldersnormalt overflaterelieff og midtstilt, lett markert ventrikkelsystem Som tidligere ses uttalte periventriculære lavattenuasjonsforandringer forenlig med kronisk ischemi, samt sekvele etter lacunære infarkter i høyre hemisfær. Påviser ingen blødning, tegn til ekspansiv prosess eller ferske infarktforandringer. Åpne basale cisternerom.

R: Uendret.

17.03[redacted] MR CAPUT

3 T. Transversal FLAIR og diffusjon.

Det er kroniske ischemiske forandringer i begge storhjernehemisfærer som sist. Det er et lite ferskt infarkt i nucleus caudatus på høyre side og mindre ferske ischemiske lesjoner inn mot bakhornene bilateralt.

R: Flere små ferske ischemiske lesjoner.

28.03[redacted] MR CAPUT

3 T. Undersøkelse i følge Norcoast protokoll. Sist undersøkt 17.03.[redacted]

Kroniske ischemiske forandringer i begge storhjernehemisfærer som tidligere. Uforandret et lite, ferskt infarkt i kanten av høyre sideventrikkel i nucleus caudatus. Diffusjonsforandringene omkring høyre bakhorn er forsvunnet mens det fortsatt er en liten lesjon på venstre side.

Figure 1: Example of descriptions from neuroradiologists of brain scans for one participant. The scans were categorised into two bands of scans (28-29.11 and 15-28.03), where the latter was used for registration, as this one was the newest one containing descriptions of an infarction.

Clinical variables:

CI was analysed using the Global Deterioration Scale for assessment of cognitive impairment (GDS) pre-stroke (Reisberg, Ferris, de Leon & Crook, 1982), through interviews with next of kin. The scale ranges from one to seven, with increasingly severe impairment, where one is no cognitive decline, and seven is severe dementia. Level one to three is considered pre-dementia stages and level four to seven is considered the dementia stages, where at level five the individual can no longer survive without assistance.

Comorbidity was registered using Charlson Comorbidity Index (CCI) (Charlson, Pompei, Ales & MacKenzie, 1987), which is based on multiple comorbidities that are weighted based on mortality risk and disease severity. Examples include myocardial infarction, cerebrovascular disease or transient ischemic disease (one point), diabetes (two points), and metastatic solid tumour (six points). The CCI has later gotten an age-adjusted version, where extra points are added for each decade above the fourth (Charlson, Szatrowski, Peterson, & Gold, 1994). Current study did not use the age-adjusted version of CCI, as age was used as a predictor variable in the statistical analyses.

Functional impairment was registered using the Modified Rankin Scale (mRS) at discharge (Banks & Marotta, 2007). This scale is commonly used for measuring the degree of disability or dependence in daily life activities. The scale ranges from zero to six with increasingly severe disability, where zero represents no symptoms, five represents severe disability, and six represents death. Levels between zero to two reflect individuals being independent, and levels over this representing the individual needing some assistance.

For the stroke severity variable, National Institutes of Health Stroke Scale (NIHSS) scores (Lyden et al., 2001) on day of inclusion were used, with available data for 381 participants. At day one NIHSS was registered in twelve, and was completely missing for eight participants. The NIHSS scale ranges from zero to forty, with zero = no stroke symptoms, one to four = minor stroke, five to fifteen = moderate stroke, sixteen to twenty = moderate to severe stroke, and twenty-one to forty = severe stroke.

Multiple MRIs registrations were categorised as the number of MRI scans within chosen band of scans.

Time from stroke to the last MRI scan was recorded. If there was only one scan done, or multiple were done on only one day, time from stroke was registered as zero.

Brain image variables:

There was a large variation in the brain scan descriptions by the different neuroradiologists, and at times also a lack of information, therefore it was impossible to register for all the variables in all cases. If this was the case, the variable was scored as not announced (NA).

Microbleeds registrations were categorised as present, not present, or NA. If SWI sequence was carried out and it was not mentioned, it was registered as not present. If SWI sequence was not carried out and it was not mentioned, it was registered as NA.

WMH registrations were categorised as present, not present, or NA. If an MRI was carried out and it was not mentioned, it was registered as not present. If an MRI was not carried out and it was not mentioned, it was registered as NA.

Stroke location and prior stroke registrations were categorised as frontal, parietal, temporal, occipital, thalamus, cerebellum, brain stem, basal ganglia, insula, multiple, no stroke, or NA. If 'capsula interna or –externa' was mentioned, it was registered as basal ganglia. If 'semiovale sentrum' or 'corona radiata' or 'corpus callosum' was mentioned, it was registered as white matter. This is due to the fact that most infarcts that hit the internal- or external capsule will also affect the basal ganglia, whereas those registered as white matter do not.

Stroke hemisphere and prior stroke hemisphere registrations were categorised as left, right, both, or NA. When there was no infarct, the hemisphere registration was based on symptoms, if given and very clear. If not, it was registered as NA.

Vascular territory registrations were categorised as anterior, posterior, middle, watershed anterior-middle, watershed posterior-middle, watershed anterior-posterior-middle, cerebellar superior, cerebellar anterior inferior, cerebellar posterior inferior, and NA. If not mentioned, it was registered as NA.

Haemorrhage registrations were categorised as present or not present. If CT scan was carried out and it was not mentioned, it was registered as not present.

Visible thrombosis registrations were categorised as present, not present, or NA. If SWI or CTA sequences were carried out and it was not mentioned, it was registered as not present. If SWI or CTA were not carried out and it was not mentioned, it was registered as NA.

Prior stroke registrations were categorised as present, not present, or NA. If not mentioned, it was registered as not present. Any mention of lacunes were registered as prior stroke, as lacunes are most likely a result of a lacunar infarct.

Lacunes registrations were categorised as present, not present, or NA. If not mentioned, it was registered as not present, unless there had been a prior subcortical stroke.

Pilot studies:

In order to examine inter-rater and intra-rater reliability and to ensure reliable data collection, two pilot studies were run using the brain image variables.

The first pilot was run by two observers concurrently; one student (EA) and one experienced neuroradiologist (MB). The pilot was run using 25 randomly chosen brain image descriptions. The pilot was conducted as described in the data collection section, and individual datasheets of the registrations of brain-image description analyses were created independently by the two observers. Several trials had to be conducted to ensure agreement between the observers, with questions emerging such as whether or not it was to be registered as 'not present' or 'not announced' when certain things (such as lacunes or prior stroke) was not specifically mentioned in the brain-scan image descriptions. Reliability of the data collection was ensured through running Cohens Kappa inter-rater reliability tests between the two observers.

The second pilot was run by the student alone, who was the one who would collect the remaining data. Blind tests were performed for the brain image variables for 100 randomly selected cases (including the pilot) about three to four weeks after the registrations were finalised. Intra-rater reliability testing was conducted through Cohens Kappa analysis between the initial data collection and the pilot collection.

Acceptable agreement percentage was set at minimum 80% for both the intra-rater and the inter-rater reliability. An acceptable percentage had to be reached between the two observers before the rest of the data collection could commence, and for the student alone before the statistical analyses could take place.

For the first pilot, inter-rater agreement between the two observers was over 90% for all variables ($p<.001$), except for post stroke hemisphere (80%), stroke location (88%), and time from stroke (84%). Cohen's κ was run, indicating substantial- to strong agreement between the two observers, with Cohen's κ ranging from .671 to 1.000 ($p<.001$). See table I in appendix for all values.

For the second pilot, intra-rater reliability blind tests for the single student observer yielded 90% agreement for all variables between the two observer timings. Cohen's κ was run, indicating generally strong agreement between the two set-points, with Cohen's κ ranging from .864 to 1 ($p<.001$) for all variables, except for stroke location (.454), vascular territory (.201), and prior stroke location (.340). See table I in appendix for all values.

Variables extracted from further analysis:

Five variables were extracted from further analysis due to a high number of missing data. As depicted in table II in the appendix, microbleeds, vascular territory, visual thrombosis, prior stroke hemisphere, and prior stroke location showed high percentages of missing data, especially in the non-NC-p group condition.

Four of the variables also exhibited low kappa scores during the second pilot (see table I in the appendix), indicating problematic data collection. These variables were stroke location, post stroke location, post stroke hemisphere, and vascular territory. Due to the difficulty of comparing the two NC-p participation groups when there is a high number of missing data and low agreement strength, the variables were extracted from further analysis.

Statistical analysis:

IBM SPSS Statistics for Mac, version 24.0 was used for conducting statistical analysis.

Inter-rater and intra-rater agreement for the pilot were measured through percentage of agreement, with Cohen's κ (Hallgren, 2012) for statistical power. Kappa statistics between .00 and .20 is seen as slight agreement, .21 to .40 as fair, .41 to 60 as moderate, .61 to 80 as substantial, and .81 to 1.00 as almost perfect to perfect agreement, with scores less than substantial commonly seen as inadequate level of agreement (Landis & Koch, 1977; McHugh, 2012).

Descriptive statistics for all cases were first calculated, with means, standard deviations (SD), and frequency tables. The data was then split in two by NC-p or non-NC-p, and descriptive statistics were done again for both groups.

Independent samples t-tests were run for age, CI, comorbidity, functional impairment, stroke severity, multiple MRIs, and time from stroke.

Chi square of independence analyses were run for the brain image variables and gender. Monte Carlo exact tests based on one million sampled tables were run for those variables with expected count less than five (stroke location). Post hoc test of variable contributions through calculation of standardised residuals were administered to the variables yielding significant results in the chi square tests. Standardised residuals less than -2 indicate an observed frequency that is less than expected, and greater than 2 indicate one that is greater than expected. Less than -2 and greater than 2 is thus regarded as significant and indicate substantial contribution to the association found (Sharpe, 2015).

Two binary logistic regression analyses were run for all of the data except for stroke location, due to the high number of categories and the 1:10 rule of thumb (Lydersen, 2015;

Peduzzi, Concato, Kemper, Holford, & Feinstein, 1996), and those extracted due to a high number of missing cases and data collection issues. The lacunes variable was also extracted, due to its overlap with the prior stroke variable, to eliminate the possible multicollinearity from the model. The multiple MRIs variable was not included in the model. A multiple imputation model of 20 (van Buuren, S., 2012) was used due to missing data (17.95%) in the remaining data set. Dummy variables were used in variables consisting of multiple categories (stroke hemisphere). The first analysis was done with the individual singular variables as a univariate unadjusted model towards NC-p participation, and the second analysis was done as a multivariate adjusted model with all the variables included. P-values and odds ratio (OR) according to Wald criteria were analysed for the predictor variables, with ORs less than 1 indicating a negative relationship and lower odds of outcome, and values over 1 indicating a positive one and higher odds.

As one variable yielded non-significant results in the multivariate adjusted model, although significant in the univariate unadjusted one, the search for a confounding variable was done through creating regression models containing the seemingly confounded variable adjusting for each of the other variables in turn, towards NC-p participation.

Ethical considerations:

Participants were only included in the Nor-COAST study after providing an informed consent. The next of kin would provide this if the participant was unable to provide a written consent. The participants were also asked to consent to the MRI sub study of the Nor-COAST study, even though they had consented to taking part in the study as a whole.

Data material was presented anonymously, as in line with Norwegian legislation for research ethics. This study received REK approval, with reference 2016/2306 REK Nord.

Results

Out of the 401 participants included, 217 (54.1%) underwent a brain MRI using a study specific protocol. The rest of the participants either only had a brain CT scan or a clinical brain MRI with a much shorter protocol.

Table 1: Baseline Characteristics for the Clinical Variables. NC-p = Nor-COAST participants in MRI sub study. Non-NC-p = Nor-COAST participants not participating in the MRI sub study

Variable		Whole group N = 401	NC-p N = 217	Non-NC-p N = 184	*p*-value
Male gender	N (%)	219 (54.6)	117 (53.9)	102 (55.4)	.761
Age	N	401	217	184	
	Mean (SD)	74.8 (10.7)	75.2 (9.2)	74.2 (12.3)	.360
GDS	N	391	214	177	
	Mean (SD)	1.9 (1.3)	1.9 (1.2)	2 (1.4)	.335
CCI	N	401	217	184	
	Mean (SD)	4.1 (1.9)	4.1 (1.6)	4.1 (2.1)	.815
mRS	N	397	215	182	
	Mean (SD)	2.8 (1.3)	2.7 (1.2)	2.9 (1.4)	.204
- no symptoms	N (%)	4 (1)	2 (.9)	2 (1.1)	
- no disability	N (%)	59 (14.7)	27 (12.4)	32 (17.4)	
- slight	N (%)	119 (29.7)	73 (33.6)	46 (25)	
- moderate	N (%)	85 (21.2)	52 (24)	33 (17.9)	
- moderate/severe	N (%)	92 (22.9)	48 (22.1)	44 (23.9)	
- severe	N (%)	34 (8.5)	12 (5.5)	22 (12)	
- dead	N (%)	4 (1)	1 (.5)	3 (1.6)	
NIHSS	N	381	212	169	
	Mean (SD)	5.1 (6.2)	4.8 (5.3)	5.5 (7.3)	.281
- no symptoms	N (%)	50 (12.5)	29 (13.4)	21 (11.4)	
- minor	N (%)	199 (49.6)	103 (47.5)	96 (52.2)	
- moderate	N (%)	99 (24.7)	67 (30.9)	32 (17.4)	
- moderate/severe	N (%)	19 (4.7)	8 (3.7)	11 (6)	
- severe	N (%)	14 (3.5)	5 (2.3)	9 (4.9)	
Multiple MRIs	**N**	**401**	**217**	**184**	
	Mean (SD)	**1.2 (.7)**	**1.5 (.6)**	**.8 (.6)**	**<.001**
Time from stroke (days)	**N**	**401**	**217**	**184**	
	Mean (SD)	**3.7 (4.8)**	**5.2 (5.5)**	**2 (5.5)**	**<.001**

*Table 1: Independent samples t-tests of independence for the association between the clinical variables and NC-p participation. P-value significant <.05. Chi square test of independence for gender. *p-value significant at <.05. GDS = Global Deterioration Scale, CCI = Charlson Comorbidity Index, mRS = the modified Rankin Scale, NIHSS = the National Institutes of Health Stroke Scale.*

As depicted in table 1, descriptive statistics for the whole group show that the participant mean age was 74.8 (*SD* = 10.7) and that there was a slight overrepresentation of males (54.6%). Non-significant associations were found for almost all of the clinical variables. Two variables did however show significant associations; multiple MRIs ($p<.001$), and time from stroke ($p<.001$). Those who participated in the MRI sub study had more MRI scans and spent more time in hospital.

Table 2: Brain Image Findings Among the Nor-COAST Participants Recruited at St Olav Hospital. NC-p = Participants in the MRI Sub Study. Non-NC-p = Not Participating in the MRI Sub Study.

Variable		Category	Whole group	NC-p	Non-NC-p	*p*-value
WMH	**N (%)**		**284 (70.8)**	**169 (77.9)**	**115 (62.5)**	**.037**
Stroke hemisphere	N (%)	Left	170 (42.4)	92 (42.4)	78 (42.4)	
		Right	154 (38.4)	87 (40.1)	67 (36.4)	
		Both	40 (10)	22 (10.1)	18 (9.8)	
						.911
Haemorrhage	**N (%)**		**66 (16.5)**	**27 (12.4)**	**39 (21.2)**	**.018**
Prior stroke	**N (%)**		**170 (42.4)**	**105 (48.4)**	**65 (35.3)**	**.008**
Lacunes	N (%)		117 (29.2)	71 (32.7)	46 (25)	.090

Table 2: Chi square tests of independence for the association between the brain image variables and NC-p participation. P-value significant <.05.

Table 2 depicts the descriptive statistics for a subset of the brain image variables, based on p-values from the chi square tests being either significant or close to significant. See table II

in appendix for full list. Most of the brain image variables displayed non-significant results, indicating independence between the variables and NC-p participation. Significant results were however found for three variables. Significant results were found for WMH ($X^2(1) = 4.349$, $p = .037$), with effect size, measured by Cramer's *V*, being weak (.106), and with the NC-p group showing a higher frequency. There was more haemorrhage in the non-NC-p group ($X^2(1) = 5.548$, $p = .018$), with effect size, measured by Cramer's *V*, being weak (.118). There was more prior stroke in the NC-p group ($X^2(1) = 6.955$, $p = .008$), with effect size, measured by Cramer's *V*, also being weak (.132). 67.7% of prior strokes in the NC-p group were lacunes and the same was true for 70.8% in the non-NC-p group.

No unexpected standardised residual values were found for any of the variables.

Table 3: Binary Logistic Regression Analysis for the Multivariate Adjusted Model Towards NC-p Participation.

Variable	*p*-value	OR	95% CI for OR
Gender	.375	.809	.506 to 1.293
Age	.505	.809	.983 to 1.036
GDS	.313	.898	.729 to 1.107
CCI	.993	1.001	.867 to 1.155
mRS	.299	.881	.694 to 1.119
NIHSS	.296	.976	.932 to 1.022
Left hemisphere	.971	.985	.449 to 2.164
Right hemisphere	.966	1.018	.457 to 2.264
WMH	.251	1.364	.803 to 2.316
Haemorrhage	**.009**	**.409**	**.209 to .798**
Prior stroke	**.008**	**1.872**	**1.178 to 2.975**
Time from stroke	**<.001**	**1.358**	**1.242 to 1.484**

Table 3: GDS = Global Deterioration Scale, CCI = Charlson Comorbidity Index, mRs = the modified Rankin Scale, NIHSS = the National Institutes of Health Stroke Scale. P-value significant at <.05

Two imputed binary logistic regression analyses were conducted for the various variables. First, a univariate unadjusted model analysis was conducted (see appendix table III). Significant individual predictors, measured by the Wald criterion, included WMH ($p = .037$),

with an odds ratio of 1.634, haemorrhage (p = .020), with an odds ratio of .528, prior stroke (p = .009), with an odds ratio of 1.716, and time from stroke (p<.001), with an odds ratio of 1.307.

Secondly, a multivariate adjusted model analysis was administered to investigate the likelihood of all of the variables within one model, leading to NC-p participation. The Wald criterion (see table 3) revealed that haemorrhage (p = .009), with and odds ratio of .409, prior stroke (p = .008), with an odds ratio of 1.872, and time from stroke (p<.001), with an odds ratio of 1.358, significantly contributed to the prediction model. From the original, non-imputed data (see appendix table III), all three variables remained significant.

The WMH variable was not significant in the multivariate adjusted model, although found significantly associated towards NC-p participation in both the chi square analysis and the unadjusted model. The search for a possible confounding variable revealed that WMH was correlated with many of the other variables, but was confounded especially by time from stroke and haemorrhage. The individual multicollinearity effects were however small and the larger obliterating effect of WMH happened only with the variables combined.

Discussion

The current study aimed to analyse what characterises those who partook in the MRI sub study of the St Olav branch of the Nor-COAST study, and those who did not. The results revealed little difference between the groups, except for haemorrhage being more prevalent in the non-NC-p group, and prior stroke and WMH being found associated with participating in the MRI sub study.

Results discussion:

As hypothesised, haemorrhage was significantly more prevalent in the non-NC-p group. As haemorrhagic strokes are generally more severe than ischemic ones (Moulin et al.,2016; Murao, Rossi, & Cordonnier, 2013), this indicates that persons with haemorrhagic strokes were more likely to be of too poor health to participate in the lengthy study-specific MRI scan. This may also have been intensified by the fact that the MRI lab at St Olav hospital only had one radiologist, so the patient had to be healthy enough to be moved with the help of only one person. These findings are in line with studies of inclusion biases (Pendlebury et al., 2015a), and also with the rest of the Nor-COAST population (Kuvås, 2018).

Stroke severity yielded no significant difference between the groups. However, the symptomatic categories show more moderately severe strokes in the NC-p group, and less

severe strokes in this group than in the non-NC-p one. The Nor-COAST study did not intend to include those of the most severe types of strokes due to ethical considerations. Patients who suffer a severe stroke will have a low suspected likelihood of survival within the three first months after the time of the index stroke (Andersen, Olsen, Dehlendorff, & Kammersgaard, 2009) and would therefore be lost for evaluation of CI at that time. In a large study with a stroke population of 1197 patients, 62% of those with very severe strokes died within six months (Jørgensen et al., 1995). The group with the most severe strokes comprise many patients with haemorrhage, as mentioned above.

The significant association of WMH towards participating in the MRI sub study conflicts with previous research showing that WMHs are a sign of impaired brain health that in turn is associated with CI (Gardener, Wright, Rundek, & Sacco, 2015). CI is found associated with both worse patient outcome and exclusion from stroke research (Moulin, & Leys, 2017; Pendlebury et al., 2015a), and has been found to be one of the most prevalent causes of such (Wall et al., 2015). The current study found no difference between the groups for pre-stroke CI, and the significant finding of WMH may thus be due to the fact that WMHs often can be found in completely asymptomatic subjects (Tomimoto, 2015; Morris et al., 2009). The current study did however only include analysis of pre-stroke CI, whereas the participants may have developed post-stroke CI. Another possibility for this divergence may also be that the tools used were insufficient in detecting accurate levels of WMH or pre-stroke CI. Both visual MRI rating scales of WMH (Sudre et al., 2017) and the scale used for CI evaluation (Rikkert et al., 2011) bear some limitations, and our findings may potentially suffer the consequences of this.

WMH was not a significant predictor of NC-p participation in the multivariate adjusted regression model. It was found that multiple variables affected the association, especially time from stroke and haemorrhage. These variables are thus negative confounding variables on the association between WMH and NC-p participation, as they are stronger predictors (Mehio-Sibai, Feinleib, Sibai, & Armenian, 2005).

Prior stroke was not only significantly associated with, but also predictive of NC-p participation. This finding was unexpected and also conflicts with previous research, as recurrent strokes are often found more disabling and fatal than first-time strokes (Hankey, 2014; Pendlebury, & Rothwell, 2009), thus indicating that the NC-p group should be of worse health than the non-NC-p group. This divergence may possibly be due to the role of familiarity, as those who have suffered strokes previously have already been through brain scans in the past, and may feel confident to go through the lengthy protocol, as the procedures of an MRI scan are not unknown (Newington & Metcalfe, 2014).

The association between NC-p and lacunes was non-significant, but was close to the $p<.05$ significance mark, and is thus of some interest. The prevalence of lacunes was found to be higher in the NC-p group, as opposed to the other group, and thus conflicts with both our expectations and other research, as lacunes are associated with worse patient outcome (Makin, Turpin, Dennis, & Wardlaw, 2013).

The divergence of these three pre-stroke factors (WMH, prior stroke, and lacunes), may be due to the St Olav branch of the Nor-COAST study trying to include a representative sample and thus also the sickest patients (Kuvås, 2018).

No difference in the age of the participants was found between the two groups, suggesting there was no inclusion bias on this matter in the St Olav branch of the Nor-COAST study. However, the thesis examining the generalisability of the findings from the Nor-COAST study as a whole revealed that the St Olav branch had a higher mean age than the NHR population, indicating that the findings from this branch of the study may represent a slightly older group (Kuvås, 2018). The St Olav branch of the Nor-COAST study has managed to include older persons, possibly due to the fact that most of the included patients were recruited from a dedicated stroke unit of the hospital, whereas the younger patients were admitted to the Neurological department. This section only recruited a few of the participants, but the stroke unit also had the possibility of recruiting older patients, as it is a part of the Department of Internal Medicine. This department is used to treating older patients and may represent a section this group of patients may be familiar with or feel is more tailored to them, thus creating trust and reassurance; an important factor in recruitment (Carroll & Zajicek, 2011).

Having had multiple MRIs was found both significantly associated with NC-p participation. This may point at patients being of better health than in the other group (Shearer, Fleury, & Beleya, 2010), or feeling more inclined to participate due to familiarity (Newington & Metcalfe, 2014). However, inclusion to the MRI sub study was done after initial diagnostic scans, thus leading to all MRI sub study participants having at least one more MRI scan than those who did not partake.

Longer times spent in hospital from the time of stroke were found both associated with, and predictive of, NC-p participation. This may point at these patients being of worse health than the patients who did not undergo study-specific MRI protocol, as longer hospital stays are associated with worse patient outcome after a stroke (Huang, et al., 2013). Those of better health often came back after the initial discharge for the MRI scans, and thus spent less time in hospital.

Our findings demonstrate that there is not a large difference between the two groups, except for mainly a higher prevalence of haemorrhagic strokes and, although non-significant, more severe strokes in the non-NC-p group, and more prior stroke and WMH in the participating group. This thus indicates that the results from the study-specific MRI scans can be generalised to most of the St Olav Hospital branch of the Nor-COAST study. Although the inclusion to the St Olav branch of the Nor-COAST study was somewhat different from the rest of the participating hospitals, these findings may also potentially suggest that the results from the larger Nor-COAST can be generalised to a large group of stroke patients. The only group to whom these findings may not be generalizable are patients suffering haemorrhagic strokes, and/or those with very severe strokes. This is a particularly difficult group to include in studies due to ethical considerations and studies therefore regularly lack generalisability for this group of patients (Pendlebury, et al., 2015a). This may however not pose a great problem for the Nor-COAST study, as those with very severe strokes are at high risk of dying (Jørgensen et al., 1995) and would not be able to participate in the follow-up test-times, thus leaving the diagnosis of PSD unknown anyway.

The current study serves a central part in the analysis of the external validity, and thus the generalisability value of the Nor-COAST study. Our findings suggest that the findings from those who provided MRI data from the St Olav branch of the Nor-COAST study, can be generalised to most of the St Olav population of stroke patients. It does not necessarily follow that when internal validity is established, external validity is guaranteed, and the assurance of external validity is crucial for permitting the correct interpretation of a finding (Ferguson, 2004). Although generally researchers are paying increasing attention to the generalisability of their study findings, many fail to complete full analyses, leading to external validity being a case for relative guesstimate (Kukull & Ganguli, 2012). The current study aimed to minimise this factor, and future interpretation of the findings from the Nor-COAST study should keep the current findings in mind.

Methodology discussion:

One strength of the current study is the large number of participants. Including a large enough sample size is crucial for ensuring high statistical power, and failing to include enough can affect the power of the study. The inclusion of a large sample size is true not only for the current study, but also for the Nor-COAST study as a whole.

Strength was also augmented through the use of a systematic analysis and approach, such as through the two pilot studies. The first pilot yielded high levels of agreement between

the student and the experienced neuroradiologist before the full data collection would commence, thus ensuring careful data collection and consequently increasing the internal validity of the study (Kukull & Ganguli, 2012). The same was true for the second pilot, where a high level of intra-rater reliability was ensured before statistical analysis would begin.

Most of the participants in the current study were recruited from the dedicated stroke section of the hospital, with the rest from a neurological unit. This ensured the inclusion of many older patients to the study, but may be a factor in reducing external validity and replicability, as the local organisation of different hospitals and of which section of the hospital the stroke patients are admitted may vary. This is thus a strength of the current study, but may also be considered a limitation.

Another factor that is both a strength and a limitation is that during the pilot, the intra-rater agreement between the two test-times revealed that some of the variables used yielded subpar intra-rater reliability kappa scores, and thus had to be excluded from further analysis. This was potentially a consequence of the student not being familiar with all of the differing terminology used by the neuroradiologists of whom had described the brain images. Several descriptions for the same variable were used by the different specialists and did potentially lead to some misunderstanding. The difference between the two pilot test-times of the student observer may therefore potentially simply reflect that the observer became more familiar with different terminology over time, and thus decreased the level of misunderstanding. However, a kappa score is affected by the prevalence of a finding, therefore for rare findings, low kappa scores may not necessarily reflect low levels of agreement (Viera & Garrett, 2005). This is also true for variables containing many categories, therefore many categories may increase the likelihood of disagreement and the consequence would be a low kappa score (Sim & Wright, 2005). As the variables with low kappa scores in the current study all had multiple categories with few cases within each category, and yielded high percentage of agreement, this may in fact only be a reflection of just these issues.

Another limitation of the current study is that a lot of the brain image descriptions lacked mentioning of several of the variables, as the descriptions were made for clinical and not research purposes. In such cases, it was registered as ‘not present’ during data collection. It is however a possibility that these were indeed present, but that the observer misunderstood some of the wording of the neuroradiologist. This could have potentially led to an underestimation of pathological findings. There was also commonly a lack of description of variables such as of vascular territory, and prior stroke hemisphere and –location, thus leading to a large number of missing data. However, there were much lower numbers of missing data in the NC-p group,

thus indicating that this was due to a lack of descriptions from the specialists rather than a lack of understanding from the observers' part. The fact that the study-specific MRI scans were used for research purposes may also have affected the way in which the neuroradiologists described the images. The likelihood of wrong data collection due to misunderstandings was also reduced through the inter-rater reliability test between the student and an experienced neuroradiologist; a test that yielded high kappa scores. Future research should include a standard protocol for what to be described by the neuroradiologists, to ensure a decrease in missing data.

Conclusion:

The characteristics of those who underwent a comprehensive study-specific MRI protocol was not much different from those who did not, except for somewhat more brain pathology in the participating group, and more haemorrhage in the non-participating group. The results from the MRI sub study can thus be generalised to the St Olav Hospital branch of the Nor-COAST study. This further suggests that the results of the whole Nor-COAST study may be generalised to a large group of stroke patients, although to a slightly older population, and except those with haemorrhagic stroke and very severe strokes. Future interpretation of the results of the Nor-COAST study should keep the results of the current study in mind. Lastly, these results indicate that it is indeed possible to conduct stroke research without large inclusion bias, although much research has found the opposite to be standard. The results of the current study are thus of importance in showing that the Nor-COAST study is of great value to the research field.

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Appendix

Table I: Inter-rater and Intra-rater Agreement Strength Analysis for the Pilot Studies

Variable	Pilot one (two observers)			Pilot two (single observer)		
	N	Mismatch N(%)	*k*	N	Mismatch N(%)	*k*
Microbleeds	25	1 (4)	.939	100	2 (2)	.969
WMH	25	2 (8)	.792	100	0 (0)	1.000
Location	25	1 (4)	.952	100	1 (1)	**.454**
Hemisphere	25	2 (8)	.883	100	3 (3)	.954
Vascular territory	25	0 (0)	1.000	100	1 (1)	**.201**
Haemorrhage	25	1 (4)	.884	100	1 (1)	.967
Visual thrombosis	25	1 (4)	.884	100	5 (5)	.895
Prior stroke	25	2 (8)	.839	100	6 (6)	.879
P.S. hemisphere	25	5 (20)	.671	100	8 (8)	.864
P.S. location	25	3 (12)	.812	100	6 (6)	**.340**
Lacunes	25	1 (4)	.834	100	4 (4)	.912
Multiple MRIs	25	2 (8)	.877	100	4 (4)	.933
Time after stroke	25	4 (16)	.787	100	10 (10)	.886

Table I: All Cohen k's were significant and of p<.001.

Table II: Descriptive Statistics for the Brain Image Variables

Variable	Category	Whole group		NC-p		Non-NC-p	
		N	%	N	%	N	%
Microbleeds	Yes	78	(19.5)	67	(30.9)	11	(6)
	No	146	(36.4)	130	(59.9)	16	(8.7)
	Missing	177	(44.1)	20	(9.2)	157	(85.3)
WMH	Yes	284	(70.8)	169	(77.9)	115	(62.5)
	No	101	(25.2)	48	(22.1)	53	(28.8)
	Missing	16	(4)	0	(0)	16	(8.7)

Location	Frontal	40	(10)	19	(8.8)	21	(11.4)
	Parietal	12	(3)	7	(3.2)	5	(2.7)
	Temporal	3	(.7)	1	(.5)	2	(1.1)
	Occipital	21	(5.2)	12	(5.5)	9	(4.9)
	Thalamus	16	(4)	12	(5.5)	12	(6.5)
	Cerebellum	23	(5.7)	14	(6.5)	9	(4.9)
	Brain stem	31	(7.7)	19	(8.8)	12	(6.5)
	White matter	12	(3)	9	(4.1)	3	(1.6)
	Basal ganglia	50	(12.5)	25	(11.5)	25	(13.6)
	Insula	4	(1)	1	(.5)	3	(1.6)
	Multiple	131	(32.7)	74	(34.1)	57	(31)
	No stroke	51	(12.7)	20	(9.2)	31	(16.8)
	Missing	7	(1.7)	4	(1.8)	3	(1.6)
Hemisphere	Left	170	(42.4)	92	(42.4)	78	(42.4)
	Right	154	(38.4)	87	(40.1)	67	(36.4)
	Both	40	(10)	22	(10.1)	18	(9.8)
	Missing	37	(9.2)	16	(7.4)	21	(11.4)
Vasc. territory	Anterior	2	(.5)	2	(.9)	0	(0)
	Posterior	19	(4.7)	11	(5.1)	8	(4.3)
	Middle	28	(7)	20	(9.2)	8	(4.3)
	Wat. a.m.	4	(1)	3	(1.4)	1	(.5)
	Wat. p.m.	1	(.2)	0	(0)	1	(.5)
	Cer. Sup.	2	(.5)	1	(.5)	1	(.5)
	Cer. Pos. I.	5	(1.2)	2	(.9)	3	(1.6)
	Missing	339	(84.5)	178	(82)	161	(87.5)
Haemorrhage	Yes	66	(16.5)	27	(12.4)	39	(21.2)
	No	335	(83.5)	190	(87.6)	145	(78.8)
	Missing	0	(0)	0	(0)	0	(0)
Vis. thrombosis	Yes	12	(3)	8	(3.7)	4	(2.2)
	No	263	(65.6)	196	(90.3)	67	(36.4)
	Missing	126	(31.4)	13	(6)	113	(61.4)

Prior stroke	Yes	170	(42.4)	105	(48.4)	65	(35.3)
	No	231	(57.6)	112	(51.6)	119	(64.7)
	Missing	0	(0)	0	(0)	0	(0)
P.S. hemisphere	Left	54	(13.5)	35	(16.1)	19	(10.3)
	Right	40	(10)	26	(12)	14	(7.6)
	Both	66	(16.5)	41	(18.9)	25	(13.6)
	No P.S.	231	(57.6)	112	(51.6)	119	(64.7)
	Missing	10	(2.4)	3	(1.4)	7	(3.8)
P.S. location	Frontal	6	(1.5)	4	(1.8)	2	(1.1)
	Parietal	5	(1.2)	4	(1.8)	1	(.5)
	Temporal	3	(.7)	2	(.9)	1	(.5)
	Occipital	12	(3)	11	(5.1)	1	(.5)
	Thalamus	1	(.2)	1	(.5)	0	(0)
	Cerebellum	9	(2.2)	5	(2.3)	4	(2.2)
	Brain stem	4	(1)	2	(.9)	2	(1.1)
	White matter	2	(.5)	2	(.9)	0	(0)
	Basal ganglia	34	(8.5)	16	(7.4)	18	(9.8)
	Insula	1	(.2)	0	(0)	1	(.5)
	Multiple	81	(20.2)	54	(24.9)	27	(14.7)
	No P.S.	231	(57.6)	112	(51.6)	119	(64.7)
	Missing	12	(3)	4	(1.9)	8	(4.3)
Lacunes	Yes	117	(29.2)	71	(32.7)	46	(25)
	No	284	(70.8)	146	(67.3)	138	(75)
	Missing	0	(0)	0	(0)	0	(0)

Table III: Regression Analyses for the Singular Models and the Original (Non-imputed) Adjusted Model

	Imputed singular models			Non-imputed adjusted model		
Variable	*p*-value	OR	95% CI for OR	*p*-value	OR	95% CI for OR
Gender	.761	.941	.634 to 1.396	.953	.984	.576 to 1.681
Age	.348	1.009	.990 to 1.028	.694	1.006	.977 to 1.036
GDS	.307	.922	.789 to 1.077	.353	.894	.706 to 1.132
CCI	.810	1.013	.911 to 1.127	.888	1.012	.861 to 1.189
mRs	.232	.910	.779 to 1.063	.557	.923	.706 to 1.207
NIHSS	.158	.977	.946 to 1.009	.245	.968	.917 to 1.022
Left hemisphere	.936	.973	.491 to 1.925	.520	1.325	.562 to 3.126
Right hemisphere	.807	1.090	.544 to 2.184	.354	1.516	.629 to 3.656
WMH	**.037**	**1.634**	**1.029 to 2.595**	.261	1.398	.779 to 2.506
Haemorrhage	**.020**	**.528**	**.309 to .903**	**.001**	**.279**	**.128 to .606**
Prior stroke	**.009**	**1.716**	**1.147 to 2.568**	**.019**	**1.851**	**1.108 to 3.094**
Time from stroke	**<.001**	**1.307**	**1.203 to 1.420**	**<.001**	**1.404**	**1.262 to 1.562**

Table III: GDS = Global Deterioration Scale, CCI = Charlson Comorbidity Index, mRs = the modified Rankin Scale, NIHSS = the National Institutes of Health Stroke Scale. P-value significant at <.05

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