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Åse Hagen Morsund

Doctoral theses at NTNU, 2020:320

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Thesis for the Degree of Philosophiae Doctor
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Trondheim, November 2020

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# Cognitive impairment in minor Stroke

**An observational study of the prevalence of cognitive impairment and emotional symptoms and consequences for social functioning and employment**

**Kognitive vansker etter små hjerneslag**

**Forekomst av kognitive vansker og emosjonelle symptomer. Betydningen av slike symptomer for yrkesaktivitet og sosial funksjon**

I min avhandling har jeg kartlagt forekomst av såkalte skjulte vansker etter små hjerneslag. I Norge er det ca 12 000 personer som får hjerneslag hvert år. En stor andel blir heldigvis selvhjulpne etter hjerneslaget. Vanligvis er de fysiske symptomene milde og går raskt over. Det betyr at flesteparten kan utskrives direkte til hjemmet etter et kort sykehusopphold. Skjulte vansker etter små hjerneslag blir gjerne ikke synlig før pasientene er tilbake i sitt hjemmemiljø. Med skjulte vansker menes hukommelses- og konsentrasjonsvansker og oppmerksomhetsvansker, såkalte kognitive vansker.
I tillegg kartla jeg symptomer som utmattelse, angst og depresjon.

Pasientene ble testet tre og tolv måneder etter hjerneslaget. Resultatene ble sammenlignet med en kontrollgruppe med små hjerteinfarkt (NSTEMI) og med data fra normalbefolkningen.
Jeg fant ingen forskjell i kognitiv funksjon mellom de to pasientgruppene, men pasientene med små hjerneslag hadde dårligere resultater på de kognitive testene sammenlignet med normalbefolkningen.
Lokalisasjonen av hjerneinfarktet i hjernen hadde ingen betydning for å utvikle skjulte vansker etter et lite hjerneslag.
Hjerneslagpasientene hadde høyere forekomst av angst og depresjon enn hjerteinfarktpasientene. De var også mer utmattet.
Pasientene med små hjerneslag ble bedre av sine kognitive vansker i tiden etter hjerneslaget, mens utmattelsen vedvarte. Forekomsten av depresjon økte med tiden.

Studien undersøkte også hvor mange som kom tilbake i arbeid etter å ha gjennomgått et lite hjerneinfarkt eller hjerteinfarkt. Det var flere pasienter som klarte å komme tilbake til arbeid etter et hjerteinfarkt enn etter et hjerneslag. Andelen pasienter som hadde kognitive vansker ett år etter hjerneslaget eller hjerteinfarktet var høy. Likevel klarte mange av pasientene å komme tilbake til arbeid på tross av dette. De yngste pasientene og de med høy utdannelse klarte i større grad å gjenoppta arbeidet i begge pasientgruppene.

Det var ingen forskjell i kognitive symptomer hos pasienter som fortsatt var yrkesaktive og de som falt ut av arbeidslivet etter ett år. Men forekomsten av depresjon var høyere hos de som falt ut av yrkeslivet. Dette kan derfor være en av hovedårsakene til arbeidsuførheten. Siden depresjon er en tilstand som kan behandles er det svært viktig å avdekke slike symptomer så raskt som mulig for å gi disse pasientene riktig behandling. Det kan øke sjansene for å komme tilbake til arbeid og kan bedre sosial funksjon.

Funnene jeg gjorde i denne studien understreker at det også er viktig å følge opp pasienter med små hjerneslag. Det blir kun gjort i liten grad i dag. Bedre oppfølging og god informasjon kan bidra til å bedre livskvaliteten hos de som strever med skjulte vansker etter et lite hjerneslag.

***Navn kandidat: Åse Hagen Morsund***
***Institutt: Institutt for klinisk og molekylær medisin***
***Veiledere: Professor Halvor Næss, Overlege, PhD Hanne Ellekjær, Overlege PhD Rune Midgard***
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**Contents**

## 1. Acknowledgements

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Last, but not least I will also thank my husband, Knut Ståle and my children Lovise and Njål for their great patience during the research period.

## 2. List of papers

I. Morsund, Åse Hagen; Ellekjær, Hanne; Gramstad, Arne; Reiestad, Magnus Tallaksen; Midgard, Rune; Sando, Sigrid Botne; Jonsbu, Egil; Næss, Halvor. (2019) Cognitive and Emotional Impairment after Minor Stroke and Non-ST-Elevation Myocardial Infarction (NSTEMI): A Prevalence Study. *Stroke Research and Treatment.* vol. 2019.

II. Morsund, Åse Hagen; Ellekjær, Hanne; Gramstad, Arne; Reiestad, Magnus Tallaksen; Midgard, Rune; Sando, Sigrid Botne; Jonsbu, Egil; Næss, Halvor. (2019) The development of cognitive and emotional impairment after a minor stroke: A longitudinal study. *Acta Neurologica Scandinavica.* vol. 140 (4).

III. Factors influencing employment after minor stroke and NSTEMI (accepted for publication in Journal of Stroke and Cerebrovascular Diseases).

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## 3. Acronyms and abbreviations

BMI: Body mass index

CERAD: Consortium to Establish a Registry for Alzheimer's disease

DALYS: Disability-Adjusted Life Year

D-KEFS: Delis–Kaplan Executive Function System

EAN: European Academy of Neurology

ECASS: European Cooperative Acute Stroke Study

ESO: European Stroke Organization

FSS: Fatigue Severity Scale

FAS: Verbal Fluency

FAS*: Fatigue Assessment Scale

GBD: Global Burden of Disease

HADS: Hospital Anxiety and Depression Scale

HADS-A: Hospital Anxiety and Depression Scale - Anxiety

HADS-D: Hospital Anxiety and Depression Scale - Depression

IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly

MCI: Mild cognitive impairment

MMSE: Mini Mental State Examination

MOCA: Montreal Cognitive Assessment

mRS: Modified Rankin Scale

NIHSS: National Institutes of Health Stroke Scale

NIPH: Norwegian Institute of Public Health.

NSTEMI: Non ST-Elevation Myocardial Infarction

PROMS: Patient-reported outcome measure

SVD: Small vessel disease

TIA: Transitory Ischemic Attack

TOAST: Trial of Org 10172 in Acute Stroke Treatment

VAS: Visual Analogue Scale

VCI: Vascular cognitive impairment

WMH: White matter hyperintensities

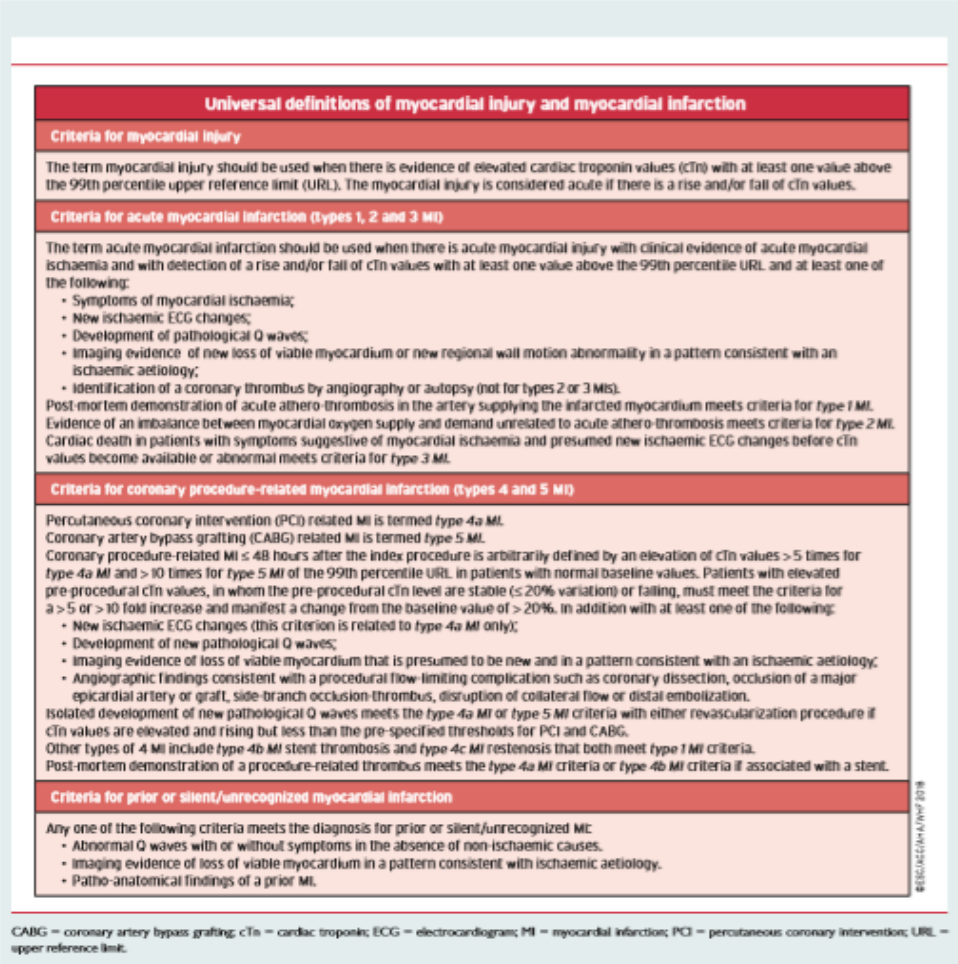
**4. Definitions**

Cerebral ischemic stroke: Ischemic stroke was defined in accordance to the criteria to the Baltimore-Washington Cooperative Young Stroke Study Criteria (1) comprising neurological deficits lasting more than 24 hours because of ischemic lesions, or transient ischemic attacks where CT or MRI showed infarctions related to the clinical findings.

Minor stroke: A cerebral ischemic stroke with a functional outcome of mRS 0-2 at day seven or discharge if before.

NSTEMI (Non ST-Elevation Myocardial Infarction): The definition by the European Society of Cardiology:

## 2 Universal definitions of myocardial injury and myocardial infarction: summary



**Universal definitions of myocardial injury and myocardial infarction**

**Criteria for myocardial injury**

The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.

**Criteria for acute myocardial infarction (types 1, 2 and 3 MI)**

The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:

- Symptoms of myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs).

Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for *type 1 MI*.
Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for *type 2 MI*.
Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for *type 3 MI*.

**Criteria for coronary procedure-related myocardial infarction (types 4 and 5 MI)**

Percutaneous coronary intervention (PCI) related MI is termed *type 4a MI*.
Coronary artery bypass grafting (CABG) related MI is termed *type 5 MI*.
Coronary procedure-related MI ≤ 48 hours after the index procedure is arbitrarily defined by an elevation of cTn values > 5 times for *type 4a MI* and > 10 times for *type 5 MI* of the 99th percentile URL in patients with normal baseline values. Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable (≤ 20% variation) or falling, must meet the criteria for a > 5 or > 10 fold increase and manifest a change from the baseline value of > 20%. In addition with at least one of the following:

- New ischaemic ECG changes (this criterion is related to *type 4a MI* only);
- Development of new pathological Q waves;
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization.

Isolated development of new pathological Q waves meets the *type 4a MI* or *type 5 MI* criteria with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.
Other types of 4 MI include *type 4b MI* stent thrombosis and *type 4c MI* restenosis that both meet *type 1 MI* criteria.
Post-mortem demonstration of a procedure-related thrombus meets the *type 4a MI* criteria or *type 4b MI* criteria if associated with a stent.

**Criteria for prior or silent/unrecognized myocardial infarction**

Any one of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology.
- Patho-anatomical findings of a prior MI.

CABG = coronary artery bypass grafting; cTn = cardiac troponin; ECG = electrocardiogram; MI = myocardial infarction; PCI = percutaneous coronary intervention; URL = upper reference limit.

“

Patients without ST-segment elevation are designated as non-ST-elevation myocardial infarction.(2). ST refers to the ST segment which is part of the EKG.

Anxiety: Defined as a HADS-score ≥ 8 of the anxiety items. HADS is a screening tool which means that a score of ≥ 8 indicates anxiety symptoms.

Depression: Defines as a HADS-score ≥ 8 of the depression items. HADS is a screening tool which means that a score of ≥ 8 indicates depressive symptoms.

Fatigue: Poststroke fatigue can be divided in objective fatigue defined as observable and measurable decrement in performance occurring with the repetition of a physical or mental task, and subjective fatigue as a feeling of early exhaustion, weariness and aversion to effort (3).

Disability adjusted life-years (DALYs): A summary measure of population health based on estimates of premature mortality and non-fatal health loss.

Cognitive impairment is defined as impairment of ≥ 2 cognitive tests.

## 5. Summary / Abstract

Hjerneslag rammer årlig ca 12 000 personer i Norge og er en av de hyppigste årsaker til invaliditet. Data fra Norsk hjerneslagregister viser at 2/3 av pasientene blir selvhjulpne etter et hjerneslag. En betydelig andel av disse pasientene har milde slag med fysiske symptomer som går raskt over. Disse pasientene trenger vanligvis ingen rehabilitering og blir utskrevet direkte til hjemmet. Det er imidlertid økende kunnskap om såkalte skjulte vansker ved små hjerneslag som ofte ikke oppdages før pasienten er tilbake i sitt hjemmemiljø. Dette kan være kognitive symptomer som hukommelses- og konsentrasjonsvansker, oppmerksomhetsvansker, utmattelse, angst og depresjon. Hensikten med vår studie var å kartlegge forekomst av slike symptomer etter små hjerneslag. Pasientene gjennomgikk kognitiv testing 3 og 12 måneder etter hjerneslaget og fylte ut spørreskjema på utmattelse, angst- og depresjonssymptomer. Resultatene ble sammenlignet med en kontrollgruppe med små hjerteinfarkt (NSTEMI) og mot normative data.

Vi fant ingen forskjell i kognitiv funksjon mellom de to pasientgruppene, men pasientene med små hjerneslag hadde dårligere resultater på de kognitive testene sammenlignet med normative data. Lokalisasjonen av hjerneinfarktet hadde ingen betydning for resultatet for hjerneslagpasientene. Det var også høyere forekomst av utmattelse og depresjon blant hjerneslagpasientene enn hos hjerteinfarktpasientene. Pasienter med små hjerneslag hadde en bedring i kognitiv funksjon i tiden etter hjerneslaget, mens utmattelsen vedvarte. Forekomsten av depresjon økte med tiden.

Studien undersøkte også hvor mange som kom tilbake i arbeid. Flere pasienter i hjerteinfarktgruppen enn hjerneslaggruppen klarte å komme tilbake i arbeid og klarte også å være i arbeid lengre (høyere alder). Samlet sett var imidlertid mange i arbeid etter ett år i begge pasientgrupper på tross av at andelen pasienter med kognitive symptomer var høy.

Graden av kognitiv svikt var imidlertid mild. De yngste pasientene og pasienter med høy utdannelse klarte i større grad å gjenoppta arbeidet i begge pasientgrupper.
Det var ingen forskjell i kognitive symptomer hos pasienter som fortsatt var yrkesaktive og de som falt ut av arbeidslivet etter ett år. Forekomst av depresjon var høyere blant pasienter som falt ut av yrkeslivet og kan derfor være en av hovedårsakene til arbeidsuførhet. Siden depresjon er en tilstand som kan behandles er det svært viktig å avdekke symptomene så raskt som mulig for å iverksette god behandling for å redusere symptomer som virker negativt inn på arbeidsevne og sosial funksjon.

In Norway about 12 000 patients suffer a stroke annually. Stroke is one of the leading causes of disability world-wide. According to data from the Norwegian Stroke Registry 2/3 of the patients get independent after a stroke. A considerable amount of the patients have minor strokes with minor sensorimotor and quickly resolving symptoms. Most of these patients are of no need of rehabilitation and are discharged directly to their home after a short stay in a stroke unit. However, there is now increasing knowlegde that patients with minor strokes may have more hidden symptoms that may first be recognized after the patients have returned to their homes and are thought to resume their normal activity. This may be cognitive symptoms such as problems with memory and concentration, attention deficits, fatigue and emotional symptoms.
The aim of our study was to explore the prevalence of cognitive and emotional symptoms after a minor stroke. The patients underwent cognitive testing at 3 and 12 months after the stroke, and filled in a questionnaire consisting of a fatigue scale, and an anxiety- and depression scale. The results were compared to a control group with minor heart attacks (NSTEMI) and with normative data.

There was no difference in the cognitive functioning between the two patient groups, but the minor stroke patients had worse results of the cognitive tests compared with normative data. For the minor stroke patients the location of the ischemic lesion had no influence on the results. The prevalence of fatigue and depression was higher amongst the minor stroke patients compared to the NSTEMI patients.

We found an improvement in cognitive functioning within a year in minor stroke patients, but the fatigue persisted. The prevalence of depression increased by time.

We also studied how many patients that returned to work after the minor stroke and NSTEMI. A larger proportion of the NSTEM patients than the stroke patients returned to work and they also stayed longer in work (higher age).

However, the prevalence of patients returning to work after a year was high in both patient groups despite a high prevalence of cognitive symptoms. It has to be mentioned that the cognitive impairment was minor. The degree of employment was highest among the youngest and highly educated patients.

There was no difference in cognitive symptoms in employed vs non-employed patients. The prevalence of depression was higher in unemployed patients and depression may be the main cause of disability. Depression is a treatable condition and recognition of depressive symptoms is important to start treatment to improve symptoms and reduce consequences for employment and social function. This suggests that a more systematically follow up of such symptoms is of great importance.

## 6. Introduction

Patients with minor stroke is thought to have a good prognosis due to limited and often quickly resolving sensorimotor symptoms. However, the patients may have other symptoms such as cognitive impairment, fatigue or emotional symptoms which may be more disabling than minor sensorimotor symptoms. The attention on this topic is growing, but still the knowledge is sparse. Studies looking at improvement beyond three months are few. Another important topic is consequences for employment.

In this study we wanted to investigate the prevalence and the development of cognitive and emotional symptoms including fatigue over time after minor strokes. We also wanted to explore if these symptoms had an impact on the employment status. The study population consists of patients with minor ischemic strokes and a control group of patients with non-ST elevation myocardial infarctions (NSTEMI).

The rationale for doing this study was to investigate whether minor stroke is a benign condition or if the patients have disabling symptoms such as cognitive and emotional symptoms and fatigue not detected by existing follow-up procedures. Neither of these symptoms are a part of the routine examination after a minor stroke. Cognitive and emotional symptoms may not be obvious for the patients before they are back in their homes resuming their normal activities. The patients may therefore be unprepared for such symptoms. Coping strategies are important in handling chronic disease. A structured follow-up of these symptoms could therefore be of great importance for the patients. Since anxiety and depression are treatable conditions, it is of great importance to explore the prevalence of these conditions.

The patients were tested with a selection of cognitive tests and filled in questionnaires consisting of a fatigue scale, an anxiety and depression scale, and an informant filled in a questionnaire to explore any change in cognitive function of the patients (IQCODE). The tests and questionnaires were done at 3 and 12 months.
We selected a control group of patients with NSTEMI infarctions which were tested with the same cognitive tests and questionnaires at 12 months. Both minor stroke and NSTEMI patients have small vascular lesions causing their symptoms. The difference between minor stroke and NSTEMI patients is due to the location of the vascular lesion as the risk factors causing the diseases are the same.

Better knowledge of prevalence and development of cognitive and emotional symptoms including fatigue is important. The results of the study may show that even patients with minor strokes need a thoroughly and long-term follow-up. The following chapter will provide a general background of the knowledge of minor ischemic stroke as well as an overview of important research studies of the topic.

***Review of research***

Cerebrovascular disease is ranked as the second leading cause of global disability-adjusted life-years (DALYS) in the Global Burden of Disease (GBD) study from 2016 (4) even though the age-standardized DALY rate and incidence rate declined in the time period from 1990-2016 (4).

Acute ischemic stroke is a syndrome of sudden loss of neuronal function due to disturbance in cerebral perfusion. It is a heterogeneous clinical syndrome with multiple etiologies. The TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification of stroke includes five

categories: 1) large artery atherosclerosis, 2) cardioembolism, 3) small vessel occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology (5).



**TABLE 2. Features of TOAST Classification of Subtypes of Ischemic Stroke**

| Features | Subtype | | | |
|---|---|---|---|---|
| | Large-artery atherosclerosis | Cardioembolism | Small-artery occlusion (lacune) | Other cause |
| Clinical | | | | |
| Cortical or cerebellar dysfunction | + | + | − | +/− |
| Lacunar syndrome | − | − | + | +/− |
| Imaging | | | | |
| Cortical, cerebellar, brain stem, or subcortical infarct >1.5 cm | + | + | − | +/− |
| Subcortical or brain stem infarct <1.5 cm | − | − | +/− | +/− |
| Tests | | | | |
| Stenosis of extracranial internal carotid artery | + | − | − | − |
| Cardiac source of emboli | − | + | − | − |
| Other abnormality on tests | − | − | − | + |

TOAST, Trial of Org 10172 in Acute Stroke Treatment.

(5)

Stroke leads to a variety of physical and cognitive symptoms. Outcome measures in the Norwegian Stroke registry from 2018 showed the following distribution of mRS at 3 months; 19.1 % of the patients had mRS 0, 21.8 % 1, 19.5 % 2, 10.4 % 3, 9 % 4, only a minor proportion 5 and 19 % were dead (mRS 6)(6). Sensorimotor deficits after a stroke are usually fairly evident, whereas cognitive deficits may be rather inconspicuous.

Treatment in stroke units are effective and well documented (7) reducing both mortality and morbidity. A Cochrane report from 2014 stated that thrombolytic therapy of an ischemic stroke was effective in reducing the proportion of dead and dependent people (8). In recent years endovascular thrombectomy has shown to have documented effect on reducing mortality and morbidity after major strokes as described in a metaanalysis of 5 randomized

studies (9). From 2019 endovascular thrombectomy is also implemented in guidelines from European Stroke Organization (ESO) (10).

Risk factors for cerebrovascular disease are well known and are the same worldwide (4). Most of the risk factors are modifiable and optimization treatment of risk factors may reduce the stroke incidence globally.

American Heart Association/American Stroke Association published guidelines for stroke rehabilitation in 2016 (11). These guidelines describe stroke rehabilitation as a sustained and coordinated effort from a large team, including the patient and social network, physicians, nurses, occupational therapists, speech therapists, psychologists, nutritionists, social workers and others.

As discussed in a publication from 2018 (12) stroke rehabilitation are mainly designed to decrease the sensorimotor symptoms after a stroke, whereas little is known about rehabilitation programs directed towards cognitive impairment, anxiety and depression. The study also raised the question of long-term effect of cognitive rehabilitation. In the recent years data on digital rehabilitation on cognitive impairment has shown promising results, both in stroke patients and other patients groups (13, 14). Good methods selecting suitable patients for cognitive rehabilitation is therefore essential. MOCA (Montreal Cognitive Assessment) may be used for this purpose as shown in a previous study (15).

*Minor stroke.*

A consensus on the term minor stroke is lacking. NIHSS and mRS are two widely used tools in examining stroke patients. A study published in 2010 tried a variety of definitions including NIHSS to define a good outcome after 3 months (mRS 0-2) and found that patients with baseline NIHSS 0-1, with normal level of consciousness and all patients with baseline NIHSS $\leq 3$ were best suited to the definition of minor stroke (16). The same study also defined mRS

between 0-2 at 3 months as a good outcome. Another study proposed NIHSS 0 - 1 as the definition of minor stroke (17). NIHSS with a cut-off in the range 3-6 is used in a selection of publications (18-22). mRS describes a functional outcome including self-reliance, dependency or bed-ridden state, while NIHSS focuses on neurological deficits such as paresis, sensory loss, ataxia, visual deficits and speech problems. In the NIHSS scale items focusing on cognitive function is limited to the patient's ability to answer questions correctly and perform instructions given during the examination. It is also well known that NIHSS is best suited for vascular lesions in the anterior circulation of the brain, while lesions in the posterior circulation especially in cerebellum is not sufficiently covered by NIHSS. Using NIHSS as an outcome measure may therefore be a challenge especially when it comes to the posterior circulation.

There is no recommendation or consensus concerning documentation of cognitive symptoms including fatigue after a stroke. Studies of fatigue after an ischemic stroke uses different fatigue scales illustrating the lack of consensus. However, a meta-analysis discussed the results of 24 studies using FSS as a fatigue measure scale but concluded that it is still much work to be done to understand the genesis of post-stroke fatigue (23).

*Minor stroke vs lacunar stroke*

According to TOAST criteria a lacunar stroke is defined as a small vessel disease containing the lacunar syndromes and subcortical or brain stem infarcts < 1.5 cm. (5). Five lacunar syndromes have been validated as being highly predictive for the presence of lacunes radiologically: Pure motor hemiparesis, pure sensory stroke, ataxic hemiparesis, sensorimotor stroke and dysarthria-clumsy hand syndrome (24).

A minor stroke is a clinical definition that differs from the definition of a lacunar stroke. Most lacunar stroke may also be a minor stroke, but also other stroke types according to the TOAST criteria may have minor symptoms.

*WMH and SVD*

White matter hyperintensities (WMH) found on MRI are assumed to be of ischemic origin and are a common finding in the elderly. WMHs are may also be a surrogate of cerebral small vessel disease (SVD) (25). However, WMH may not only be of vascular origin but also caused by neurodegenerative processes which also are common in the elderly. This may explain why intervention on risk factors only have a limited effect on the development of cognitive impairment as discussed under the paragraph of risk factors below. The etiology behind SVD is not fully understood as discussed in a recent publication but risk factors as hypertension and cardiac abnormalities are mentioned as possible contributing factors (26).

*Clinical endpoints after a minor stroke.*

A usual endpoint in stroke research is mRS and a favorable clinical outcome is often defined as mRS $\leq 2$. Cognitive and emotional symptoms may not be discovered using mRS as an endpoint, which means that other endpoint measures are needed to detect these symptoms.

The range of disability after an ischemic stroke is wide. According to the Norwegian Stroke Registry NIHSS at admission was between 0-5 in 67.4 % of the stroke patients in 2018 (6). Most of these patients are discharged directly to their homes after a few days in the stroke unit. Deficits other than sensorimotor symptoms after a minor stroke may first be obvious to the patients after discharge from hospital, presenting with problems such as mild cognitive impairment, emotional symptoms and fatigue**.** Assessment of cognitive dysfunction and

emotional symptoms is not routinely performed during follow-up and knowledge of the long-term impact of cognitive and emotional symptoms is sparse (27-30). The long-term outcome of these patients is therefore less known even though the attention to this issue is growing. The lack of consensus on diagnostic criteria for minor stroke (16-22) also hampers research on this topic. There is consequently a need for more studies investigating the consequences of cognitive and emotional impairment of minor strokes.

*Vascular cognitive impairment (VCI).*

VCI refers to cognitive impairment caused by cerebrovascular disease. Impairment encompasses all levels of cognitive decline included mild cognitive impairment (MCI). However, the criteria for VCI is vague as discussed in a review from 2012 (31). The authors state that the criteria needs more specific description including data on vascular changes as lacunes and microbleeds and a better understanding of the etiology of microstructural changes in the brain. The diagnostic criteria for VCI still need validation according to a publication from 2019 (32).

*Mild cognitive impairment (MCI).*

A consensus group has proposed a definition of mild cognitive impairment (MCI) (33). MCI is defined as a subjective and objective decline in cognition and function greater than expected for an individual's age and education level that does not meet criteria for a dementia diagnosis. The consensus group presented the following recommendation:

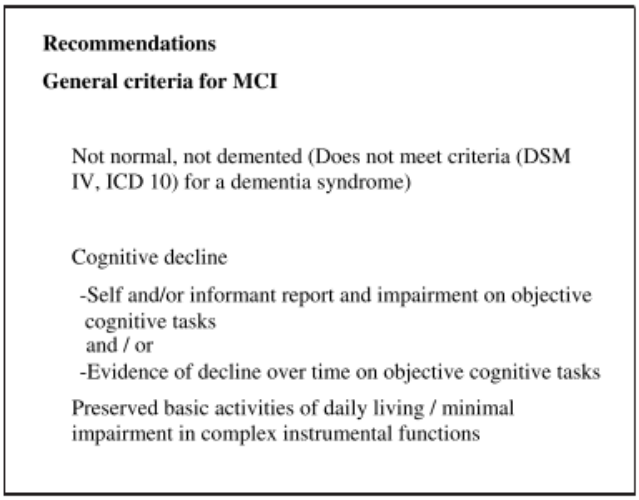



**Fig. 2** Recommendations for the general criteria for mild cognitive impairment (MCI).

(33)

They also propose a classification in three subtypes: Amnestic, multiple domain and and single, nonmemory domain with following flowchart:

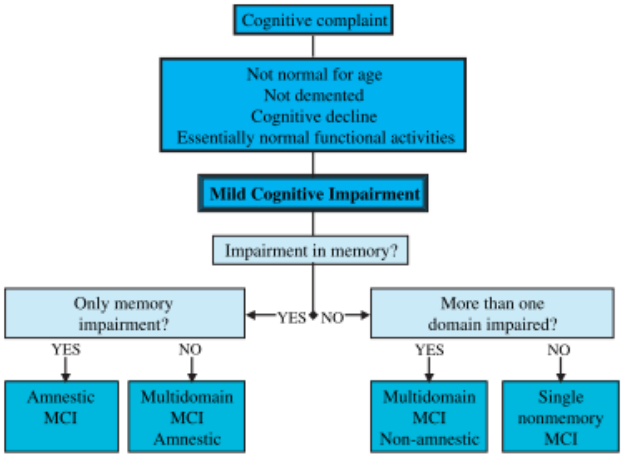



**Fig. 3** MCI classification process (adapted with permission from Lippincott-Raven Publishers, Williams & Wilkins.)

(33)

However, there are a number of different cognitive tests/ test batteries measuring the different cognitive domains, and no consensus of which one to use.

Routine neurological examination is insufficient to detect mild cognitive impairment. Neuropsychological assessment is time-consuming and not ordinarily used in stroke units. A prospective study from Turkey found significant cognitive impairment in patients with minor stroke and transient ischemic attack compared to controls (28). High prevalence of cognitive impairment after TIA and minor stroke are discussed in a systematic review from 2014 (27), but the authors conclusions were that only a few of the included studies were of high quality. The studies revealed large variations in methodology and distribution of included cases (27). A review publication found that the reported prevalence of cognitive deficits after a stroke varied from 10-82% mainly because the criteria used to define cognitive impairment were different in different studies (34). A recently published study found that minor stroke patients experienced a significantly higher rate of whole brain atrophy and that a changes in brain volume over time preceded cognitive decline (18). The challenge is how to implement this knowledge in a clinical setting. It is not feasible to recommend neuropsychological examination of all minor stroke patients because it is too time-consuming and the availability of neuropsychologists is limited. We therefore need a reliable and simple diagnostic tool to achieve this information.

*Emotional symptoms*

Depression any time prior to stroke is a risk factor for developing post stroke depression (35). High prevalence of depression after TIA and minor stroke is discussed in a systematic review from 2014 (27), but only a few of the included studies were of high quality. The studies revealed large variations in methodology and distribution of included cases (27).

The authors also concluded that the knowledge of post stroke anxiety was limited.
The prevalence of anxiety after stroke is estimated to 22-28%, the prevalence of depression 33% in another study (35). These prevalence numbers represent the estimates for a total stroke population and are not representative for patients with minor strokes. A review article from 2018 refers to a prevalence of depression after minor stroke ranging from 29-40% (30) in three different studies (36-38).

*Fatigue*

A proper definition of the term fatigue is lacking as discussed in a publication from 2013 (39). In spite of this fatigue is described as a common and debilitating symptom in a large number of diseases. A variety of fatigue severity scales exists. Lack of definition and a variety of fatigue severity scales may create difficulties in interpreting the results in fatigue studies.

Studies of fatigue in minor stroke are few and prevalence varies between 17 – 35 % (40, 41). One publication found persisting fatigue in a longitudinal study (41). A review article from 2014 found high prevalence of fatigue, but the studies were few and lacked relevant comparison groups (27). How to implement this in clinical practice may therefore be a challenge.

*Long-term outcome*

Most studies of long-term outcome after an ischemic stroke focus on new vascular events and mortality. Studies looking at long-term outcome of other endpoints are scarce as discussed by others (42, 43). Some data suggest that early cognitive impairment is a predictor for developing long-term cognitive impairment (44). In a study from 2011 TIA and minor stroke patients were followed up for five years. The authors found that patients with early cognitive

impairment were at increased risk of subsequent decline during the following five years (44). A more recent study from 2018 followed minor stroke patients for three years and also concluded that persisting cognitive symptoms were common after three years (45). However, the overall number of studies looking at long-term outcomes are few.

Traditionally the outcome measures have been clinician-reported. More recently there have been increasing focus on collecting health information directly from the patients themselves so-called patient-reported outcomes (PROMS) as discussed in a publication from 2018 (46). Systematic implementation of patient related outcome measures (PROMS) in the stroke care is a new way to improve the knowledge of patient outcome and the quality of care as discussed in this paper (46) .

*Risk factors and minor stroke.*

Endothelian dysfunction plays a role in development of atherosclerosis. Even though the impact of endothelian cells in health and disease are not fully understood, these cells play a major role in ion and molecule movement in and out of the brain. Endothelian cells also play a role in antiplatelet, antithrombotic and fibrinolytic mechanisms. Dysfunction of the endotelian cells may lead to damage in these mechanisms in various manners leading to development of atherosclerosis. The progression of atherosclerosis is accelerated when combined to risk factors such as hypertension and diabetes mellitus (47). A publication of a consensus review found that diabetes mellitus type2 is a risk factor for both Alzheimer's disease and vascular dementia (48). Hyperhcolesterolaemia and smoking seems to be of less importance (47).

The literature offers some evidence of an association between hypertension (49), atrial fibrillation (50), diabetes mellitus (18), smoking (51), hypercholesterolemia (52) and

cognitive impairment, brain atrophy ( diabetes mellitus) and white matter hyperintensities (smoking). However, there are also studies showing that intensive risk factor intervention had no effects on cognitive function after stroke and TIA (53).

Obstructive sleep apnea has shown to be a risk factor for cerebrovascular disease (54). A study looking at sleep disturbance after minor ischemic strokes found that patients with post stroke cognitive impairment had higher prevalence of obstructive sleep apnea (55).

*Employment*

The patients with minor strokes are traditionally assumed to have a good clinical outcome. However, in the discussion above a number of publications have shown that a considerable amount of patients have cognitive impairment, fatigue and emotional symptoms after a minor stroke. The symptoms may cause inability to stay in work for some patients. One study found an association of risk factors and return to work after cerebrovascular disease (56). Cognitive impairment was a statistically significant predictor of return to work in other studies (57, 58). Another study found psychiatric comorbidity as a predictor for returning to work (59), whereas others did not (60).

Pre-stroke employment also seems to result in better patient-reported outcome of functional level, depression and fatigue after a minor stroke (61).

Sociodemographic differences between countries and the retirement politics in the society may influence the employment of minor stroke patients even though the cognitive impairment and emotional symptoms may be minor. In Norway early retirement is an option, and some patients may choose this solution. A recent Finnish study also discussed this option (62) .

*Summary of existing knowledge.*

There is increasing knowledge that patients suffering a minor stroke may have persisting symptoms other than sensorimotor symptoms with great impact on daily functioning. The literature reveals both persisting cognitive and emotional symptoms including fatigue in a considerable amount of patients. Even though the knowledge is growing it is still sparse, especially on long-term outcome.

The follow-up of patients with minor stroke of other issues than optimization of risk factors is still limited. If there is evidence of persisting cognitive and emotional symptoms after a minor stroke, this patients should be offered a better follow-up. Treatable conditions such as anxiety and depression are also important to assess in order to reduce the patients' symptoms.

The aim of our study was to explore the prevalence of cognitive impairment, anxiety, depression and fatigue 3 and 12 months after a minor stroke and to study the development of symptoms between 3 and 12 months in order to look at long-term effects. Consequences of cognitive impairment, anxiety, depression and fatigue on employment were also studied.

Our findings may be reveal a need for more systematically follow-up of patients with minor stroke, to identify symptoms other than sensorimotor symptoms influencing social function and employment and to start proper intervention.

## 7. Aims and hypotheses.

**7.1**. *Are cognitive impairment and emotional symptoms including fatigue more prevalent among minor stroke patients than among non-ST elevation myocardial infarction (NSTEMI) (controls)?*

a. To estimate the prevalence of cognitive impairment, fatigue and emotional symptoms 12 months after a minor stroke compared to controls (paper I).

**7.2.** *Is there an association between the location of the minor stroke and cognitive symptoms?*

a. The effect of the location of the stroke at the development of cognitive symptoms after a minor stroke (paper I).

**7.3.** *Is there a change in cognitive and emotional symptoms including fatigue over time after a minor stroke (paper II)?*

a. The development of cognitive and emotional impairment including fatigue from 3 to 12 months after a minor stroke.

b. Cognitive impairment at 12 months (long term) as a function of early cognitive impairment (at 3 months).

**7.4.** *Is there an association between risk factors and cognitive function after a minor stroke (paper II)?*

The impact of premorbid risk factors such as hypertension, diabetes, hypercholesterolemia, smoking and overweight on the development of cognitive and emotional symptoms after a minor stroke.

**7.5.** *Is there a difference in returning to work between minor stroke and NSTEMI patients (paper III)?*

a. Employment after a minor stroke.

b. Factors associated with employment after minor stroke and NSTEMI.

## 8. Materials and Methods

### 8.1 Study design.

This is a prospective observational multicenter study of patients aged 18-70 with minor ischemic strokes consecutively admitted to the stroke units in Møre and Romsdal Health Trust, Sør-and Nord-Trøndelag Health Trust and Haukeland University Hospital. A control group of NSTEMI patients was chosen. The study was runned locally at Molde Hospital, in close collaboration with the Bergen Stroke Research Group and the Research Group on Stroke at St Olavs Hospital. Study nurses with special training performed the testing at all hospitals except Molde hospital where the Phd student responsible for the study did this.

The reason for choosing a control group was to increase the strength of the study by comparing the results in two different populations. NSTEMI patients were chosen as the control group because they share the same risk factors as the stroke patients but differs in the location of the vascular event.

### 8.2 Study population

#### 8.2.1 Inclusion criteria

*Recruitment procedure:*

Ischemic stroke: Patients were recruited consecutively from stroke units at Molde Hospital, Haukeland University Hospital and St Olav's Hospital. Patients from other participating stroke units; Department of Neurology at St Olavs Hospital, Kristiansund Hospital, Volda Hospital and Ålesund Hospital were included whenever practical, but not always consecutively. The recruitment period was 01/01/13 - 12/31/16. The inclusion age was 18-70 years and stroke patients with mRS 0-2 at day 7 or at discharge if before, were included.

The recruitment procedures were asking the patients admitted at stroke units or contact by a phone call or a letter after discharge. The drop-out between 3 and 12 months was 37 patients.
NSTEMI: Patients were recruited from Haukeland University Hospital, Ålesund Hospital, Molde Hospital and Kristiansund Hospital in the same time period.
NSTEMI patients aged 18-70 years with a functional mRS 0-2 were included as the control group.
The recruitment procedure was contact by a phone call or a letter after discharge.

The upper age limit was 70 years because exploring consequences for employment was an important aim of the study.

Ischemic stroke was defined in accordance to the criteria to the Baltimore-Washington Cooperative Young Stroke Study Criteria (1) comprising neurological deficits lasting more than 24 hours because of ischemic lesions, or transient ischemic attacks where CT or MRI showed infarctions related to the clinical findings.

### 8.2.2 Exclusion criteria

Ischemic stroke: Patients with a major stroke defined as mRS > 2 day 7 or at discharge if before, and patients with deterioration in mRS to more than 2 in the observational period of any cause were excluded from the study. Two patients were excluded because of deterioration according to the exclusion criteria.
NSTEMI: Patients with mRS > 2 of any cause were excluded. No patients were excluded because all patients asked to participate in the study fulfilled the inclusion criteria.

### 8.3 Method.

### 8.3.1 Clinical and therapeutically assessment

Baseline data of gender, premorbid health, educational level, employment status and social status were registered. Ischemic stroke patients underwent routine examination with NIHSS, traditional risk factors including hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, smoking, overweight defined as BMI $\geq$ 25, and brain imaging with CT and/or MRI. Stroke patients were treated according to Norwegian guidelines for ischemic stroke. Most patients with mRS $\leq$ 2 after 7 days or at discharge if before had no need for further rehabilitation and were discharged to their home.

Baseline mRS and NIHSS scores were recorded at day 7 or at discharge if before.

Aphasia was specifically emphasized because the possibility of aphasia influencing the results of the cognitive tests.

A list of medication in use was registered at discharge.

### 8.3.2 Study specific assessment

#### 8.3.2.1. Cognitive impairment tests

*Clock drawing test* assesses visuospatial function (63). The person being tested is given a paper with a pre-drawn circle and is asked to draw the numbers on the clock. Then he or she is asked to draw the hands to show a specific time. Scoring is from 0 to 5, with 5 indicating full score. Visuospatial function refers to cognitive processes necessary to identify, integrate and analyze space and visual forms, details, structure and spatial relations in more than one dimension. Visuospatial skills are needed for movement, depths and distance perception and spatial navigation.

*MMSE* (64): Assesses orientation, registration, short term memory attention, calculation and language. Scoring is from 0 to 30, with 30 indicating intact cognition.

Clock drawing test and MMSE were used as screening of global cognitive function.

Following tests were drawn from the Delis–Kaplan Executive Function System (D-KEFS): Trail-making A and B, Verbal fluency and Color-Word Interference tests. D-KEFS was developed to provide reliable normative data for a range of executive functions. D-KEFS is a sample of nine individually cognitive tests designed to be stand-alone measures of cognitive function (65).

*Trail-making test A and B* (66): Trail-making test A requires an individual to draw lines sequentially connecting 25 encircled numbers distributed on a sheet of paper. In Trail-making test B the person must alternate between numbers and letters. The tests provide information on visual search, scanning, speed of processing, mental flexibility and executive functions.

*Verbal fluency (FAS):* The examinee is asked to generate words that begin with a particularly letter as quickly as possible (the letters F, A and S were used in this test). For each letter the examinee is allowed 60 seconds.

*Color-Word Interference test*: The test consists of two basic tests, color naming of color patches (condition 1) and reading of color-words printed in black ink (condition 2). In condition 3 (inhibition) the individual must inhibit reading the words in order to name the dissonance in colors in which those words are printed. For condition 4 (inhibition/switching)

the individual is asked to switch back and forth between naming the dissonant ink colors and reading the words. This is testing cognitive flexibility, mental speed and inhibition.
Trail-making test A and B, Verbal fluency (FAS) and Color-Word Interference test were used to test executive function.

*CERAD ten-words learning task* (67). This test measures recall and delayed recall after about 5 minutes. The test presents 10 unrelated words which are printed on 10 different cards. The individual is instructed to read each word out loud and to remember each word. After the presentation of all 10 words, immediate recall is assessed. After about 5 minutes the individual is asked to recall as many as possible of the 10 words. CERAD (the Consortium to Establish a Registry for Alzheimer's Disease) is a standardized validated test battery for the assessment of Alzheimer disease (67) with normative data adjusted for age and education (68).

Scores falling below 1.5 SD of the mean were characterized as abnormal.

Normative data on the cognitive tests is obtained from a large, randomly selected representative sample of a large population.

#### 8.3.2.2 Aphasia

Ischemic stroke patients were screened by the Ullevaal aphasia screening test (UAS) (69). The test covers the following aspects of language: Expression, comprehension, repetition, reading, reproduction of a string of words, writing and free communication.

#### 8.3.2.3 Questionnaires

*IQCODE:* This is an informant questionnaire which is used as a screening of premorbid cognitive function and a possible change after the vascular event. It contains 16 questions of different cognitive functions such as memory, attention and decision making, scored from 1 (much improved) to 5 (much worse) (70).

*Hospital Anxiety **a**nd Depression scale (HADS)* is a screening questionnaire which consists of 14 questions of which 7 assess anxiety (HADA-A) and 7 assess depression (HADS-D) (71). A score ≥ 8 on the anxiety (HADS-A) or depression (HADS-D) items indicates possible presence of anxiety or depression disorders (71), a total score ≥ 15 on HADS indicates a mixture of anxiety and depression.

*Fatigue Severity scale (FSS).*

FSS is a nine-item questionnaire that assesses the effect of fatigue on daily living (72). Each item is a statement on fatigue that the subject rates from 1, "completely disagree" to 7, "completely agree". Fatigue is defined as FSS score ≥ 5 (73) .

**8.3.2.4.** Control population

The study planned to include age- and sex-matched controls from patients with NSTEMI. However, recruitment of control patients was difficult and therefore we did not achieve the age mathcing as planned.

Both groups had suffered a vascular event and were considered to be relatively similar in terms of cardio- /cerebrovascular risk before the vascular event. Both patient groups were treated at the local hospital. However, we do not know if the patients who wanted to participate in the study are representative for the patient populations. Control patients with mRS > 2 of any cause were not included.

#### 8.3.3.5. Long-term follow-up (12 months)

The follow up time in the study was 12 months. The minor stroke patients were tested for cognitive and emotional symptoms at 3 and 12 months. A selection of cognitive tests and a questionnaire consisting of fatigue (FSS), anxiety and depression (HADS) were used to measure the outcome of the study. The control patients were tested once at 12 months.

### 8.4 Ethical aspects

Written informed consent was obtained from the ischemic stroke and NSTEMI patients for their anonymized information to be published.

The regional ethics committee of Rogaland, Hordaland and Sogn and Fjordane (REC west) approved the study (REC number: 2012/1708).

### 8.5 Statistical analysis.

In this section scoring procedures and details of the statistical methods will be outlined.

STATA 14 (Statacorp 4905 Lakeway Drive, College Station, Texas 77845 USA) was used for analyses.

The cognitive tests except MMSE and the clock drawing test was converted into an age-adjusted scaled score. An abnormal test result of the cognitive tests was defined as beyond a standard deviation of 1.5. The CERAD ten-words learning task was also adjusted for educational level.

For MMSE, clock drawing test,Ullevaal Ahpasia score and IQCODE the raw score was used.

HADS-score was converted to a dichotomous variable of 0 or 1 based on the cut-off value for anxiety or depression and the mixture of anxiety and depression as explained in section 8.3.2.3.

FSS was converted to a dichotomous variable of 0 or 1 based on a cut-off value defining fatigue as explained in section 8.3.2.3.

Student's *t*-test was used to assess differences in mean values of continuous variables such as age, BMI, mRS and NIHSS.

Pearsons Chi square test was used to assess associations between categorical variables and case/control status. Important categorical variables were e.g. educational level, employment before event, prevalence of risk factors measured as yes/no, prevalence of impairment of cognitive tests and abnormal results of the questionnaires of HADS and FSS in ischemic stroke vs NSTEMI patients. Comparison of prevalence of impaired cognitive tests, emotional symptoms (HADS) and fatigue in employed vs non-employed patients was also analyzed by the Pearsons Chi square test.

McNemars test is a test used on paired nominal data. It is applied to 2 x 2 contingency tables with a dichotomous trait. The test was used to compare the prevalence of cognitive impairment, fatigue and emotional symptoms in ischemic stroke at 3 and 12 months.

Spearmans test can be used to analyze the dependence between two variables that are not necessarily linearly related or measured continuously. We used it to analyze the correlation between cognitive function, emotional symptoms and fatigue, and cerebrovascular risk factors.

Multivariable linear regressions were used to assess the association between a dependent variable and two or more independent variables. All significance testing was done as two-tailed tests. Cognitive test scores were defined as dependent variables and variables such as age, gender, ischemic stroke vs NSTEMI, educational level, marital stage, HADS-score and FSS were the independent variables.

Linear regression was also used to assess changes in cognitive function, fatigue and emotional symptoms from 3 to 12 months in ischemic stroke patients. In the linear regression analyses in paper 2 change in test results between 3 and 12 months was used as the dependent variable. Gender, age and education were forced into each analysis to adjust for potential confounding. Analyses of other independent variables such as number of risk factors, marital stage, and employment were done, but excluded because lack of significant correlation.

Binary logistic regression is a regression model with a dependent variable with two possible values, 0 or 1. The independent variables can be either categorical or continuous. Univariable logistic regression was used to assess association between a dichotomous dependent variable and one independent variable. In our study univariable logistic regression was used to estimate the odds ratio of being employed according to age, the vascular event, educational level, cognitive function and depression.

Multivariable logistic regressions were used to assess association between a dichotomous dependent variable and two or more independent variables. All significance testing was done as two-tailed tests. This model was used to estimate the odds ratio between dependent variables such as age, partner, educational level, vascular risk factors, and localization of the cerebral infarction, and employment status.

In Paper 3 stepwise backwards method was performed to remove variables with high p-values.

MANOVA test can be used to look at association of two or more dependent variables, and independent variables. A Manova test was performed on the result of overall cognitive tests to compare employed and unemployed minor stroke patients in paper.

The level of significance was set to p=.05 in all statistical analyses.

## 9. Summary of the results

In this section a short summary of each of the three papers is presented. Paper 1 and 2 are published in peer-reviewed journals, and paper 3 is accepted for publication in a peer-reviewed journal.

**Paper 1: Cognitive and emotional impairment after minor stroke and non-ST-elevation myocardial infarction (NSTEMI). A prevalence study**.

The aim of the study was to explore the prevalence of cognitive and emotional impairment following a minor ischemic stroke compared to an age-matched group with non-ST-elevation myocardial infarction (NSTEMI). We included patients aged 18-70 years with a minor ischemic stroke defined as modified Rankin Scale (mRS) 0-2 at day 7 or at discharge if before, and age-matched NSTEMI patients with the same functional mRS. We applied a selection of cognitive tests and the patients completed a questionnaire comprising of Hospital Anxiety and Depression scale (HADS) and Fatigue Severity Scale (FSS) at follow-up 12 months after the vascular event. Results of cognitive tests were also compared to normative data.

In total 325 ischemic stroke and 144 NSTEMI patients were included. We found no significant difference in cognitive functioning between ischemic stroke and NSTEMI patients. Minor stroke patients and to a lesser extent NSTEMI patients scored worse on more complex cognitive functions including planning and implementation of activities compared to validated normative data. For the minor stroke patients the location of the ischemic lesion had no influence on the result. The prevalence of anxiety, depression and fatigue was significantly higher in the stroke group compared to the NSTEMI group. Depression was independently associated with reduced cognitive function.

To conclude we found that minor ischemic stroke patients, and to lesser degree NSTEMI patients, had reduced cognitive function compared to normative data, especially executive function, on 12 months follow-up. The difference in cognitive function between stroke and NSTEMI patients was not significant. Depression was associated with low scores on cognitive tests highlighting the need to adequately address emotional sequelae when considering treatment options for cognitive disabilities.

**Paper 2. The development of cognitive and emotional impairment after minor strokes.**

The aim of this study was to follow the development of cognitive and emotional symptoms between 3 and 12 months after a minor stroke. We included patients from stroke units at hospitals in the Central Norway Health Authority and from Haukeland University Hospital. We administered a selection of cognitive tests and the patients completed a questionnaire 3 and 12 months post stroke. We defined cognitive impairment as impairment of more than two cognitive tests.

In total 324 patients completed the 3 months testing, whereas 37 patients were lost to follow-up at 12 months. The results showed significant improvement of cognitive function defined as impairment of more than two cognitive tests from month 3 to 12. However, most patients still showed cognitive impairment at 12 months with a prevalence of 35.4 %. We found a significant association between several of the cognitive tests and hypertension and smoking. The prevalence of depression, but not anxiety, increased significantly from 3 to 12 months. The prevalence of fatigue did not change and was thus still high with 29.5% after 12 months. To conclude this study showed that an improvement of cognitive function still occurred between 3 and 12 months. Despite this, the prevalence of mostly minor cognitive impairment still remains high 12 months after the stroke. The increasing prevalence of depressive

symptoms highlights the importance of being vigilant of depressive symptoms throughout the rehabilitation period. Furthermore, high prevalence of fatigue persisted

**Paper 3. Employment after a minor stroke and factors that influence employment.**

The aim of the study was to look at employment after a minor ischemic stroke compared to a control group with non-ST-elevation myocardial infarction (NSTEMI) and the influence of factors such as cognitive function, fatigue and emotional symptoms. We included patients between 18 and 70 years with a minor ischemic stroke or NSTEMI. Minor stroke was defined as modified Rankin scale (mRS) 0-2 at day 7 or at discharge if before. Included NSTEMI patients had the same functional mRS. We applied a selection of cognitive tests and the patients completed a questionnaire comprising the Hospital Anxiety and Depression scale (HADS) and Fatigue Severity Scale (FSS) at follow up. Stroke patients were tested at 3 and 12 months and NSTEMI at 12 months. In total 217 stroke and 133 NSTEMI patients employed at baseline were included. NSTEMI patients were significantly older than the stroke patients with a mean age of 59 vs 55 years. In total, 82 % of stroke patients and 90 % of the NSTEMI patients were still employed at 12 months but the stroke patients were significantly younger. Ischemic stroke patients still employed at 12 months had higher education than unemployed patients. There was no difference in risk factors between employed and unemployed stroke and NSTEMI patients. The location of the cerebral ischemic lesion did not differ in employed and unemployed stroke patients. The cognitive function did not change significantly in the stroke patients from 3 to 12 months, nor did the employment rate differ in stroke and NSTEMI patients at 12 months. For stroke patients, we found a significant association between HADS and HADS-depression and unemployment at 12 months, an association that was not apparent at 3 months. Lower age and high educational level was

associated with employment at 12 months for all patients, and NSTEMI patients had higher odds to stay employed.

To conclude we found that lower age and higher education was the main factors influencing the ability to stay in work after a minor stroke. Employed stroke patients at 12 months were younger than the NSTEMI patients but there was no difference in the employment rate. We found a high employment rate at 12 months despite the high prevalence in mild cognitive impairment in both groups.

## 10. Discussion

The results of this study show a high prevalence of abnormal cognitive tests in both minor stroke and NSTEMI patients at 12 months, but there were no significant differences between the two patients groups. However, compared to normative data, there was a significant reduction in cognitive function, especially executive function. The difference was most obvious in the minor stroke group. Prevalence of cognitive impairment increased with increasing age. Presence of risk factors and gender seemed not to substantially influence cognitive function. We also found that depression was independently associated with low scores on cognitive tests.

For the stroke patients we found a small, but significant improvement in cognitive function from 3 to 12 months. However, the prevalence of mild cognitive impairment was still high at 12 months. Hypertension and smoking was the most important risk factors associated with persistent cognitive impairment.

Even though the prevalence of cognitive impairment was high at 12 months, the employment rate was high for the stroke patients. The cognitive impairment was relatively mild on a group level, with an average number of impairment of cognitive tests of 1.7. This may explain the high employment rate. The main factors influencing the ability to stay in work after a minor stroke was lower age, higher education and lack of affective symptoms such as anxiety and depression. Even though NSTEMI patients had the same prevalence of cognitive impairment as minor stroke patients the employment rate was significantly higher compared to the stroke patients.

The prevalence of anxiety, depression and fatigue was significantly higher in the stroke group compared to the NSTEMI group and the prevalence of depression increased from 3 to 12 months in the stroke group.
Fatigue remained as a persistent symptom with a high prevalence one year after a minor stroke.

White matter hyperintensities may be present in both patient groups and may be the main cause of cognitive impairment since there is a lack of difference in the cognitive tests between the minor stroke and NSTEMI patients. It is reason to believe that also some NSTEMI patients have ischemic brain lesions influencing cognitive function. This finding is consistent with a study which found that cognitive outcomes after a coronary syndrome were similar to minor stroke (74). A meta-analysis of several studies between 1997 and 2015 found evidence suggesting that silent strokes could be associated with cognitive dysfunction (75). Silent stroke and other cerebrovascular changes may be present in both minor stroke and NSTEMI patients in our study. If this is the case it may be one of the reasons for the lack of difference between the groups. MRI data at baseline on both patient groups could offer better knowledge of this. One publication found that chronic white matter hyperintense lesions predict persistent cognitive impairment in transient ischemic attack and minor stroke (76). This may also be the case for NSTEMI patients. Many NSTEMI patients undergo coronary intervention, which can cause silent infarctions in the brain, even though some studies did not find significant cognitive impairment after coronary angiography and percutaneous coronary intervention (77, 78). However, NSTEMI patients in our study were significantly older compared to the minor stroke patients which increases the risk of neurodegenerative diseases such as early Alzheimer's disease. Higher age may partly explain high prevalence of cognitive impairment in NSTEMI patients.

Another explanation may be the selection of patients in both groups. As shown in paper 1, the ischemic stroke patients had a low NIHSS at 0.8 and mRS of 1.2 at baseline. This may reflect a bias in selection of the patients with very minor symptoms. On the other hand, recruiting patients to the control group may have favored NSTEMI patients with persisting cognitive symptoms. The ischemic stroke patients scored numerically worse on all but two of the cognitive tests compared to the NSTEMI patients. This trend may suggest that the ischemic stroke patients have slightly more encompassing cognitive problems than NSTEMI patients do. MRI examination of the control group in our study could contribute important information including the presence of silent infarctions, leukoaraiosis and atrophy.

The neuropsychological defined criteria for cognitive impairment are impairment of $\geq 2$ cognitive tests. The proportion with more than two abnormal cognitive tests in our study was 77 % in ischemic stroke patients and 84 % in NSTEMI patients. This suggests that both patient groups are associated with a generalized cognitive dysfunction. It also highlights that there are important cognitive sequelae following vascular disease for the majority of the patients regardless of where the disease manifests itself.

Increasing age showed significant correlation with lower scores on several cognitive tests, as expected because cerebrovascular changes increases with increasing age. Males showed significantly lower scores on several cognitive tests than females at the same age, despite no difference in educational level, which can possibly be explained by higher load of vascular disease in males (79). This effect was clearer in the NSTEMI patients.

Patients with ischemic strokes showed significant deficits in several cognitive domains compared to normative data. Areas of dysfunction include mental flexibility, mental speed and inhibition. These higher order cognitive functions underpin executive functioning, which encompass supervisory skills that are crucial to successful and purposeful goal-directed

behavior (80). These functions are important in planning and implementation of activities. Impaired executive function can have detrimental effect on social function and the ability to stay in work.

The location of the ischemic lesion only influenced two of 13 cognitive tests, and did not seem to be a strong determining factor for cognitive impairment. However, both tests were verbal and were more affected by left hemisphere lesions, which is to be expected given that language normally is located in the left hemisphere. It has to be mentioned that the data of MRI examination was not good enough to be used in detailed analyses. There is growing evidence that the development of cognitive impairment after an ischemic stroke depends on the location of the vascular lesions (81). More detailed data on the location of vascular changes should therefore be a part of further studies of this topic.

In paper 2 we found a significant improvement in cognitive function from 3 to 12 months in minor stroke patients. This is an important clinical finding confirming a certain improvement of cognitive function beyond 3 months. Still 35 % of the patients had persisting cognitive impairments at 12 months. This is a high number considering the low NIHSS of 0.2 at 12 months. However, the impairment was relatively mild on a group level, with an average number of impairment of cognitive tests of 1.7. The finding of persistent cognitive impairment beyond 3 months is important considering the long-term consequences of a minor stroke (45). A paper published in 2018 discusses the fact that there are few studies of long-term outcome of minor stroke patients including cognitive function (45). The authors found that 44 % had cognitive impairment after three years. They also found that cognitive impairment was independent of physical functioning. Another study found recovery of some cognitive domains over time (82). However, as time increases there is a risk for more cerebrovascular events contributing to impaired cognition (82).

We found a high prevalence of cognitive impairment at 12 months. Persisting cognitive symptoms with negative impact on daily life activities may contribute to the increase in depressive symptoms from 3to 12 months. On the other hand, cognitive symptoms is common in depressive patients as shown in some publications (19) (83). Depression may be a causal mechanism of cognitive impairment and fatigue as discussed in a previous study (83). The association between cognitive impairment and depression is important and should be better explored. The knowledge of the possible effect an untreated depression may have on cognitive function emphasizes the need for a more systematic follow-up of minor stroke patients.

*Cerebrovascular risk factors*

We did not find a strong association between risk factors and cognitive impairment in either minor stroke or NSTEMI patients (paper 1). We only found a modest association between the risk factors diabetes and overweight, and impairment on the cognitive tests. Hypertension and smoking were the most important risk factors associated with long-term cognitive impairment such as impairment of memory and executive functions in the stroke patients (paper 2). We found no significant correlation between atrial fibrillation and cognitive impairment.

The number of risk factors (hypertension, atrial fibrillation, smoking, diabetes mellitus, BMI > 25) had a modest influence of the cognitive function at 12 months.

Some earlier studies have found an association between hypertension and cognitive decline, while others did not. One large study however, found that hypertension was associated with faster cognitive decline in persons at risk for dementia (49). The study also found that intervening strokes did not influence on these findings. Heavy smokers (>20 cigarettes daily) showed a faster decline in cognitive function than non-smokers in a previous study (51). Smoking is also identified as a risk factor for reduced cerebral perfusion, cerebral atrophy and

cerebrovascular changes (84). Another study found an association between smoking and the amount of neuritic plaques which is important in development of dementia (85).

Atrial fibrillation was associated with cognitive impairment in another study (50) in contrast to our findings. The low number of patients with atrial fibrillation in our study may explain why our results did not reach statistical significance. Atrial fibrillation causes embolic stroke which is usually associated with major ischemic strokes. This may also be an explanation of the low number of patients with atrial fibrillation in our study.

Cerebrovascular risk factors are associated with development of cerebrovascular changes on imaging, which increases with increasing age. An age-dependent association between smoking and white matter hyperintensities was found in one study (52). Our patient population is relatively young, which may explain the lack of association between cognitive impairment and risk factors. It is known that cerebrovascular risk factors increases the risk of Alzheimer's disease (86) and the cognitive impairment showed in our study may reflect a preclinical stage of this neurodegenerative disease in some patients. In a recent publication the authors found that the incidence of dementia associated with minor stroke in a follow-up period of five years was low (87). They also found that vascular risk factors (including hypertension, atrial fibrillation, hyperlipidemia and vascular disease) were not predictive of post-stroke dementia.

However, a publication from the Joint Programme for Neurodegenerative Disease Research discusses that vascular disease contributes to cognitive decline and neurodegeneration (88). The interaction between vascular disease and neurodegeneration are the two major causes of cognitive impairment and the authors recommend an implementation of both vascular and neurodegenerative issues in future research. This may lead to a better understanding of this topic.

High prevalence of overweight may indicate that a considerable number of the patients also has obstructive sleep apnea syndrome (OSAS). OSAS patients may have cognitive and depressive symptoms (89) which may explain some of our findings, but our study has no data on the prevalence of OSAS in our patients.

The closest relatives (spouse, children, parents etc.) may notice cognitive symptoms earlier in minor stroke patients than other. It may be easier to hide slight cognitive difficulties to the surroundings than to the closest relatives. The questionnaire IQCODE was used to explore if the stroke patients had slight cognitive symptoms. IQCODE is a tool used in early recognition of dementia. The mean value of IQCODE at three months was unchanged compared to prestroke condition. Since the mean number of impaired cognitive tests in this study is low, IQCODE may not be sensitive enough to reveal subtle changes in cognitive function.

The possibility of a learning effect of repeated cognitive or neuropsychological testing is described in previous studies (90, 91). However, another publication did not find a learning effect at one-month test-retest interval (91). Since the minor stroke patients were tested twice, learning effect at 12 months theoretically may contribute to the lack of difference between the stroke and NSTEMI groups. However, the interval of 9 months for repeated testing in our study is probably too long to cause a significant influence on the results.

*The impact of anxiety and depression after a minor stroke .*

The prevalence of combined anxiety and depression (HADS>15) was significantly higher in the ischemic stroke patients than NSTEMI patients, but the difference in pure anxiety or depression symptoms was not significant. Reported depression was associated with lower scores on the cognitive tests. Reported anxiety was not associated with change in cognitive

performance in neither of the patients groups. There was no significant difference of anxiety between 3 and 12 months in the minor stroke patients, but the prevalence was relatively high with 20 and 18 % respectively.

A considerable amount of the minor stroke patients had persisting depressive and/or anxiety symptoms 12 months poststroke. We also found increasing depressive symptoms from 3 to 12 months after a minor stroke. The prevalence was significant higher at 12 months with 12 %, in contrast to 9 % at 3 months.

The depression scores were compared to the prevalence of anxiety and depression in the population-based study of HUNT (The Nord-Trøndelag Health study) (92) where about 9 % of the population reported anxiety and 5% depression (on HADS). There were significantly more anxiety and depression disorders in our ischemic stroke patients than in the study of HUNT. However, this was not the case for the NSTEMI group.

Cognitive dysfunction among patients with reported depression is a common finding (83). Depression is in itself found to be associated with worsening and enduring cognitive dysfunction even after remission of the depression (93). The current finding of a broad cognitive dysfunction in both patient groups suggests that they may have less cognitive reserves and may therefore be extra vulnerable to events of adverse effects on cognitive function including depression.

Reported anxiety was not associated with change in cognitive performance in neither of the patients groups. In contrast to our findings, one study investigating a stroke population (94) and one of healthy individuals (95) found that anxiety had a detrimental impact on cognitive functions.

A previous study using the same questionnaire (HADS) and same cut-off score as our study found a prevalence of anxiety in minor stroke patients of 25 % at 12 months (96) compared to 18 % in our study.

Another study found a decrease in depressive symptoms over time from 12.9 % to 8.1 % in the same time interval as in our study (37), in contrast to our findings. Patient characteristics in that study were quite similar except higher NIHSS (2 vs to 0.2). One study found a stable situation for depressive symptoms between 3 and 12 months (97). In that study population about 20 % of the patients had mRS > 2 in contrast to our study where mRS > 2 was an exclusion criteria and the patients were older than our patients. This makes a comparison difficult.

High prevalence of both cognitive impairment and fatigue at 12 months may contribute to the increase in depressive symptoms. Patients with persisting cognitive symptoms and fatigue with negative impact on daily life activities may be more prone to develop a depression over time, even though the cognitive impairment is minor.

We found no correlation between development of anxiety and prevalence of depression at 12 months, in contrast to previous studies (98).

Treatment of depression may reduce cognitive symptoms as discussed previously. Since there is some evidence of persisting cognitive symptoms after successfully treating of a depression, this also emphasizes the important of early detection of depressive symptoms (83). Prevention of development of depressive symptoms may be even better and more studies are recommended. A paper published in 2018 discusses the fact that there are few studies of long-term outcome of minor stroke patients including depressive symptoms (45). In that study 39 % of the patients were depressed after three years. A review article from 2018 recommends screening patients with minor stroke for mental health problems (30). However, the authors found few appropriate screening tools, and recommend further research.

*Prevalence of fatigue after a minor stroke.*

The prevalence of fatigue did not improve from three to 12 months in the minor stroke group and a third of the patients still had fatigue 12 months after the stroke. Surprisingly there was no correlation between fatigue and cognitive impairment in our study.

The high prevalence of fatigue among the ischemic stroke patients is consistent with prior studies (27, 41, 44, 99-102). The prevalence in other studies varies between 23-65 %, compared to 29 % in our study. A previous study found that 77.3% of the patients reporting fatigue at 6 months still reported fatigue at 12 months follow-up (41). Another study found that fatigue had a significant impact on the health-related quality of life emphasizing that fatigue may be a disabling condition (102). Other studies have found a correlation between fatigue and cognitive impairment (41) whereas other did not (102). The different studies used different tools measuring fatigue, something which may explain the different results (FSS in our study, FAI: Fatigue Assessment Instrument (41) and FAS*: Fatigue Assessment Scale (102)). FAI is more detailed than FSS and may be more sensitive to detect significant correlations, whereas FAS seems to be quite similar to FSS.

*Employment rate after a minor stroke.*

Employment at 12 months was more frequent among NSTEMI patients than among ischemic stroke patients even though NSTEMI patients were older. This may be caused by a selection bias because the NSTEMI patients were older at baseline. By contrast, NSTEMI patients may be able to stay longer in work after their vascular event compared to minor stroke patients. This may support our hypothesis of lower employment rate after a minor stroke compared to a NSTEMI. Stroke patients likely have more cerebral ischemic lesions than NSTEMI patients before the index vascular event possibly explaining this age difference. Even after correcting for age, a higher proportion of NSTEMI patients were still employed at 12 months. In paper 3 we have shown the distribution of impaired cognitive tests in the stroke and NSTEMI groups.

The number of impaired cognitive tests was significantly higher in the stroke group compared to tne NSTEMI group , but the prevalence of cognitive impairment defined as impairment of ≥ 2 cognitive tests did not differ.

For both patient groups high age and low education were associated with unemployment at 12 months follow-up in patients employed at baseline. Highly educated people may have a larger "cognitive reserve" which may explain the higher degree of employment. We found no difference in cognitive performance between employed and unemployed ischemic stroke patients suggesting that cognitive impairment is not the major cause of unemployment in our stroke patients. Another explanation may be that the cognitive tests in our study are not good enough to detect minor cognitive deficits.

As explained earlier our study did not find a strong association between cerebrovascular risk factors and cognitive impairment. However, we found an association between diabetes mellitus, atrial fibrillation and hypercholesterolemia and unemployment in ischemic stroke patients. Dealing with diseases may be demanding enough in itself. If this is the case for the patients a minor stroke on top of it may be too much to deal with may lead to unemployment.

For the NSTEMI patients, atrial fibrillation, smoking and overweight were associated with ending up unemployed in our study. Because the number of unemployed NSTEMI patients was small the results must be interpreted with caution.

The prevalence of some of the risk factors was higher in the NSTEMI group compared to the stroke group. Nevertheless NSTEMI patients seem to stay longer in work than ischemic stroke patients which suggests that this difference does not influence the employment rate in our patients.

The employment rate for ischemic stroke patients in our study was high even though the prevalence of cognitive impairment was high at 12 months. One explanation may be that our

study have used cognitive tests that are too sensitive and demonstrate findings with little impact on employment.

The cognitive impairment is relatively mild on a group level, with an average number of impairment of cognitive tests of 1.7. This may explain the high employment rate in our study. Another study found that 72 % of stroke patients with baseline NIHSS 0-5 had returned to work at one year (103) in contrast to 82 % of the stroke patients in our study.

The prevalence of unemployment in ischemic stroke patients in our study increased between 3 and 12 months. Some of the employed patients at three months may still have been on sick leave. At 12 months these patients may have converted to disability benefits due to a more clarified health status which may explain the difference in employment.

Prevalence of anxiety and depressive symptoms were higher in unemployed stroke patients at 12 months, but not at three months. Since the prevalence of cognitive impairment was unchanged from 3 to 12 months, the increasing prevalence of anxiety and depression may be the main cause for the increased unemployment rate. However, our study does not answer whether the depression causes the unemployment or if the unemployment causes the depression.

Other studies found the same association with education and employment (104) as our study. The lack of association between cognitive function and employment in our study is in contrast to a study of mild to moderate stroke that found impaired global cognitive function as the only statistically significant independent predictor for return to work (57). Another study found that patients that returned to work three months after a minor stroke had sigificantly more years of education and they had a significantly better cognitive performance (58).

Lack of hypertension and diabetes and a non-smoker status before stroke was associated with a higher likelihood of return to work after cerebrovascular disease in one study (56). However, the association was not very strong, as also shown by others (87).
In contrast to our study another study found an association between risk factors and return to work after cerebrovascular disease (56). Functional outcome (mRS and NIHSS) was not reported in that study.

In a study of spinal cord infarctions all surviving patients younger than 60 years with mRS ≥ 1 day 7 had been re-employed after discharge compared to 65% of patients younger than 60 years with cerebral infarctions and mRS ≥ 1 at day 7 (105). This may suggest that the cerebral lesions had an impact on the ability to stay in work even though the functional status as evaluated with mRS was similar. Patients with spinal cord infarction also have a lower risk factor load than patients with cerebral infarction according to another study (106) suggesting that spinal cord infarction patients may have less cerebrovascular changes related to risk factors. One study found that the participants thought that a stroke was more serious than a heart attack, which may influence the patients' expectation of function and the ability to stay in work after the illness (107). This illustrates the importance of using more patient-related outcome measures (PROMS) such as appropriate questionnaires to get even better knowledge of the reasons for unemployment after a stroke.

The high employment rate in our study is in contrast to another study (108) where only 41 % of patients had returned to work after six months , even though the NIHSS at discharge was low (NIHSS 1 compared to 0.8 in our study). An unpublished subgroup analysis of seven of our ischemic stroke patients showed that patients returning to work had less demanding tasks or less responsibility in their work than before the stroke (109). This may also explain the high employment rate among our patients.

The higher prevalence of anxiety and depressive symptoms in unemployed stroke patients in our study correlates with the findings in another study which found significant differences in depression in employed and unemployed patients (58). A study from 2008 found that psychiatric comorbidity 28 days after a stroke was a predictor of not returning to work (110). Further studies are needed to clarify the interaction between emotional symptoms and cognitive function.

Other than health related issues may also contribute to determine whether our patients were able to return to their work. In Norway early retirement is an option, and some of our patients may have chosen this solution. A recent Finnish study also discussed early retirement as an option that may contribute to lower prevalence of employment after a stroke (62). Another study found that having a qualified occupation and working in a large organisation predicted shorter time to return to work after a stroke (111). Our study did not study the patients' occupation.

*Special consideration of the NSTEMI group.*

It may not be surprising that NSTEMI patients also have cognitive impairment. NSTEMI patients have a vascular disease and may have ischemic brain lesions influencing cognitive function. The proportion of NSTEMI patients with cognitive impairment defined as impairment of $\geq 2$ cognitive tests in our study was high (84%).

The literature offers some evidence of the association between NSTEMI and cognitive impairment, but our findings suggest that this topic should be more emphasized in the follow-up of NSTEMI patients. The Norwegian Myocardial Infarction Registry from 2018 contains some PROMS of activities of daily living, general health and a quality of life-questionnaire (112) illustrating an increasing attention of the patients' general functioning.

A prior study found that cognitive outcomes after a coronary syndrome were similar to minor stroke (74). A review article from 2017 found that patients with coronary heart disease had an increased risk of cognitive impairment. Among the explanation the authors discuss are the effect the underlying atherosclerosis may have on cerebrovascular changes in the brain (113). Many NSTEMI patients are treated with a coronary intervention, which can cause silent infarctions in the brain, even though a recent study did not find significant cognitive impairment after coronary angiography and percutaneous coronary intervention (77, 78).

**11. Strenghts and limitations.**

A strength of this study is the large number of patients and inclusion of a control group.

It is a well-defined study cohort based on the functional classification.

It is a multicenter study and reflects the patients in the middle and western part of Norway. The existence of normative data made it possible to detect a significant difference for both patients and controls compared to the normative data. The study has a long follow-up time with repeated testing of the ischemic stroke patients. We did not achieve the desired case-control design mainly because of difficulties in recruiting control patients.

mRS 0-2 at baseline was used as the inclusion criteria. This is a functional outcome measure and contains no details of sensorimotor symptoms, visual function, language and consciousness. NIHSS was registered in all stroke patients at baseline and was low on 0.8. Even though there is no consensus of which NIHSS score that represents a minor stroke, a value of 0.8 is below any suggested limit. Our inclusion criteria may therefore have selected patients with very mild strokes compared to other studies.. This may have influenced the results by contributing to the lack of difference between ischemic stroke and NSTEMI patients. The high prevalence of employed patients after a minor stroke may also be influenced by this.

Different study nurses and one neurologist performed testing because of the multicenter design. This may create an interrater-variability.

A selection of patients may exist. It may be a possibility that patients with cognitive and emotional complaints in a larger extent wanted to be included in the study, which may create a bias. However this is in contrast to our finding of minor cognitive impairment as discussed above.

Some patients live far from the hospital. A long traveling distance may have influenced the ability to concentrate in performing cognitive tests and may influence the result.

Lack of registration of proportion of percutaneous coronary intervention (PCI) in the NSTEMI-group is another limitation, because PCI may cause ischemic lesions in the brain as shown in a study from 2016 (77, 78). This may contribute to the lack of difference in cognitive function between ischemic stroke and NSTEMI patients.

IQCODE was not registered at baseline. A possibility of preexisting cognitive impairment, e.g. early Alzheimer's disease may therefore be a bias.

Prestroke fatigue and obstructive sleep apnea were not recorded.

The learning effect of repeated cognitive testing has to be considered even though the time period between the test points at nine months was considered to be sufficient to avoid this.

Depression and anxiety were based on self-report (HADS), no diagnostic interviews were performed.

Of NSTEMI patients employed at baseline only 9 patients were unemployed at 12 months which means that the interpretation of results must be done with caution.

An observation period of 12 months may be too short. A recent meta-analysis have found that presence and severity of white matter disease at baseline of an ischemic stroke patients increase the risk of dementia (114). A longer follow-up time could have identified differences in cognitive function based on the severity of white matter disease.

A weakness is that NSTEMI patients did not undergo a cerebral MRI and thus the presence of white matter changes in NSTEMI patients are not known.

The MRI-data on the stroke patients were not of good enough quality to perform detailed studies on the location of the stroke and the association with cognitive and emotional symptoms.

We have not studied factors in the workplace or the patients' occupation. Such factors may influence the ability to stay in work after minor stroke and NSTEMI infarct.

*Validity and reliability of the cognitive tests and questionnaires*

MMSE and clock drawing test is widely used tests in Alzheimer disease. However, these screening tools are not sensitive to mild cognitive impairments and only was used as a screening in our study.

Delis-Kaplan Executive Function System (D-KEFS is based on a sample of over 1700 individuals ranging from 8-89 years. In that way it provides normative data adjusted for age.

CERAD was funded by the National Institute on Aging in 1986 to develop standardized, validated measures for assessment of Alzheimer disease (67). CERAD consists of several instruments including a neuropsychology battery. In our study we used one of the tests ten-words learning task. CERAD represents a continuous work to standardize and improve the assessment of Alzheimers disease.

HADS has been found to perform well in assessing in the symptom severity and casesness of anxiety disorders and depression in both somatic, psychiatric and primary care patients as well as in the general population (71). The Norwegian version of HADS was also found to be a relatively well validated screening instrument for symptoms of psychological distress according to a report from the Norwegian Institute of Public Health (NIPH) (115). However, in spite of a large amount of Norwegian research and a large HADS databank site on the internet, a validated set of norm data is missing according to NIPH.

FSS is a widely used tool to measure post-stroke fatigue. The test-retest reliability, internal consistency and concurrent validity in measure post-stroke fatigue is published in a study from 2017 (73). The conclusion was that FSS is a reliable and valid tool to measure post-stroke fatigue and is readily to be used in clinical settings. The Norwegian translation is also evaluated and the conclusion is that the psychometric properties of the Norwegian version is satisfactory (116).

Ullevaal Aphasia score (UAS) was developed at Department of Geriatric Medicine at Ullevaal University Hospital and the conclusion was that UAS seemed to be a valid screening instrument for aphasia in the acute stage of stroke (69), but the authors of the study state that further studies is needed to confirm this. We used the test in stroke patients 3 and 12 months after a stroke, which the test is not validated for. However, aphasia is not a prominent symptoms in minor stroke because a serious aphasia may contribute to a higher mRS than 2 which is one of the exclusion criteria in our study.

IQCODE is a screening tool for dementia. The questionnaire is validated in Norwegian by Harald Nygård and Asgeir Bragason. In our study there was no difference in IQCODE before and after the ischemic stroke. A publication found that IQCODE also was useful in screening of mild cognitive impairment, and correlated with the sensitivity of MMMSE (117). However, our patients are younger and the tool may not be suitable for a younger population..

Cognitive impairment defined as impairment of $\geq 2$ cognitive tests is used in a neuropsychological practice. A study from 2001 discussed the rationale behind this (118) and concluded that impairment of $\geq 2$ cognitive tests seemed to correlate with the clinical diagnosis of a cognitive impairment.

Our study used a selection of cognitive tests recommended by some of my advisors as mentioned under acknowlegdements. The selection was based on the scientific and clinical

experience. A full neuropsychological test battery would be too time-consuming but could have revealed more cognitive impairment than our study did. On the other hand, a cognitive test battery used in assessment of dementia may have missed minor but significant cognitive deficits.

Before the inclusion of patients started we did a power analysis based on a prevalence of cognitive impairment in the general population of 4 % based on a publication describing a prevalence between 3 and 5 % (119). We postulated a prevalence of cognitive impairment in our stroke patients of at least twice (about 8 %) and found a power of 83 % given a total number of 600 patients. However, we did not succeed to include that many patients during the inclusion period. This may explain why our study only detected minor differences between minor stroke and NSTEMI patients and between employed versus non-employed stroke patients.

**12. Clinical implications.**

Our study demonstrates that the prevalence of cognitive and emotional symptoms is high and persisting after a minor stroke. The clinical implications of these findings reveals a need of a structured follow-up with focus on these symptoms. According to the findings in the Norwegian Stroke Registry this comprises the majority of the stroke patients. Therefore a screening to select the patients who will benefit of this kind of follow-up should be done (30). A recommended screening tool for cognitive testing is MOCA which is easy to perform and not very time-consuming. This could be considered done before discharge.

The Norwegian version of the MOCA test was formally validated in 2011/2012 (120). Our study was planned in 2012 and started in 2013. Because limited experience with MOCA-test in Norway at that time we chose not to use this tool. Symptoms of depression, anxiety and fatigue will probably not be very dominating the first days after a stroke and an early screening may be wasted. In Norway most stroke patients are offered an outpatient control or a contact by phone three months after the stroke. A screening of emotional symptoms and fatigue as a questionnaire could be considered at this same time.

**13. Future directions.**

Our study did not find a strong association between location of infarction and the prevalence of cognitive impairment, fatigue or emotional symptoms. The explanation of this may be that our MRI-data were not good enough as to the exact location, size of the lesion, classification (lacunar or embolic) of stroke, or the presence of old ischemic strokes. Better MRI data would contribute to more precise classification of ischemic stroke and more robust data on predicting cognitive function.

Studies of cerebrovascular changes in NSTEMI patients and the association of cognitive symptoms may be interesting to study in more detail.

The attention of cognitive impairment after minor strokes is growing. When searching the literature it is obvious that lack of consensus of classification of a minor stroke contribute to different results in different studies. However, since cognitive impairment may cause a major disability, a consensus may contribute to better and more uniform studies looking at more comparable groups of patients.

There are few studies of patient-related outcome measures (PROMS) after an ischemic stroke (46). The most commonly measured domains for stroke patients are physical, cognitive and social function. There are recommendations from a number of organizations (The World Health Organization International Classification of Functioning, Disability and Health Framework and The International Consortium for Health Outcome Measures Stroke working group) to study items such as activity limitations and more detailed functional status than traditionally done (121, 122). The results of our study reveals a high prevalence of both cognitive impairment and fatigue, but do not answer in detail the consequences for the

patients except for the employment status. Our results support the recommendations of research areas as discussed in the references mentioned above.

Introduction of a tool measuring the cognitive function may be a method selecting patients in need for a more thoroughly follow-up. The MOCA-test may be a good choice because it is not very time-consuming and can be done by an occupational therapist that is available in most stroke units.
A research question may be: Is cognitive impairment at baseline a predictor of long-term cognitive impairment after a minor stroke?

Implementation other than medical factors in studies of employment after cerebrovascular disease such as sociodemographic factors and work-related factors needs to be considered. Our study showed an association between education and employment, but do not answer if it is the intellectual capacity or differences in the flexibility in professions that predicts return to employment.

Cognitive rehabilitation by an internet-based training program could be the next step with the knowlegde of the high and persisting prevalence of cognitive impairment after a minor stroke. However, it has to be mentioned that the cognitive impairment is mild for most of the patients.

## 14. Conclusion

In our study we have looked at the prevalence of cognitive impairment, fatigue and emotional symptoms in two patient groups and also compared both groups with normative data. Second we looked at the development of the same items from 3 to 12 months. At least we studied the consequences for employment at 12 months.

We found no significant difference in cognitive function between minor ischemic stroke patients and NSTEMI patients. However, the stroke patients and to a lesser degree NSTEMI patients had reduced cognitive function compared to normative data, especially executive function, on long term follow-up. Prevalence of cognitive impairment increased with increasing age. Presence of risk factors and gender seemed not to substantially influence cognitive function. Depression was independently associated with low scores on cognitive tests, suggesting that treatments targeting depression may be a valuable approach to improve cognitive disabilities in these patients. The prevalence of anxiety, depression and fatigue were significantly higher in the stroke group compared to the NSTEMI group.

The study showed a small, but significant improvement in cognitive function from 3 to 12 months. However, the prevalence of mild cognitive impairment was still high at 12 months. The most important risk factors for persistent cognitive impairment were hypertension and smoking.

The prevalence of depression increased from 3 to 12 months. Early detection and treatment of depression is important in order to enhance recovery including improvement of cognitive symptoms.

Fatigue was a persistent symptom with a high prevalence one year after a minor stroke.

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The majority of patients employed at baseline retained their employment 12 months after an ischemic stroke and NSTEMI. The main factors influencing the ability to stay in work after a minor stroke were lower age, higher education and lack of affective symptoms. Significantly more NSTEMI patients were employed after 12 months even though they had the same prevalence of cognitive impairment as the stroke group.

Overall the findings in our study emphasize the importance of a longer term follow up of patients with minor stroke. This is not done routinely today. For the future we suggest a follow-up with a test battery testing memory and executive functions because these are functions of great importance in the daily living. We also recommend a screening for fatigue, anxiety and depression. The study suggests that identifying stroke patients with emotional symptoms is important since affective manifestations might contribute to employment.

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**15. Publications**

# Paper I

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*Research Article*

# Cognitive and Emotional Impairment after Minor Stroke and Non-ST-Elevation Myocardial Infarction (NSTEMI): A Prevalence Study

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*Aim*. To study the prevalence of cognitive and emotional impairment following a minor ischemic stroke compared to an age-matched group with non-ST-elevation myocardial infarction (NSTEMI). *Methods*. We included patients aged 18-70 years with a minor ischemic stroke defined as modified Rankin Scale (mRS) 0-2 at day 7 or at discharge if before and age-matched NSTEMI patients with the same functional mRS. We applied a selection of cognitive tests and the patients completed a questionnaire comprising of Hospital Anxiety and Depression scale (HADS) and Fatigue Severity Scale (FSS) at follow-up 12 months after the vascular event. Results of cognitive tests were also compared to normative data. *Results*. 325 ischemic stroke and 144 NSTEMI patients were included. There was no significant difference in cognitive functioning between ischemic stroke and NSTEMI patients. Minor stroke patients and to a lesser extent NSTEMI patients scored worse on more complex cognitive functions including planning and implementation of activities compared to validated normative data. For the minor stroke patients the location of the ischemic lesion had no influence on the result. The prevalence of anxiety, depression, and fatigue was significantly higher in the stroke group compared to the NSTEMI group. Depression was independently associated with reduced cognitive function. *Discussion and Conclusion*. Minor ischemic stroke patients, and to lesser degree NSTEMI patients, had reduced cognitive function compared to normative data, especially executive functioning, on 12-month follow-up. The difference in cognitive function between stroke and NSTEMI patients was not significant. Depression was associated with low scores on cognitive tests highlighting the need to adequately address emotional sequelae when considering treatment options for cognitive disabilities.

## 1. Introduction

Acute ischemic stroke is a heterogeneous clinical syndrome and can lead to a variety of physical and cognitive clinical manifestations. Sensorimotor deficits are usually fairly evident, whereas cognitive deficits may be rather inconspicuous. However, a recent review [1] reported that poststroke dementia might affect as many as 30% of stroke patients. Fatigue has been reported in 34.7% of patients following a minor stroke [2].

Patients with minor strokes are thought to have good long-term prognosis. Sensorimotor symptoms are often marginal at admission and improve quickly the first days and weeks. Most patients are discharged directly to their homes and may have no physical neurological deficits at follow-up after few weeks. However, they may have cognitive symptoms compatible with a mild cognitive impairment or dementia [3–8] and suffer from fatigue [2, 9] and emotional symptoms [3, 10] of longer duration. Anxiety following a minor stroke is less explored [3, 11], whereas subsequent depression and fatigue after minor strokes are better known [2, 3, 10]. These symptoms may have substantial impact on daily functions, rehabilitation, and the patients' ability to stay in employment after an ischemic stroke [3, 12, 13].

High prevalence of cognitive impairment and depression after TIA and minor stroke are discussed in a systematic review from 2014 [3], but only a few of the included studies were of high quality. The studies revealed large variations in methodology and distribution of included cases [3]. The authors concluded that the knowledge of poststroke anxiety was limited. The prevalence of fatigue was high, but the studies were few and lacked relevant comparison groups. A prospective study from Turkey found significant cognitive impairment in patients with minor stroke and transient ischemic attack compared to controls [5], and, in a prospective Swiss study, poststroke fatigue was found in 34.7% at 12 months after a minor stroke [2].

Assessment of cognitive dysfunction and emotional symptoms is not routinely performed during follow-up and knowledge of the long-term impact of cognitive and emotional symptoms is sparse [3, 5], but attention to this issue is growing [13, 14]. There is no consensus on diagnostic criteria for minor stroke [15–19] which hampers research on this topic. There is consequently a need for studies investigating the consequences of cognitive and emotional impairment of minor strokes. The aim of this study was to assess the prevalence of cognitive and emotional impairment, in patients with minor ischemic stroke. Non-ST-Elevation myocardial infarction (NSTEMI) patients were selected as a control-group because both conditions implicate symptomatic vascular disease and related risk factors with the intracerebral lesion as the difference. Comparison with normative data was included for the cognitive tests.

## 2. Material and Methods

A 12-month follow-up was performed with a selection of cognitive tests and a questionnaire on anxiety, depression, and fatigue. The presence of anxiety and/or depression is defined as emotional impairment. A control group of NSTEMI patients was chosen.

Emotional symptoms in our study is defined as anxiety and depressive symptoms and fatigue.

*Patients* were as follows*:* ischemic stroke was defined in accordance to the Baltimore-Washington Cooperative Young Stroke Study Criteria [20] comprising neurological deficits lasting more than 24 hours because of ischemic lesions or transient ischemic attacks where CT or MRI showed infarctions related to the clinical findings. *Inclusion criteria* were as follows: ischemic stroke patients 18-70 years with minor ischemic stroke defined as mRS 0-2 [21] at day 7 or at discharge if before and TIA-patients with an ischemic lesion verified at MRI. NSTEMI patients aged 18-70 years with mRS 0-2.

*Exclusion criteria* were as follows: patients with a major stroke defined as mRS > 2 day 7 or at discharge if before and patients with deterioration in mRS to more than 2 in the observational period of any cause. NSTEMI patients with mRS > 2 of any cause.

*Recruitment* was as follows; ischemic stroke patients were recruited consecutively from stroke units at Molde Hospital, Haukeland University Hospital, and St Olav's Hospital. Patients from other participating stroke units, Department of Neurology at St Olavs Hospital, Kristiansund Hospital, Volda Hospital, and Aalesund Hospital, were included whenever practical, but not always consecutively. Recruitment period was 01/01/13-12/31/16. NSTEMI patients were recruited from Haukeland University Hospital, Ålesund Hospital, Molde Hospital, and Kristiansund Hospital in the same time.

*Baseline investigation* was as follows: ischemic stroke patients underwent routine examination with NIHSS [22], traditional risk factors including hypertension, diabetes mellitus, hypercholesterolemia, smoking, BMI $\geq$ 25, and brain imaging with CT and/or MRI. Patients were treated according to Norwegian guidelines for ischemic stroke. Most patients with mRS $\leq$ 2 after 7 days or at discharge had no need for further rehabilitation and were discharged to their home.

Demographic data were collected from the initial admission time for the ischemic stroke and NSTEMI.

## 3. Assessment of Cognitive and Emotional Function

Clock drawing test [23] were used as screening of global cognitive function. Clock drawing test assesses visuospatial function [23]. Trail-making tests A and B, Color-Word interference test, and Verbal fluency (FAS) were used to test executive function [24].The Color-Word interference test is divided into 4 items: color naming, color reading, inhibition and inhibition/switching, testing mental flexibility, mental speed, and inhibition. These tests were drawn from the Delis–Kaplan Executive Function System (D-KEFS). D-KEFS was developed to provide reliable normative data for a range of executive functions [25].

Memory was tested with the CERAD ten-words learning task [26]. CERAD (Consortium to Establish a Registry for

Table 1: Characteristics of patients and controls at baseline (time for event).

| | Ischemic stroke n 324 (%) | NSTEMI n 144 (%) | p value |
|---|---|---|---|
| Age (mean) | 58.0 (10.0∗) | 60.3 (6.6∗) | .009 |
| Females | 120 (37) | 31 (22) | .001 |
| | 51 (16) | 20 (14) | |
| Education (1,2,3)[a] | 148 (46) | 68 (47) | .07 |
| | 121 (37) | 56 (39) | |
| Employed before event | 217 (67) | 111 (77) | .03 |
| Risk factors | | | |
| Hypertension | 174 (54) | 68 (47) | .2 |
| Diabetes mellitus | 39 (12) | 22 (15) | .3 |
| Atrial fibrillation | 46 (14) | 15 (10) | .3 |
| Hypercholesterolemia[b] | 151 (47) | 80 (56) | .07 |
| Smoking[c] | 114 (35) | 65 (45) | .04 |
| BMI mean | 26.7 (4.4∗) | 27.4 (3.7∗) | .06 |
| Overweight (BMI≥25) | 189 (58) | 98 (68) | <.001 |

[a]1 ≤ 10 years of education, 2 10-13 years of education, ≥ 14 years of education, [b] hypercholesterolemia is defined as treatment with cholesterol lowering medication, and [c]smoking is defined as current smoker or smoking within the last 12 months. ∗SD.

Alzheimer's Disease) is standardized validated test battery for the assessment of Alzheimer disease [26] with normative data adjusted for age and education [27]. Minor stroke and NSTEMI patients were compared with validated normative data for Trail-making test A and B, Color-Word interference test, Verbal fluency, and Ten-word learning task [26, 28].

Scores falling below 1.5 SD of the mean were characterized as abnormal.

Ischemic stroke patients were screened by the Ullevål aphasia screening test [29].

*3.1. Questionnaires.* Hospital Anxiety and Depression scale (HADS) was used to assess anxiety and depression [30]. A score ≥ 8 on the anxiety (HADS-A) or depression (HADS-D) items indicates possible presence of anxiety or depression disorders [30]; a total score ≥ 15 indicates a mixture of anxiety and depression.

Fatigue Severity scale (FSS) was used to assess fatigue [31]. FSS is a nine-item questionnaire that assesses the effect of fatigue on daily living. Each item is a statement on fatigue that the subject rates from 1, "completely disagree", to 7, "completely agree". [32] Fatigue is defined as FSS score ≥ 5 [32].

Cognitive testing was performed by trained research nurses or by the neurologist responsible for the study.

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

The ethics committee of Rogaland, Hordaland, and Sogn and Fjordane (REC west) approved this study (REC no. 2012/1708).

## 4. Statistics

Student's *t*-test was used to assess differences in mean values. Chi square was used to assess differences in categoric variables. Multivariable linear regressions were used to assess association between more than two variables. The level og significans was set to p=.05. All significance testing was done as two-tailed tests.

STATA 14 (Statacorp 4905 Lakeway Drive, College Station, Texas 77845 USA) was used for analyses.

## 5. Results

In total, 324 ischemic stroke patients were included at admission and followed up at 3 months, and 288 were followed up at 12 months. Either a phone call or a letter recruited the NSTEMI group after their vascular event. 144 of 146 NSTEMI patients who accepted participation completed the questionnaire and cognitive tests. Table 1 shows baseline demographic data on ischemic stroke and NSTEMI patients. The mean age for ischemic stroke patients was significantly lower than for the NSTEMI group, 58 years (SD = 10.0) and 60 years (SD = 6.6), respectively. Proportion of women was significantly higher in the ischemic stroke group. There were significantly more NSTEMI patients who smoked compared to the ischemic stroke patients (p =.04). More NSTEMI patients than ischemic stroke patients were employed (p =.03). The mean value for premorbid mRS in ischemic stroke patients was 0.3 (SD = 0.6), mRS at discharge/day 7 was 1.2 (SD= 0.8), and NIHSS at discharge/day 7 was 0.8 (SD = 1.0). The number of patients treated with antidepressant was 24 (8%) and in the control group 10 (7%).

*5.1. Cognitive Function.* Table 2 shows results of the cognitive tests, HADS, and FSS in ischemic stroke and NSTEMI patients. Cognitive tests were compared with each other and normative data for both groups.

Clock-drawing test score was 5 in both groups, indicating no deficit in either group on this test.

There were no differences between ischemic stroke and NSTEMI patients in Ten-word learning task, Trail-making tests A or B, Verbal fluency, or Color-Word Interference tests

Table 2: Chi square test to compare cognitive tests HAD and FSS among minor ischemic strokes and NSTEMI patients. Proportion of patients and controls with abnormal results based on 5 percentile for normative data. Significant difference with normative data is labeled with∗.

| | Ischemic stroke N=288(%) | NSTEMI N=144 (%) | P-value[h] |
|---|---|---|---|
| 10-words learning task[a] | 17(6) | 9(6) | 1.0 |
| 10-words learning task, delayed recall[ab] | 27(10) | 12(8) | .7 |
| Trail-making A[c] | 15(5) | 4(3) | .2 |
| Trail-making B[c] | 39(14)∗ | 16(11) | .4 |
| Verbal fluency[c] | 32(11) | 17(12) | .8 |
| *Color-Word Interference tests* | | | |
| Color naming[c] | 59(20)∗ | 20(14) | .09 |
| Color reading[c] | 52(18)∗ | 17(12) | .07 |
| Color inhibition[c] | 58(20)∗ | 20(14)∗ | .1∗ |
| Color inhibition/switching[c] | 58(20)∗ | 17(12) | .03 |
| Error scores | | | |
| Naming errors[d] | 16(6) | 5(3) | .8 |
| Reading errors[d] | 29(10) | 17(12) | .6 |
| Inhibition errors[c] | 18(6) | 6(4) | .4 |
| Inhibition/switching errors[cc] | 25(9) | 8(6) | .1 |
| Proportion with ≥2 abnormal cognitive tests | 220(77) | 122(84) | .05 |
| *Questionnaire* | | | |
| HADS [e] | 45(16) | 0(0) | <.001 |
| HADS-A[f] | 52(19)∗ | 19(13) | .2 |
| HADS-D [f] | 34(9)∗ | 9 (6) | .06 |
| FSS (n=279/142) [g] | 81(29) | 22(15) | .002 |

[a]Adjusted for age and educational level, [b]tested with 5 minutes delay, [c]scaled score, and [d]cumulative percentage. [5]Anxiety and/or depression was defined as HADS ≥ 15, [f]anxiety was defined as HADS-A≥8, and [f]depression was defined as HADS-D≥8. Fatigue defined as FSS ≥ 5. [h]p value between ischemic stroke and NSTEMI ∗P value ≤0.05 compared with normative data.

except for the subtest Inhibition/Switching (p =.03) where the stroke group scored worse.

Ischemic stroke patients scored worse than normative data for Trail making test B (p =.02), Color naming (p <.001), Color reading (p =.001), Inhibition (p <.001), and Inhibition/Switching (p =.000). NSTEMI patients scored worse than normative data in the subtest Color naming (p =.02) and Inhibition/Switching (p =.02).

The percentage of subjects with ≥2 abnormal cognitive tests was 77% in the ischemic stroke patients, and 84% in the NSTEMI patients (p=.05).

There was a significant gender difference in the color-word inhibition test in the patient group where males soored worse (p=.05), but no significant gender difference in the control group (table available on request).

Table 3 shows that performance on most tests (memory, mental flexibility, mental speed, and inhibition and executive functions) was independently associated with education and depression and, to a lower degree, with age, gender, and fatigue. Stratifying age groups did not change this (table available on request). We performed the same analyses in the stroke and NSTEMI patients separately and found that the association between age and cognitive impairment became significant in one more test (5 of 13 cognitive tests), wheras the result for the NSTEMI group was unchanged. There was an association between diabetes mellitus and color inhibition and between overweight and inhibition error (table ii in suppmelentary data).

There were significant differences as a function of laterality in Verbal fluency and the inhibition part of the Color-Word inhibition test, with higher prevalence of deficient scores if infarctions were located in the left versus right hemisphere (Table 4). There were no significant differences in cognitive impairment, anxiety, depression, and fatigue between subcortical and cortical infarctions (Table 4).

The mean value of the aphasia score at 12 months in the ischemic stroke patients was 51.7 (SD = 1.1) of a total of 52 points.

*Fatigue* was as follows: the prevalence of fatigue was higher in the ischemic stroke than NSTEMI patients (29% versus 15%, p =.002).

*5.2. Anxiety and Depression.* There was a difference in the prevalence of combined anxiety and depression measured

Table 3: Linear regression analyses with cognitive tests as dependent variables showing beta values for all independent variables (beta).

| | Age | Males | Ischemic stroke vs NSTEMI | Higher education | Marital stage | HAD-A | HAD-D | FSS |
|---|---|---|---|---|---|---|---|---|
| 10-words learning task[a] | -.17∗ | -.18∗ | .19∗ | .15∗ | -.04 | -.08 | -.03 | -.06 |
| 10-words learning task- delayed[ab] | -.20∗ | -.17∗ | .04 | .13∗ | -.05 | -.07 | -.03 | -.13 |
| Trail-making A[c] | -.04 | -.002 | -.04 | .26∗ | -.09 | .08 | -.09 | .02 |
| Trail-making B[c] | -.04 | -.08 | -.03 | .33∗ | -.04 | -.03 | -.13∗ | -.02 |
| Verbal fluency[c] | -.09∗ | -.10∗ | .01 | .30∗ | -.01 | .01 | -.08 | -.10 |
| *Color-word interference tests* | | | | | | | | |
| Color naming[c] | .01 | -.12 | -.06 | .19∗ | -.06 | .03 | -.19 | -.08 |
| Color reading[c] | .08 | -.003 | -.07 | .24∗ | -.02 | .12 | -.15∗ | -.10 |
| Color inhibition[c] | -.02 | -.10∗ | -.08 | .27∗ | -.002 | .02 | -.09 | -.13∗ |
| Color inhibition/switching[c] | -.02 | -.09∗ | -.06 | .24∗ | .01 | .03 | -.09 | -.15∗ |
| Error scores | | | | | | | | |
| Naming errors[d] | -.11∗ | -.02 | -.04 | .03 | .06 | -.02 | -.17∗ | .06 |
| Reading errors[d] | -.04 | -.11 | .04 | -.04 | .14 | .07 | .06 | -.10 |
| Inhibition errors[c] | -.09 | .06 | -.06 | -.01 | -.04 | .06 | -.13 | -.05 |
| Inhibition/switching errors[c] | .06 | -.06 | -.07 | .16∗ | .01 | .03 | .00 | -.13∗ |

[a]Not adjusted for age and educational level in a linear model, [b]tested with 5 minutes delay, [c]scaled score adjusted for age, and [d]cumulative adjusted for age percentage. Significant difference with normative data is labeled with ∗.

Table 4: Chi square analyses of correlation between cognitive and emotional symptoms and location of infarction.

| | Subcortical infarctions n= 108 (%) | Cortical infarctions n=97 (%) | p | Left side n= 94 (%) | Right side n= 85 (%) | p |
|---|---|---|---|---|---|---|
| 10-word learning task[a] | 10 (9.4) | 3 (3.1) | .07 | 7 (7.5) | 4 (4.6) | .4 |
| 10-word learning task delayed[ab] | 10 (9.4) | 6 (6.3) | .4 | 7 (7.6) | 7 (8.2) | .9 |
| Trail-making A[c] | 6 (5.6) | 5 (5.2) | .9 | 5 (5.3) | 6 (6.9) | .7 |
| Trail-making B[c] | 19 (17.6) | 12 (12.4) | .3 | 17 (18.1) | 8 (9.2) | .08 |
| Verbal fluency[c] | 15 (13.9) | 15 (15.5) | .8 | 17 (18.1) | 7 (8.1) | .05 |
| *Color-Word Interference tests* | | | | | | |
| Color naming[c] | 23 (21.3) | 21 (21.7) | 1.0 | 18 (19.2) | 14 (16.1) | .6 |
| Color reading[c] | 24 (22.4) | 15 (15.5) | .2 | 21 (22.3) | 11 (12.6) | .09 |
| Color inhibition[c] | 16 (14.8) | 15 (15.6) | .9 | 21 (22.3) | 5 (5.6) | .001 |
| Color inhibition/switching[c] | 24 (22.2) | 22 (22.3) | .9 | 21 (22.3) | 15 (17.2) | .4 |
| Error scores | | | | | | |
| Naming errors[d] | 6 (5.6) | 6 (6.2) | .8 | 8 (8.5) | 5 (5.6) | .5 |
| Reading errors[d] | 9 (8.3) | 10 (10.3) | .6 | 8 (8.5) | 10 (11.5) | .5 |
| Inhibition errors[c] | 8 (7.4) | 4 (4.2) | .3 | 11 (11.8) | 5 (5.8) | .2 |
| Inhibition/switching errors[c] | 6 (5.6) | 10 (10.4) | .2 | 8 (8.6) | 9 (10.3) | .7 |
| No of abnormal cogn tets | 40 (38.8) | 32 (33.3) | .4 | 36 (39.6) | 24 (28.2) | .1 |
| *Questionnaires* | | | | | | |
| HADS[e] | 23 (22.6) | 11 (12.1) | .06 | 18 (19.8) | 11 (13.4) | .3 |
| HADS-A [f] | 25 (24.3) | 15 (16.1) | .2 | 22 (23.9) | 12 (14.5) | .1 |
| HADS-D [f] | 13 (12.4) | 12 (12.9) | .9 | 11 (12.0) | 11 (12.9) | .8 |
| Fatigue severity scale (FSS) [g] | 32 (30.2) | 24 (25.5) | .5 | 26 (27.7) | 23 (28.1) | 1.0 |

[a]Adjusted for age and educational level, [b]tested with 5 minutes delay, [c]scaled score, and [d]cumulative percentage.[e]Anxiety and/or depression was defined as HADS ≥ 15, [f]anxiety was defined as HADS-A≥8, and [f]depression was defined as HADS-D≥8. Fatigue was defined as FSS ≥ 5.

by total HADS score between ischemic stroke and NSTEMI patients, with a significantly larger proportion of stroke patients (16%) scoring above the cutoff than NSTEMI patients (0%) (p =.00). However, there were no significant differences in the symptoms of either anxiety (p =.2) or depression (p =.06).

## 6. Discussion

*6.1. Cognitive Function.* The differences between patients with ischemic stroke and NSTEMI were not statistically significant on most tests, even though the ischemic stroke patients scored numerically worse on all cognitive tests except verbal fluency and reading errors. This trend may suggest that the ischemic stroke patients have slightly more encompassing cognitive problems than NSTEMI patients do. However, given that ischemic stroke patients have demonstrated brain lesions, it is surprising that the difference on cognitive function between the two groups is so slight. One explanation may be the low NIHSS. We only found a modest association between the risk factors diabetes and overweigt, and impairment of the cognitive tests as shown in table ii in supplemental material. Cerebrovascular risk factors are associated with development of cerebrovascular changes, which increases with increasing age. An age-dependent association between smoking and white matter hyperintensities is found [33]. Our patients population is relatively young, something which may explain the lack of association between cognitive impairment and risk factors. It is known that cerebrovascular risk factors also increases the risk of Alzheimer's disease [34] and our findings may reflect a preclinical stage of this neurodegenerative disease. NSTEMI patients may also have vascular changes in the brain; this is unknown because no brain imaging was done in the NSTEMI group.

The NSTEMI group scored significantly worse on some cognitive tests compared to the normative data (Table 2), which suggests that NSTEMI patients also have a cerebrovascular disease. This finding is consistent with a prior study that found that cognitive outcomes after a coronary syndrome were similar to minor stroke [35]. Both ischemic stroke and NSTEMI patients may have prior cerebrovascular lesions, but our study has no data on this. We therefore do not know if prior cerebrovascular lesions can explain this lack of difference. Furthermore, many NSTEMI patients are treated with a coronary intervention, which can cause silent infarctions in the brain, even though a recent study did not find significant cognitive impairment after coronary angiography and percutaneous coronary intervention [36, 37]. However, NSTEMI patients in our study are significantly older compared to the minor stroke patients which increases the risk of neurodegenerative diseases such as early Alzheimer's disease.

The proportion with more than two abnormal cognitive tests was 77% in ischemic stroke patients and 84% in NSTEMI patients. This suggests that both patient groups are associated with a generalized cognitive dysfunction. It also highlights that there are important cognitive sequelae following vascular disease for the majority of the patients regardless of where the disease manifests itself.

Patients with ischemic stroke showed significant deficits in several cognitive domains compared to normative data. Areas of dysfunction include mental flexibility, mental speed, and inhibition. These higher order cognitive functions underpin executive functioning, which encompass supervisory skills that are crucial to successful and purposeful goal-directed behavior [38]. These functions are important in planning and implementation of activities. Impaired executive dysfunction can have detrimental effect on social function and the ability to stay in work.

Increasing age showed significant correlation with lower scores on several cognitive tests, as expected because cerebrovascular changes increase with increasing age. The slight difference in the results of the cognitive tests in the stroke and NSTEMI group is hardly clinical significant. Males showed significantly lower scores on several cognitive tests than females at the same age, despite no difference in educational level, which can possibly be explained by higher load of vascular disease in males [39]. This effect was clearer in the NSTEMI patients.

Employment was more frequent among NSTEMI patients than among ischemic stroke patients even though NSTEMI patients were older. A possible explanation is that some ischemic stroke patients may have had cognitive disabilities prior to the index stroke because of chronic cerebrovascular disease. Perhaps a more insidious onset of cognitive difficulties in the NSTEMI patients permits a gradual accommodation to their vocation despite cognitive difficulties.

The location of the ischemic lesion only influenced two of 13 cognitive tests and did not seem to be a strong determining factor for cognitive function. However, both tests were verbal and were more affected by left hemisphere lesions, which is in the direction expected given that language normally is located in the left hemisphere.

*6.2. Fatigue.* We found a high prevalence of fatigue among the ischemic stroke patients, which is consistent with prior studies [2, 3, 9, 40–42]. The prevalence in other studies varies between 23 and 40%, compared to 29% in our study. The prevalence in the NSTEMI-group was low compared to the study of Eckhardt et al. [43]. Younger NSTEMI patients and fewer patients with cardiac failure in our study may partly explain these discrepancies.

*6.3. Anxiety and Depression.* The prevalence of combined anxiety and depression (HADS>15) was significantly higher in the ischemic stroke patients than NSTEMI patients, but the difference in pure anxiety or depression symptoms was not significant. The scores were compared to the prevalence of anxiety and depression in the population-based study of HUNT (The Nord-Trondelag Health study) [44] where about 9% of the population reported elevated anxiety and 5% elevated depression (on HADS). There were significantly more anxiety and depression disorders in the ischemic stroke group than in the study of HUNT. However, this was not the case for the NSTEMI group.

As expected, reported depression was associated with lower scores on some cognitive tests. Cognitive dysfunction among patients with reported depression is a common

finding [45]. Reported anxiety was not associated with change in cognitive performance. This finding is in contrast to prior studies investigating a stroke population [46] and in healthy individuals [47]. Both of these studies found that anxiety had a detrimental impact on cognitive functions. Anxiety and depression disorders are treatable and may hamper recovery if untreated. Depression is in itself found to be associated with worsening and enduring cognitive dysfunction even after remission [48]. The current findings of a broad cognitive dysfunction in both patient groups suggest that they may have less cognitive reserves and may therefore be extra vulnerable to events of adverse effects on cognitive function including depression.

*Strengths and weaknesses* are as follows: strength of this study is the large number of patients and inclusion of controls. It is a multicenter study and reflects the patients in the middle and western part of Norway. The existence of normative data made it possible to detect a significant difference for both patients and controls compared to the normative data.

There are some weaknesses. Recruitment of individuals to the control group was difficult which may have biased selection. Different study nurses and one neurologist performed testing. Some patients live far from the hospital. A long traveling distance may have influenced the ability to concentrate in performing cognitive tests. Lack of registration of proportion of percutaneous coronary intervention (PCI) in the NSTEMI-group is another limitation, because PCI may cause ischemic lesions in the brain as shown in a study from 2016 [36, 37].

## 7. Conclusion

We found no significant difference in cognitive function between minor ischemic stroke patients and NSTEMI patients. However, the stroke patients and to a lesser degree NSTEMI patients had reduced cognitive function compared to normative data, especially executive function, on long term follow-up. Prevalence of cognitive impairment increased with increasing age. Presence of risk factors and gender seemed not to substantially influence cognitive function. Depression was independently associated with low scores on cognitive tests, suggesting that treatments targeting depression can be a valuable approach to improve cognitive disabilities in these patients. The prevalence of anxiety, depression, and fatigue was significantly higher in the stroke group compared to the NSTEMI group.

## Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

Halvor Næss is the main supervisor. He has been involved in protocol development, gaining ethical approval, data analysis, and the first draft of the manuscript. Hanne Ellekjær is a cosupervisor and has been involved in protocol development and advice in the study period. Arne Gramstad is a neuropsychologist and has been involved in protocol development, especially the selection of cognitive tests and data analysis and interpretation. Magnus Tallaksen Reiestad is a neuropsychologist and has been involved in data analysis and interpretation. Rune Midgard is a cosupervisor and has been involved in protocol development. Sigrid Botne Sando has been involved in the protocol development, especially the selection of cognitive tests. Egil Jonsbu has been involved in the protocol development with focus on anxiety and depression tests. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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## Supplementary Materials

Table i. Chi square test of gender differences in risk factors∗, cognitive tests, HADS, and FSS in minor stroke and NSTEMI patients. Table ii. Linear regression analyses with cognitive tests as dependent variables showing beta values for all independent variables (beta). *(Supplementary Materials)*

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# Paper II

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ORIGINAL ARTICLE

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# The development of cognitive and emotional impairment after a minor stroke: A longitudinal study

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**Objectives:** To study the development of cognitive and emotional symptoms between 3 and 12 months after a minor stroke.

**Material and Methods:** We included patients from stroke units at hospitals in the Central Norway Health Authority and from Haukeland University Hospital. We administered a selection of cognitive tests, and the patients completed a questionnaire 3 and 12 months post-stroke. Cognitive impairment was defined as impairment of ≥2 cognitive tests.

**Results:** A total of 324 patients completed the 3-month testing, whereas 37 patients were lost to follow-up at 12 months. The results showed significant improvement of cognitive function defined as impairment of ≥2 cognitive tests ($P$ = .03) from months 3 to 12. However, most patients still showed cognitive impairment at 12 months with a prevalence of 35.4%. There is significant association between several of the cognitive tests and hypertension and smoking ($P$ = .002 and .05). The prevalence of depression, but not anxiety, increased from 3 to 12 months ($P$ = .04). The prevalence of fatigue did not change and was thus still high with 29.5% after 12 months.

**Conclusions:** This study shows that an improvement of cognitive function still occurs between 3 and 12 months. Despite this, the prevalence of mostly minor cognitive impairment still remains high 12 months after the stroke. The increasing prevalence of

depressive symptoms highlights the importance of being vigilant of depressive symptoms throughout the rehabilitation period. Furthermore, high prevalence of fatigue persisted.

**KEYWORDS**
cerebrovascular diseases, depression, mild cognitive impairement, psychiatry, quality of life, strokes

## 1 | INTRODUCTION

A majority of ischemic stroke patients have mild and quickly resolving, usually sensorimotor symptoms. National institute of health stroke scale (NIHSS) ≤5 is used as a definition of minor stroke in earlier publications[1] but a consensus on the definition is lacking. There is growing evidence that even minor strokes and transitoric ischemic attack (TIA) can cause persisting disabling cognitive symptoms.[2] A recent study found brain atrophy and cognitive decline after a TIA suggesting that even a transient cerebrovascular event leads to secondary damage in the brain[3] independent on the focal ischemic lesion.

Improvement of cognitive impairment occurs in a substantial amount of patients. One study found significant improvement of neuropsychological test results from baseline to 6 and 12 months, but significant and persistent residual cognitive impairment after minor stroke and TIA.[2] Patients with coronary artery disease, atrial fibrillation, and >50% stenosis of the internal carotid artery had the most severe cognitive impairment. A stroke registry study[4] reported cognitive functioning, using the Mini-Mental State Examination (MMSE), to be impaired in 13% of patients after 12 months.[4]

Minor strokes may also have psychological consequences. The prevalence of depression and anxiety 12 months after a minor stroke has been reported to be 26%[5] and 25%[6] 1 year after the stroke. Poststroke fatigue was found in 34.7% of the patients at 12 months,[7] suggesting fatigue to be a relatively common and persistent complaint.

Cognitive and psychological symptoms are not necessarily detected before discharge and may first be recognized when the stroke patient meets demands in daily life.

Studies looking at improvement beyond 3 months are few. One study found that the recovery rate was greatest within the first 6 months but continued for up to 18 months for some patients.[8] Significant predictors of recovery included stroke severity, no history of previous stroke, diabetes, peripheral artery disease, women aged <65 years, and decreasing time between the stroke and the baseline assessment.[8]

A consensus of criteria for vascular cognitive impairment is also lacking. In one study, vascular cognitive impairment is proposed as a combination of cognitive disorder and history of vascular disease where the vascular disease is the dominant pathology behind the cognitive deficits.[9]

The aim of this study was to describe the prevalence and development of cognitive impairment, anxiety, depression and fatigue between 3 and 12 months after an ischemic stroke, and factors associated with persisting symptoms.

## 2 | MATERIAL AND METHODS

Ischemic stroke was defined according to the Baltimore-Washington Cooperative Young Stroke Study Criteria[10] comprising neurological deficits lasting more than 24 hours because of ischemic lesions, or transient ischemic attacks where CT or MRI showed infarctions related to the clinical findings. Inclusion criteria: To include subjects in working age, patients 18-70 years with minor ischemic stroke with preserved function in the range of the modified Rankin Scale (mRS) 0-2 were chosen.

Emotional impairment is used to define anxiety and/or depression.

### 2.1 | Recruitment

Patients were recruited consecutively from stroke units at Molde Hospital, Haukeland University Hospital, and St Olav's Hospital. Patients from other participating stroke units in hospitals in the Central Norway Health Authority (department of neurology at St Olav's Hospital, department of medicine at Kristiansund, Volda, and Ålesund Hospitals) were included whenever practical, but not always consecutively. The recruitment period lasted from Janaury 1, 2013 to December 31, 2016.

### 2.2 | Exclusion criteria

Patients with a major stroke defined as mRS >2 day 7/at discharge if before and patients with deterioration in mRS to more than 2 in the observational period of any cause were excluded.

### 2.3 | Baseline investigation

The patients underwent routine examination with NIHSS[11] and risk factors including hypertension, diabetes mellitus, hypercholesterolemia, smoking, overweight, and brain imaging with CT and/or MRI. They were treated according to Norwegian guidelines for ischemic stroke. Most patients with mRS ≤2 after 7 days/at discharge if earlier had no need for further rehabilitation and were discharged to their home.

Prestroke mRS and prevalence of anxiety and depression were registered.

Demographic data were collected from the initial hospital stay.

### 2.4 | Assessment of cognitive and emotional function

#### 2.4.1 | Global and visuospatial cognitive function

Mini-Mental State Examination[12] and clock drawing test[13] were used as a screening of global cognitive function. Clock drawing test assesses also visuospatial function.[13]

*Executive function* was tested with trail-making A and B,[14] color-word interference test, and verbal fluency. The color-word interference and verbal fluency tests are subtests from the Delis-Kaplan Executive Function System (d-kefs) neuropsychological test battery.[15]

*Memory* was tested with the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) ten-Word learning task.[16]

Cognitive impairment was defined as impairment of ≥2 cognitive tests.

Scores below 1.5 SD of the mean were characterized as abnormal.

The Ullevål aphasia screening test was used to test aphasia.[17]

Informant questionnaire for cognitive decline in the elderly (IQCODE) graded from 1 to 5 (much better, better, unchanged, worse, and much worse) was registered at 3 months.

#### 2.4.2 | Anxiety and depression

Hospital and Anxiety and Depression Scale (HADS) was used to assess anxiety (HADS-A) and depression (HADS-D).[18] A score ≥8 on HADS-A or HADS-D items indicates possible presence of anxiety or depression, with sensitivity and specificity about 0.80 for both scales,[19] and a total score ≥15 indicates combined anxiety and depression.

#### 2.4.3 | Fatigue

Fatigue Severity Scale (FSS) was used to assess fatigue.[20] FSS is a nine-item questionnaire that assesses the effect of fatigue on daily living. Each item is a statement on fatigue that the subject rates from 1 "completely disagree" to 7 "completely agree."[21] Fatigue is defined as FSS score ≥5.[21]

Cognitive testing was performed by trained research nurses or by the neurologist responsible for the study.

Testing and completing of questionnaires was done at 3 and 12 months after onset of the stroke.

### 2.5 | Statistics

Correlation factor test, Mc Nemars test, and linear regression were used in the analyses.

In the linear regression analyses, change in results between 3 and 12 months was used as the dependent variable. Gender, age, and education were forced into each analysis to adjust for potential confounding. Analyses of other independent variables as number of risk factors, marital stage, and employment were done, but excluded because of lack of significant correlation.

STATA 14 (Statacorp) was used for analyses.

## 3 | RESULTS

In total, 325 ischemic stroke patients were included; 1 was excluded because of wrong diagnosis and 2 because of deterioration to mRS >2 at 12 months. Lost to follow-up between 3 and 12 months was 37 patients. The reason was mainly that patients did not meet their appointment. Table 1 shows baseline demographic data and vascular risk factors.

The mean age was 58 (SD 10) years. Baseline mRS was 0.3. Prevalent risk factors were hypertension (54%), BMI >25 (58%), hypercholesterolemia (47%), and smoking (35%). Assessment of function status by mRS score prestroke and day 7/at discharge was 0.3 (SD 0.6) and 1.1 (SD 0.8). National institute of health stroke scale day 7/at discharge was 0.8 (SD 1.0), at 3 months 0.2 (SD 0.6), and at 12 months 0.2 (SD 0.4). The mean value of the aphasia scores at 3 and 12 months was 51.7 (SD 1.1) and 51.8 (SD 1.0) of a total of 52 points.

The average number of impairment of cognitive tests at 3 and 12 months was 1.8 (SD 2.1) and 1.7 (SD 2.4).

Table 2 shows significantly lower prevalence of impairment in 10-Word test delayed recall, naming error test and impairment

**TABLE 1** Baseline data

| | Patients (%) |
|---|---|
| Total | 324 (%) |
| Age (mean) | 58.0 (SD 10.0) |
| Females | 120 (37) |
| Males | 204 (63) |
| Married/partner | 244 (75) |
| Single | 67 (21) |
| Widow/widower | 12 (4) |
| Education (1, 2, 3)[a] | 51 (16) |
| | 148 (46) |
| | 121 (37) |
| Employed before event | 217 (67) |
| Anxiety and/or depression before event | 46 (10) |
| Risk factors | |
| Hypertension | 174 (54) |
| Diabetes mellitus | 39 (12) |
| Atrial fibrillation | 46 (14) |
| BMI mean (SD) | 26.7 (4.4) |
| Overweight (BMI ≥25) | 189 (58) |
| Hypercholesterolemia[b] | 151 (47) |
| Smoking[c] | 114 (35) |
| Prestroke mRS | 0.3 (SD 0.6) |
| Baseline mRS (SD) | 1.1 (SD 0.8) |
| Baseline national institute of health stroke scale (SD) | 0.8 (SD 1.0) |
| Lost to follow-up | 37 (11) |

*Note:* [a]1 Primary school, 2 high school, 3 bachelor/university.
[b]Treatment with cholesterol-lowering medication.
[c]Current smoker or smoking within the last 12 mo.

**TABLE 2** Prevalence of cognitive impairment, fatigue, anxiety, and depression at 3 and 12 mo (McNemars test)

| | Prevalence 3 mo (%) | Prevalence 12 mo (%) | Odds ratio | *P* |
|---|---|---|---|---|
| Memory | | | | |
| 10-word learning task[a,b] | 7.7 | 6.0 | 2 | .2 |
| 10-word learning task, delayed recall[a,b,c] | 14.0 | 7.8 | 2.9 | .003 |
| Executive function | | | | |
| Trail-making A[a] | 6.2 | 5.2 | 1.4 | .6 |
| Trail-making B[a] | 15.0 | 11.5 | 1.5 | .3 |
| Verbal fluency[a] | 14.2 | 11.2 | 1.8 | .2 |
| Color-word interference tests | | | | |
| Color-word naming[a] | 25.2 | 20.1 | 2 | .07 |
| Color-word reading[a] | 18.7 | 18.1 | 0.8 | .6 |
| Color-word inhibition[a] | 16.3 | 13.2 | 1.6 | .2 |
| Color-word inhibition/switching[a] | 24.1 | 20.1 | 1.4 | .2 |
| Error scores | | | | |
| Naming errors[d] | 7.8 | 5.2 | 1.4 | .04 |
| Reading errors[d] | 13.0 | 10.0 | 1.7 | .09 |
| Inhibition errors[a] | 12.9 | 5.9 | 1.3 | .7 |
| Inhibition/switching errors[a] | 6.9 | 8.7 | 0.6 | .2 |
| Impairment ≥2 cognitive tests | 41.6 | 35.4 | 1.8 | .03 |
| Anxiety and depression | | | | |
| HADS[e] | 15 | 16 | 0.7 | .3 |
| HADS-A[f] | 20 | 18 | 1.3 | .4 |
| HADS-D[g] | 9 | 12 | 0.4 (2.6) | .04 |
| Fatigue | | | | |
| Fatigue Severity Scale (FSS)[h] | 25.6 | 29.5 | 0.7 (1.5) | .2 |

*Note:* Correction for multiple variable testing is not done.
[a]Scaled score.
[b]Adjusted for age and educational level.
[c]Tested with 5-min delay.
[d]Cumulative percentage defined as 2 (naming errors) and 1 (reading error).
[e]Anxiety and/or depression defined as HADS ≥15.
[f]Anxiety was defined as HADS-A ≥8.
[g]Depression was defined as HADS-D ≥8.
[h]Fatigue defined as FSS ≥5.

in ≥2 cognitive tests after 12 months compared with 3 months. In contrast, the number of patients with HADS-D >8 increased significantly from 3 to 12 months.

Of a total of 15 cognitive tests, Table 3 shows a significant correlation between hypertension, five cognitive tests, and HADS-anxiety at 12 months. There was a significant correlation between diabetes mellitus and one cognitive test, and for BMI >25, there was a significant correlation with three cognitive tests. For atrial fibrillation and hypercholesterolemia, there were no significant correlations for any of the cognitive tests, HADS-A, HADS-D, or fatigue. There was a significant correlation between smoking and eight cognitive tests.

There was a significant correlation between increasing number of risk factors and 3 of 15 cognitive tests at 12 months, but no significant correlation with HADS-A, HADS-D, or fatigue (Table S1).

Table 4 shows the correlation between the difference in test results between 3 and 12 months and age, gender, education, and depression. There was a significant correlation between age and the difference in test results of 10-word learning task, and gender and the difference in inhibition/switching errors. For prevalence of depression at 12 months, there was a significant correlation between the difference in the trail-making A, 10-word learning task delayed, inhibition error, and inhibition/switching errors.

**TABLE 3** Correlation between cognitive function, anxiety, depression, and fatigue at 12 mo and vascular risk factors (Spearmans test; *P*)

| | Hypertension | Diabetes mellitus | BMI >25 | Atrial fibrillation | Hyper cholesterolaemia | Smoking |
|---|---|---|---|---|---|---|
| Global cognitive function and visuospatial test | | | | | | |
| MMSE[a] | −0.1 (0.02) | −0.08 (0.2) | −0.07 (0.2) | 0.02 (0.6) | 0.04 (0.5) | −0.1 (0.04) |
| Clock drawing test | −0.01 (0.9) | 0.07 (0.3) | −0.06 (0.3) | −0.04 (0.5) | 0.05 (0.4) | 0.02 (0.8) |
| Memory | | | | | | |
| 10-word learning task[b] | −0.2 (0.003) | −0.04 (0.5) | −0.08 (0.2) | −0.01 (0.8) | −0.08 (0.2) | −0.09 (0.1) |
| 10-word learning task delayed recall[c] | −0.1 (0.05) | 0.02 (0.8) | −0.1 (0.06) | 0.05 (0.4) | −0.05 (0.4) | −0.1 (0.1) |
| Executive function | | | | | | |
| Trail-making A | 0.1 (0.01) | 0.06 (0.03) | 0.09 (0.1) | 0.05 (0.4) | −0.07 (0.2) | −2 (0.006) |
| Trail-making B | 0.2 (0.002) | −0.03 (0.6) | 0.2 (0.004) | 0.04 (0.5) | −0.06 (0.3) | 0.1 (0.03) |
| Verbal fluency | 0.02 (0.8) | −0.05 (0.4) | −0.01 (0.9) | −0.05 (0.4) | −0.01 (0.9) | −0.1 (0.04) |
| Color-word interference tests | | | | | | |
| Color-word naming[d] | −0.01 (0.9) | −0.07 (0.2) | −0.05 (0.4) | 0.05 (0.4) | −0.02 (0.8) | 0.1 (0.02) |
| Color-word reading[d] | −0.05 (0.4) | 0.01 (0.9) | −0.04 (0.5) | −0.01 (0.8) | 0.05 (0.4) | 0.2 (0.01) |
| Color-word inhibition[d] | −0.07 (0.2) | −0.06 (0.3) | −0.06 (0.3) | 0.05 (0.4) | 0.02 (0.8) | 0.2 (0.002) |
| Color-word inhibition/switching[d] | −0.02 (0.7) | −0.00 (1.0) | −0.01 (0.9) | 0.06 (0.3) | 0.05 (0.4) | 0.1 (0.04) |
| Naming errors[e] | 0.04 (0.5) | 0.07 (0.2) | 0.00 (0.9) | −0.02 (0.8) | −0.06 (0.3) | −0.01 ( 0.8) |
| Reading errors[e] | −0.03 (0.6) | 0.03 (0.6) | 0.03 (0.6) | −0.02 (0.7) | −0.05 (0.3) | 0.05 (0.4) |
| Inhibition errors[d] | 0.1 (0.04) | −0.1 (0.8) | 0.1 (0.01) | −0.5 (0.3) | 0.0 (0.7) | 0.06 (0.3) |
| Inhibition/switching errors[d] | −0.01 (0.8) | −0.02 (0.6) | 0.1 (0.04) | −0.02 (0.7) | 0.7 (0.3) | 0.5 (0.3) |
| Anxiety and depression | | | | | | |
| HADS[f] | −0.08 (0.2) | 0.05 (0.4) | −0.01 (0.8) | −0.02 (0.8) | 0.01 (0.9) | 0.00 (1.0) |
| HADS-A[g] | −0.2 (0.01) | 0.09 (0.1) | −0.04 (0.4) | −0.05 (0.4) | −0.02 (0.8) | −0.04 (0.5) |
| HADS-D[h] | 0.01 (0.9) | 0.2 (0.8) | 0.01 (0.9) | 0.02 (0.7) | 0.03 (0.5) | 0.05 (0.4) |
| Fatigue | | | | | | |
| Fatigue Severity Scale (FSS)[i] | −0.06 (0.3) | 0.02 (0.7) | 0.01 (0.8) | 0.03 (0.7) | −0.02 (0.8) | 0.1 (0.09) |

*Note:* Correction for multiple variable testing is not done.
[a]Mini-mental state.
[b]Adjusted for age and educational level.
[c]Tested with 5-min delay.
[d]Scaled score.
[e]Cumulative percentage defined as 2 (naming errors) and 1 (reading error).
[f]Anxiety and/or depression defined as HADS ≥15.
[g]Anxiety was defined as HADS-A ≥8.
[h]Depression was defined as HADS-D ≥8.
[i]Fatigue defined as FSS ≥5.

## 4 | DISCUSSION

### 4.1 | Cognitive function

Table 2 shows a significant reduction in prevalence of impairment of ≥2 cognitive domains from 3 to 12 months. This may be the most important clinical finding confirming a certain improvement of cognitive function beyond 3 months. Nevertheless, 35% of the patients had persisting cognitive impairments after 12 months in the meaning of impairment of ≥2 cognitive domains. The number is high considering the low NIHSS at 12 months. However, the impairment is relatively mild on a group level, with an average number of impairment of cognitive tests of 1.7.

**TABLE 4** Regression analyses of the difference (raw scores) between 12 and 3 mo, beta (*P*)

| | Age | Gender | Education | HADS-depression (3 mo) |
|---|---|---|---|---|
| Global cognitive function and visuospatial test | | | | |
| MMSE[a] | −0.11 (0.07) | 0.08 (0.2) | −0.07 (0.2) | 0.04 (0.5) |
| Clock drawing test | 0.08 (0.2) | 0.04 (0.5) | 0.07 (0.3) | −0.08 (0.2) |
| Memory | | | | |
| 10-word learning task[b] | −0.15 (0.02) | −0.02 (0.7) | −0.11 (0.07) | −0.02 (0.7) |
| 10-word learning task delayed recall[c] | −0.08 (0.2) | 0.08 (0.2) | −0.08 (0.2) | −0.2 (0.001) |
| Executive function | | | | |
| Trail-making A | 0.003 (0.9) | 0.06 (0.3) | 0.08 (0.2) | −0.2 (0.001) |
| Trail-making B | −0.05 (0.5) | 0.06 (0.4) | −0.08 (0.2) | 0.1 (0.1) |
| Verbal fluency (FAS) | −0.09 (0.2) | −0.13 (0.04)* | 0.03 (0.6) | −0.06 (0.3) |
| Color-word interference tests | | | | |
| Color-word naming[d] | −0.08 (0.2) | 0.04 (0.6) | −0.16 (0.008) | −0.03 (0.6) |
| Color-word reading[d] | 0.08 (0.2) | −0.06 (0.3) | −0.10 (0.1) | −0.04 (0.5) |
| Color-word inhibition[d] | −0.02 (0.8) | 0.06 (0.3) | −0.03 (0.6) | −0.05 (0.4) |
| Color-word inhibition/switching[d] | 0.02 (0.8) | 0.04 (0.5) | −0.08 (0.2) | 0.07 (0.3) |
| Error tests | | | | |
| Naming error[e] | −0.03 (0.6) | −0.05 (0.4) | 0.04 (0.5) | 0.01 (0.9) |
| Reading error[e] | −0.08 (0.2) | 0.001 (0.9) | −0.14 (0.03) | 0.03 (0.7) |
| Inhibition error[d] | 0.06 (0.3) | −0.03 (0.6) | −0.04 (0.5) | 0.16 (0.01) |
| Inhibition/switching error[d] | −0.02 (0.7) | −0.07 (0.2) | 0.06 (0.3) | 0.13 (0.04) |
| Anxiety and depression | | | | |
| HADS[f] | 0.07 (0.2) | 0.09 (0.2) | −0.03 (0.6) | |
| HADS-A[g] | 0.1 (0.1) | 0.08 (0.2) | 0.04 (0.5) | 0.05 (0.4) |
| HADS-D[h] | 0.02 (0.7) | 0.08 (0.2) | −0.1 (0.1) | |
| Fatigue | | | | |
| Fatigue Severity Scale (FSS) | 0.05 (0.4) | 0.02 (0.7) | −0.07 (0.3) | −0.08 (0.1) |

*Note:* Correction for multiple variable testing is not done.
[a]Mini-mental state.
[b]Adjusted for age and educational level.
[c]Tested with 5-min delay.
[d]Scaled score.
[e]Cumulative percentage defined as 2 (naming errors) and 1 (reading error).
[f]Anxiety and/or depression defined as HADS ≥15.
[g]Anxiety was defined as HADS-A ≥8.
[h]Depression was defined as HADS-D ≥8.

Hypertension and smoking are the most important risk factors associated with long-term cognitive impairment such as impairment of memory and executive functions. Some earlier studies have found an association between hypertension and cognitive decline, while others did not. One large study however found that hypertension was associated with faster cognitive decline in persons at risk for dementia.[22] The study also found that intervening strokes did not explain these findings. Heavy smokers (>20 cigarettes daily) showed a faster decline in cognitive function than non-smokers in a previous study.[23] Smoking is also identified as a risk factor for reduced cerebral perfusion, cerebral atrophy, and cerebrovascular changes.[24] Another study found an association between smoking and the amount of neuritic plaques.[25]

We found no significant correlation between atrial fibrillation and cognitive impairment in contrast to another study.[26] The low

number of patients with atrial fibrillation in our study may explain why our results did not reach statistical significance.

Depressive symptoms at 12 months seem to have some effect on the cognitive function. This is as expected because cognitive symptoms is a common finding in depressive patients.[5,27]

The number of risk factors (hypertension, atrial fibrillation, smoking, diabetes mellitus, BMI >25) had a modest influence of the cognitive function at 12 months. Vascular risk factors are also associated with development of Alzheimer's disease.[28] Our patient was younger than a typical patient developing Alzheimer's disease and had a low NIHSS at follow-up at 12 months. The plasticity of the brain is higher and the risk of neurodegeneration lower at lower age. This may explain our findings. Twelve-month observation may also be a too short period to study the development of cognitive impairment.

The mean value of IQCODE at 3 months is 3 or unchanged (SD 0.3) compared with prestroke condition.

High prevalence of overweight may indicate that a considerable number of the patients also have obstructive sleep apnea syndrome (OSAS). OSAS may have cognitive and depressive symptoms[29] which may explain some of our findings, but our study has no data on this.

Depression may be a causal mechanism of cognitive impairment and fatigue as discussed in a previous study.[27]

The possibility of a learning effect of repeated cognitive or neuropsychological testing is described in previous studies,[30,31] and one study did not find a learning effect at 1-month test-retest interval.[31] The interval of 9 months for repeated testing in our study is probably too long to cause a significant influence on the results.

### 4.2 | Anxiety and depression

There was no significant difference in anxiety between 3 and 12 months, but the prevalence was relatively high with 20% and 18%. A previous study using the same questionnaire (HADS) and same cutoff score found a prevalence of anxiety in minor stroke patients of 25% at 12 months.[6]

The prevalence of depression was significant higher with 12% at 12 months in contrast to 9% at 3 months. This is in contrast to another study which found a decrease over time from 12.9% to 8.1% between 3 and 12 months.[32] Patient characteristics in this study were quite similar except higher NIHSS (2 vs 0.2). One study found a stable situation for depressive symptoms between 3 and 12 months.[33] In that study, population about 20% of the patients had mRS >2 in contrast to our study where mRS >2 was an inclusion criterion and patients were older than our patients. This makes a comparison difficult. Early identification and treatment of depression is important as it may reduce the cognitive symptoms.

High prevalence of both cognitive impairment and fatigue at 12 months may contribute to the increase in depressive symptoms. Patients with persisting cognitive symptoms and fatigue with negative impact on daily life activities may be more prone to develop a depression over time, even though the impairment is minor.

There was no correlation between development of anxiety and prevalence of depression at 12 months, in contrast to previous studies.[34] A considerable amount of our patients had persisting depressive and/or anxiety symptoms 12 months post-stroke (Table 2).

### 4.3 | Fatigue

We found no significant difference in fatigue between 3 and 12 months. The prevalence was still high after 12 months (29.5%). A previous study found that 77.3% of their patients reporting fatigue at 6 months still reported fatigue at 12-month follow-up.[7] Fatigue is a disabling condition, and persistent fatigue is therefore important to identify. Surprisingly, there was no correlation between fatigue and cognitive impairment in our study in contrast to another study.[7] A possible explanation is that the tools used to measure fatigue are different (FSS vs FAI: Fatigue Assessment Instrument). FAI is more detailed and may be more sensitive to detect significant correlations.

### 4.4 | Strengths and weaknesses

One strength of this study is the large number of patients. It is a well-defined study cohort based on the functional classification. There were relatively few dropouts between 3 and 12 months. It is a multicenter study and reflects minor stroke patients in the middle and western part of Norway. Different study nurses performed the testing because of the multicenter design. This may create an inter-rater variability.

We do not have information about the patient's previous state, and there might be a possibility that an earlier stroke can influence on the results. Informant questionnaire for cognitive decline in the elderly was not registered at baseline. A possibility of preexisting cognitive impairment, for example, early Alzheimer's disease may therefore be a bias.

Prestroke fatigue and obstructive sleep apnea were not recorded.

The learning effect of repeated cognitive testing has to be considered.

Depression and anxiety were based on self-report (HADS), and no diagnostic interviews were performed.

## 5 | CONCLUSION

This study shows a small, but significant improvement in cognitive function from 3 to 12 months. However, the prevalence of mild cognitive impairment was still high at 12 months. The most important risk factors for persistent cognitive impairment were hypertension and smoking.

The prevalence of depression increased from 3 to 12 months. Early detection and treatment of depression is important to contribute to recovery including improvement of cognitive symptoms.

Fatigue remains a persistent symptom with a high prevalence 1 year after a minor stroke.

Overall, the findings in our study emphasize the importance of a longer term follow-up of patients with minor stroke. This is not done routinely today. For the future, we suggest a follow-up with a test battery testing memory and executive functions because these are functions of great importance in the daily living. We also recommend a screening for fatigue, anxiety, and depression.

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## CONFLICT OF INTEREST

None.

## AUTHOR CONTRIBUTIONS

HN is the main supervisor. He has been involved in protocol development, gaining ethical approval, data analysis, and the first draft of the manuscript. HE is a co-supervisor and has been involved in protocol development and advice in the study period. AG is a neuropsychologist and has been involved in protocol development, especially the selection of cognitive tests and data analysis and interpretation. MTR is a neuropsychologist and has been involved in data analysis and interpretation. RM is a co-supervisor and has been involved in protocol development. SBS has been involved in the protocol development, especially the selection of cognitive tests. EJ has been involved in the protocol development with focus on anxiety and depression tests. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

## ETHICAL APPROVAL

The ethics committee of Rogaland, Hordaland and Sogn and Fjordane (REC west) approved this study (REC number: 2012/1708).

## DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## INFORMED CONSENT

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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# Paper III

# Factors influencing employment after minor stroke and NSTEMI

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Aim: To study the effect of cognitive function, fatigue and emotional symptoms on employment after a minor ischemic stroke compared to non-ST-elevation myocardial infarction (NSTEMI).

Material and methods: We included 217 patients with minor ischemic stroke and 133 NSTEMI patients employed at baseline aged 18−70 years. Minor stroke was defined as modified Rankin scale (mRS) 0−2 at day seven or at discharge if before. Included NSTEMI patients had the same functional mRS. We applied a selection of cognitive tests and the patients completed questionnaires measuring symptoms of anxiety, depression and fatigue at follow up. Stroke patients were tested at three and 12 months and NSTEMI at 12 months.

Results: The patients still employed at 12 monthswere significantly younger than the unemployed patients and the NSTEMI patients employed were significantly older than the stroke patients (59 vs 55 years, $p < .001$). In total, 82 % of stroke patients and 90 % of the NSTEMI patients employed at baseline were still employed at 12 months ($p = 06$). Stroke patients at work after 12 months had higher education than unemployed patients. There were no difference between employed and unemployed patients in risk factors or location of cerebral ischemic lesions. Cognitive function did not change significantly in the stroke patients from three to 12 months. For stroke patients, we found a significant association between HADS-depression and unemployment at 12 months ($p = 04$), although this association was not present at three months. Lower age and higher educational level were associated with employment at 12 months for all patients.

Discussion and conclusion: Age and education are the main factors influencing the ability to stay in work after a minor stroke. Employed stroke patients were younger than the NSTEMI patients, but there was no difference in the frequencies in remaining employed. The employment rate at 12 months was high despite the relatively high prevalence of cognitive impairment in both groups.

**Keywords:** Minor stroke—Minor cognitive impairment after stroke—Poststroke fatigue—Poststroke anxiety and depression—Poststroke employment

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## Introduction

Globally, cerebrovascular disease is the second most frequent cause of disability-adjusted life-years (DALYS)[1]. The range of disability is wide. In the Norwegian stroke registry 65.3% of the patients have a relatively mild impairment defined as NIHSS (National Institute of Health Stroke Scale) between 0−5 at admission[2]. Although a consensus on the definition of minor stroke is lacking, NIHSS ≤ 5 is used in other publications[3]. Low NIHSS scores are thought to represent a good outcome. However, the scale emphasizes sensorimotor symptoms and largely ignores other important aspects, such as cognitive symptoms, fatigue, anxiety and depression, which can cause serious disability and reduced quality of life in the patients. Even minor cognitive symptoms can cause employment difficulties after a stroke. Knowledge of factors influencing the ability to return to work after an ischemic stroke is clinically important. However, few studies focus on this topic[4]. A recent study of a stroke population aged 15−49 years showed that 37.6% of the patients were out of work 1 year poststroke[5]. The study showed an association between failure to return to work and large anterior strokes, strokes caused by large artery atherosclerosis, high-risk of cardio embolism, aphasia, limb paresis and visual deficit. The majority of patients in the study[5] had a low NIHSS score at discharge. In another study, the authors found that only 41 % had returned to work after 6 months despite relatively minor neurological and functional impairments, with median NIHSS 1 at discharge from the acute care unit[6]. Early cognitive deficit was the only significant predictor for the inability to return to work. In contrast, a study of spinal cord infarctions showed that all surviving patients younger than 60 years returned to work[7] even if mRS (modified Rankin Scale) was higher among the patients with spinal cord strokes than in a control group with cerebral infarctions. This difference may be due to cognitive deficits in the cerebral infarction patients[7]. Furthermore, pre-stroke employment resulted in better patient-reported outcome of depression, fatigue, cognitive symptoms and total burden of dysfunction after a minor stroke in one study[8]. The degree of physical disability, sociodemographic factors and psychiatric comorbidity might play an important role in the post-stroke employment. A population-based study from South London Stroke Register found that black ethnicity, women, older age, diabetes and dependence in the acute phase were independently associated with lower odds of return to work[9]. Another population-based study from New Zealand showed that psychiatric comorbidity measured at 28 days after a stroke was a strong independent predictor for not returning to work[10]. However, an association between depression and the ability to return to work was not confirmed in a more recent study[11]. In a publication addressing employment after acute myocardial infarction in a large patient cohort, only seven % of the patients employed at baseline were unemployed at 12 months[12]. This is a markedly lower prevalence compared to studies of stroke patients.

The aims of our study was to investigate employment in a patient population after a minor stroke compared to a control group of non-ST elevation myocardial infarction (NSTEMI) and assess predictors associated with the ability to return to work. We chose NSTEMI patients as the control group under the assumption that both patients had a vascular disease with a similar profile of risk factors.

## Material and methods

We performed a 12 months follow-up of patients employed at baseline with ischemic stroke with a selection of cognitive tests and questionnaires measuring symptoms of anxiety, depression and fatigue. A control group of NSTEMI patients was included.

Regarding power we did a power calculation before study start indicating a need for 600 patients in each group. Due to practical reasons the final sample size was a lot lower, meaning that the study is probably too small to detect all of the relevant differences between groups.

*Ischemic stroke patients:* Ischemic stroke was defined in accordance with the Baltimore-Washington Cooperative Young Stroke Study Criteria[13] comprising neurological deficits lasting more than 24 h due to ischemic lesions, or transient ischemic attacks where CT or MRI showed infarctions related to the clinical findings.

### *Inclusion criteria*

Ischemic stroke patients aged 18−70 years with minor stroke defined as mRS 0−2[14] at day 7 or at discharge if before. NSTEMI patients aged 18−70 years with mRS 0−2. Stroke and NSTEMI patients were included in the same time period.

### *Exclusion criteria*

Patients with a major stroke defined as mRS > 2 at day 7 or at discharge if before, and patients with deterioration in mRS to more than 2 of any cause in the observational period. NSTEMI patients with mRS > 2 of any cause were excluded.

### *Recruitment*

We recruited ischemic stroke patients consecutively from stroke units at Molde hospital, Haukeland University hos-

pital and St Olav's hospital. Patients from other participating stroke units (Department of Neurology at St Olavs hospital, Kristiansund hospital, Volda hospital and Aalesund hospital) were included whenever practical, but not always consecutively. The recruitment period lasted for four years from 1 Jan 2013 until 31 Dec 2016. NSTEMI patients were recruited from Haukeland University Hospital, Ålesund, Molde and Kristiansund Hospitals in the same time period.

The stroke patients were assessed at three and 12 months and the NSTEMI patients at 12 months after initial inclusion.

*Baseline investigation*

Ischemic stroke patients underwent routine examination with NIHSS at admission[15], including risk factors (hypertension, diabetes mellitus, hypercholesterolemia, smoking, overweight defined as BMI ≥ 25), and brain imaging with CT and/or MRI. Patients were treated according to Norwegian guidelines for ischemic stroke[16].

Demographic data were collected at the time of initial admission.

*Employment status*

Employment status was further recorded at three and 12 months for the stroke patients and at 12 months for the NSTEMI patients. Employment include both part time and full-time employment. Patients on sick leave at baseline were defined as employed. Patients who retired after the vascular event are included in the analyses.

*Assessment of cognitive and emotional function*

We applied trail-making test A and B, Color-Word Interference test and Verbal Fluency (FAS) as tests of executive function[17]. The Color-Word interference test is divided in four items: Color naming, color reading, Inhibition and Inhibition/Switching, thus testing mental flexibility, mental speed and inhibition. These tests were drawn from the Delis-Kaplan Executive Function System (D-KEFS) which was developed to provide reliable measures for a range of executive functions[18].

Memory was tested with the CERAD ten-words learning task[19]. CERAD (Consortium to Establish a Registry for Alzheimer's Disease) is a standardized validated test battery for the assessment of Alzheimer disease[19] with normative data adjusted for age and education[20]. Scores falling below 1.5 SD of the mean were characterized as abnormal.

It is expceted that healthy adults achieve some low scores when a battery of neuropsychological tests are administered[21, 22]. In order to avoid potential misclassifications cognitive impairment was defined as iscores below 1.5 SD of ≥ 2 cognitive tests.

Ischemic stroke patients were screened by the Ullevaal aphasia screening test at three and 12 months[23]. The maximal total score is 52 points.

*Questionnaires*

The Hospital-Anxiety and Depression scale (HADS) was used to assess anxiety and depression[24]. A score ≥ 8 on the anxiety (HADS-A) or depression (HADS-D) items indicates possible presence of anxiety or depression disorders[25], a total score ≥ 15 indicates a mixture of anxiety and depression.

The Fatigue Severity Scale (FSS) was used to assess fatigue[26]. FSS is a nine-item questionnaire that assesses the effect of fatigue on daily living. Each item is a statement on fatigue that the subject rates from 1, completely disagree to 7, completely agree[27]. Fatigue was defined as FSS score ≥ 5[27].

Except for the baseline data, the analyses are done on patients employed at baseline to explore factors influencing employment after the vascular event.

Trained research nurses or the neurologist responsible for the study performed the cognitive testing.

*Ethical approval*: The ethics committee of Rogaland, Hordaland and Sogn and Fjordane (REC west) approved this study (REC number: 2012/1708).

*Statistics*

We used the Student's *t*-test to assess differences in mean values, and the Chi square test to assess differences in categorical variables. Univariate logistic regression was used to assess association between two variables. We used multivariate logistic regression to assess associations between more than two variables. The level of significance was set to p=.05. All significance testing was done as two-tailed tests. Stepwise backwards method to remove variables with high p-values was employed.

We used STATA 14 (Statacorp 4905 Lakeway Drive, College Station, Texas 77845 USA) for statistical analyses.

## Results

A total 330 patients were included in the study. Of these 217 were ischemic stroke and 113 NSTEMI patients. Nineteen of the 217 ischemic stroke patients were lost to follow-up after 12 months (Table 1).

Ischemic stroke patients were younger than NSTEMI patients (p < 001) at baseline. The proportion of women was higher in the ischemic stroke group than in the NSTEMI group (p = 001). There was no significant difference in educational level between groups (p = 07) or between men and women in the stroke group. The prevalence of hypercholesterolemia (p = 04) and smoking (p = 001) were higher in NSTEMI than in ischemic stroke patients and the NSTEMI patients had higher BMI (p = 05) at baseline (Table 1).

In total 82 % of the stroke patients and 90 % of the NSTEMI patients were still employed at 12 months (p = 06).

Of the ischemic stroke patients, 92 % were employed at three months vs 82 % at 12 months (p.003). Ischemic

**Table 1.** *Characteristics of ischemic stroke and NSTEMI patients employed at baseline.*

| | Ischemic stroke n 217 (%) | NSTEMI n 113 (%) | p value |
|---|---|---|---|
| Age (SD) | 55 (10.2) | 59 (6.2) | <.001 |
| Females patients | 67[31] | 20[18] | .001 |
| Education 1[a] | 21[10] | 14[12] | .07 |
| Education 2 | 96 (45) | 53 (47) | |
| Education 3 | 95 (45) | 46 (41) | |
| Risk factors | | | |
| Hypertension | 102 (48) | 51 (45) | .6 |
| Diabetes mellitus | 24[11] | 17[15] | .3 |
| Atrial fibrillation | 23[11] | 9[8] | .4 |
| Hypercholesterolemia[b] | 92 (43) | 62 (55) | .04 |
| Smoking[c] | 59[28] | 52 (46) | .001 |
| BMI mean (SD) | 26.6 (4.1) | 27.3 (3.2) | .05 |
| Overweight (BMI≥25) | 126 (59) | 78 (69) | .08 |

[a]1 primary school, 2 high school, 3 bachelor/university
[b]Treatment with cholesterol lowering medication
[c]Current smoker or smoking within the last 12 months

stroke patients were younger than NSTEMI patients at 12 months ($p < 001$) (Table 1).

The screening for aphasia among stroke patients showed test scores of 51.7 at three months and 51.9 at 12 months (maximum total test score = 52) underlining that aphasia did not influence the results.

Ischemic stroke and NSTEMI patients employed at 12 months were younger and had a higher educational level than unemployed patients (Table 2).

Diabetes mellitus (OR .5, CI .2−1.3), atrial fibrillation (OR .6, CI .2−21.6) and hypercholesterolemia (OR .6, CI .3−1.3) were associated with unemployment in ischemic stroke patients (Table 2). Atrial fibrillation (OR .4, CI .1−2.0), smoking (OR .4, CI .1−1.4) and overweight (OR .4, CI .1−31.9) were associated with unemployment in the NSTEMI patients.

There was a trend towards more subcortical and infratentorial lesions (OR .8, CI .4−1.6 and OR .9, CI .4−2.1) in employed ischemic stroke patients as opposed to more cortical lesions (OR 3.0, CI .9−10.5) in unemployed patients. However, the difference did not reach significance.

Ischemic stroke: There were no significant differences in cognitive function between employed and unemployed patients at three months except for Color-Word Inhibition error with more errors in the unemployed group (Table 3). There were significant differences in Color-Word Inhibition error, total HADS and HADS-depression between unemployed and employed patients at 12 months with worse scores in the unemployed group (Table 3).

We performed calculations of the cognitive variables with the scaled scores Trail-making A and B, Verbal fluency and the Color-Word Interference tests with three different cut-offs (-.5, -1 and -1.5 SD). However, by narrowing the cut-off levels, no clear tendency appeared although we detected variation in significance both along the time scale and according to the chosen cut-off level as shown in Table 3.

The results of the cognitive tests done as continuous variables did not change the results listed in table three. A table of the results are available as additional material.

NSTEMI: There were no significant differences in cognitive function, HADS-A or HADS-D between employed and unemployed NSTEMI patients at 12 months. The number of NSTEMI patients who did not return to work after the NSTEMI was small (11 patients).

Lower age and higher education were associated with employment at 12 months both in ischemic stroke and NSTEMI patients (Table 4) . The regression model shows that a higher proportion of NSTEMI than ischemic stroke patients were employed at 12 months. Adjusting for sex, risk factors or cognitive impairment measured as impairment of two or more cognitive tests did not change the result.

There was no association between the total number of impaired cognitive tests and employment at 12 months in the two patient groups.

## Discussion

High age and low education were associated with unemployment at 12 months follow-up for both stroke and NSTEMI patients employed at baseline (Table 4). Highly educated people may have a larger cognitive reserve which may explain the higher degree of employment, as also found by another study[28]. The age effect on employment at 12 months in patients employed at baseline was not explained by reduced cognitive function. The lack of difference in cognitive performance between employed and unemployed ischemic stroke patients at three and 12 month in our study also suggests that cognitive impairment is not the major cause of unemployment. This is in contrast to a study of mild to moderate stroke that found impaired global cognitive function as the only statistically significant independent predictor for return to work[29]. Another study found that patients that returned to work three months after a minor stroke had sigificantly

**Table 2.** *Unadjusted odds ratios for employment at 12 months according to sociodemographic factors and risk factors in ischemic stroke and NSTEMI patient and location of ischemic lesions in employed and unemployed stroke patients*. Proportion of impaired cognitive tests.*

| | Employed stroke 12 months n = 163 (%) | Unemployed 12 months n = 35 (%) | OR (95% CI) | p | NSTEMI employed at 12 months (%) n = 102 | NSTEMI unemployed at 12 months (%)n = 12 | OR (95%CI) | p |
|---|---|---|---|---|---|---|---|---|
| Age[a] | 54 | 62 | .9 (.8−9) | <.001 | 58 | 65 | .8 (.6−9) | .002 |
| Partner | 129 (79) | 27 (77) | 1.1 (.5−2.7) | .8 | 88 (86) | 9 (75) | 2.1 (.5−8.7) | .3 |
| Education 1[b] | 15 (9) | 9 (26) | ref | | 12 (12) | 4 (33) | ref | |
| Education 2[b] | 74 (46) | 15 (44) | 3.0 (1.1−8.0) | .03 | 48 (47) | 4 (33) | 4.0 (.9−18.4) | .08 |
| Education 3[b] | 73 (45) | 10(29) | 4.4 (1.5−12.6) | .006 | 42 (41) | 4 (33) | 3.5 (.8−16.1) | .1 |
| Hypertension | 81 (50) | 18 (51) | .9 (.4−1.9) | .9 | 47 (46) | 5 (42) | 1.2 (.4−4.0) | .8 |
| Diabetes mellitus | 18 (11) | 7 (20) | .5 (.2−1.3) | .1 | 15 (15) | 2 (17) | .9 (.2−4.3) | .9 |
| Atrial fibrillation | 18 (11) | 6 (17) | .6 (.2−21.6) | .3 | 7 (7) | 2 (17) | .4 (.1−2.0) | .3 |
| Hyper-cholesterolaemia[c] | 73 (45) | 20 (57) | .6 (.3−1.3) | .2 | 57 (56) | 7 (58) | .9 (.3−3.0) | .9 |
| Smoking[d] | 47 (29) | 9 (26) | 1.2 (.5−2.7) | .7 | 45 (44) | 8 (67) | .4 (.1−1.4) | .1 |
| Overweight[e] | 99 (61) | 20 (57) | 1.2 (.6−2.4) | .7 | 68 (67) | 10 (83) | .4 (.1−31.9) | .2 |
| Subcortical ischemic lesion | 37 (23) | 3 (9) | .8 (.4−1.6) | .6 | | | | |
| Cortical ischemic lesion | 59 (36) | 12 (35) | 3.0 (.9-10.5) | .08 | | | | |
| Infratentorial ischemic lesion | 32 (20) | 8 (24) | .9 (.4−2.1) | .9 | | | | |
| | Number of impaired cognitive tests at 12 months* | | | | | | | |
| | 158 stroke patients (%) | | | | 95 NSTEMI patients (%) | | | |
| 0 | 77 (49) | | | | 49 (52) | | P = 02[f] | |

(*Continued*)

**Table 2** (*Continued*)

| | Employed stroke 12 months n = 163 (%) | Unemployed 12 months n = 35 (%) | OR (95% CI) | p | NSTEMI employed at 12 months (%) n = 102 | NSTEMI unemployed at 12 months (%)n = 12 | OR (95%CI) | p |
|---|---|---|---|---|---|---|---|---|
| 1 | 23 (15) | | | | 25 (26) | | | |
| 2 | 18 (11) | | | | 10 (7) | | | |
| 3 | 8 (5) | | | | 5 (5) | | | |
| 4 | 8 (5) | | | | 2 (2) | | | |
| 5 | 6 (4) | | | | 3 (3) | | | |
| 6 | 8 (5) | | | | 1 (1) | | | |
| 7 | 4 (3) | | | | 0 | | | |
| 8 | 5 (3) | | | | 0 | | | |
| 9 | 1 | | | | | | | |

*Patients employed at baseline. [a]p < .001 between age difference of employed stroke and NSTEMI patients. [b]1 primary school, 2 high school, 3 bachelor/university. [c] Treatment with cholesterol lowering medication, [d] Current smoker or smoking within the last 12 months , [e] BMI ≥ 25.[f]p of 0 and 1 impaired cognitive test between stroke and NSTEMI.

**Table 3.** . *Comparison of cognitive test scores assessed at 3 months and 12 months in employed vs non-employed ischemic stroke patients at 12 months (scaled scores)*.*

| | Cognitive tests at 3 months associated with employment at 12 months (%) | | | | | Cognitive tests 12 months (%) associated with employment at 12 months | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | SD -1.5 | SD -1 | SD -.5 | | | SD -1.5 | SD -1 | SD -.5 |
| n | Employed 166 | Non-employed 36 | p | p | p | Employed 166 | Non-employed 36 | p | p | p |
| Trail-making A[a] | 10 (6) | 2 (6) | .9 | .7 | .9 | 6 (4) | 1 (3) | .8 | .6 | .8 |
| Trail-making B[a] | 15 (9) | 7 (19) | .07 | .04 | .05 | 14 (8) | 6 (17) | .1 | .04 | .05 |
| 10-words test[b] | 11 (7) | 2 (6) | .8 | | | 7 (4) | 1 (3) | .7 | | |
| 10-words test delayed[bc] | 20 (12) | 8 (22) | .1 | | | 11 (7) | 3 (8) | .8 | | |
| Verbal fluency (FAS) | 18 (11) | 8 (22) | .07 | .04 | .09 | 16 (10) | 6 (17) | .2 | .09 | .2 |
| Color-word interference tests | | | | | | | | | | |
| Color naming[a] | 43 (26) | 9 (25) | .9 | .4 | .9 | 34 (21) | 9 (25) | .6 | .9 | .9 |
| Color reading[a] | 30 (18) | 6 (17) | .8 | .3 | .9 | 30 (18) | 6 (17) | .9 | .4 | .9 |
| Color-word inhibition[a] | 26 (16) | 6 (17) | .9 | .7 | .4 | 22 (13) | 1 (3) | .07 | .3 | .7 |
| Color-word inhibition/switching[a] | 37 (22) | 11 (31) | .3 | .09 | .8 | 33 (20) | 5 (14) | .4 | 1.0 | 1.0 |
| Namingerror[d] | 12 (7) | 3 (8) | .8 | | | 11 (7) | 1 (3) | .4 | | |
| Readingerror[d] | 30 (15) | 2 (14) | .9 | | | 16 (10) | 5 (14) | .5 | | |
| Inhibition error[a] | 9 (5) | 6 (17) | .02 | .1 | .2 | 5 (3) | 5 (14) | .007 | .2 | .04 |
| Inhibition/switching error [a] | 7 (4) | 3 (8) | .3 | .3 | .1 | 10 (6) | 3 (8) | .6 | .4 | .4 |
| Pooled data of cognitive tests | | | .2 | .3 | .5 | | | .05 | .2 | .4 |
| Impairment ≥ 2 cognitive tests | 62 (40) | 16 (44) | .6 | .8 | .3 | 57 (37) | 11 (31) | .6 | .6 | .4 |
| Questionnaires | | | | | | | | | | |
| FSS[e] | 44 (27) | 6 (17) | .2 | | | 45 (28) | 10 (31) | .7 | | |
| HADS[f] | 21 (13) | 5 (14) | .8 | | | 19 (12) | 9 (27) | .02 | | |
| HADS-A[g] | 32 (20) | 7 (20) | .9 | | | 28 (18) | 7 (21) | .6 | | |
| HADS-D[g] | 11 (7) | 3 (8) | .7 | | | 13 (8) | 7 (19) | .04 | | |

*Patients employed at baseline. [a]scaled score, [b]Adjusted for age and educational level,[c] tested with 5 min delay , [d] cumulative percentage, [e] Fatigue defined as FSS ≥ 5, [f] Anxiety and/or depression defined as HADS ≥ 15, [g] anxiety was defined as HADS-A ≥ 8, and [g]depression as HADS-D ≥ 8

**Table 4.** . *Odds ratio of being employed at 12 months according to event (stroke vs NSTEMI), educational level and cognition at 12 months in stroke and NSTEMI patients employed at baseline (n = 330).*

| Employment at 12 months | | |
|---|---|---|
| | OR (95% CI) | p |
| Age (baseline) | .8 (.8−9) | <.001 |
| Sex (males) | 1.2 (.5−2.8) | .7 |
| Education 1[a] | Ref | |
| Education 2[a] | 2.4 (.8−6.8) | .1 |
| Education 3[a] | 3.2 (1.0−10.2) | .05 |
| Stroke vs NSTEMI patients | .3 (.1−7) | .01 |
| Number of impaired cognitive tests[b] | 1.1 (.9−1.5) | .4 |
| HADS-D[c] | .6 (.2−2.0) | .4 |

Multivariat OR adjusted for [a]1 primary school, 2 high school, 3 bachelor/university, [b]distribution of impaired cognitive tests 0−10, [c]depression as HADS-D ≥ 8
Tests done at 12 months

more years of education and they had a significantly better cognitive performance[30].

Other factors than health related issues may determine whether our patients are able to return to their work. In Norway early retirement is an option, and some of our patients may have chosen this solution. A recent Finnish study also discussed this option[31].

More NSTEMI patients were employed at baseline even though they were older than the stroke patients. Stroke patients may have more cerebral ischemic lesions than NSTEMI patients before the index vascular event possibly explaining this age difference. Correcting for age, a higher proportion of NSTEMI patients were still employed at 12 months.

Cerebrovascular risk factors are associated with ischemic brain damage which may lead to cognitive impairment. In our study, diabetes mellitus, atrial fibrillation and hypercholesterolemia were associated with unemployment in ischemic stroke patients (Table 2). Lack of hypertension and diabetes and a non-smoker status before stroke was associated with a higher likelihood of return to work after cerebrovascular disease in another study[32].

For the NSTEMI patients, atrial fibrillation, smoking and overweight were associated with ending up unemployed in our study. However, the number of unemployed NSTEMI patients was small and the results must be interpreted with caution.

The prevalence of some of the risk factors was higher in the NSTEMI group compared to the stroke group. Nevertheless NSTEMI patients seem to stay longer in work than ischemic stroke patients which suggests that this difference does not influence the employment rate in our patients. This is in contrast to another study which found an association between risk factors and return to work after cerebrovascular disease[32]. Functional outcome (mRS and NIHSS) was not reported in that study. Cerebrovascular changes may be more prevalent in minor stroke patient than NSTEMI patients and may be more more important for employment than the prevalence number of risk factors according to our findings.

A study of spinal cord infarctions found that all surviving patients younger than 60 years with mRS ≥ 1 day 7 had been re-employed after discharge compared to 65% of patients younger than 60 years with cerebral infarctions and mRS ≥ 1 at day 7[7], which may illustrate that the cerebral lesions had an impact on the ability to stay in work even though the functional status as evaluated with mRS was similar. One study found that the participants thought that a stroke was more serious than a heart attack, which may influence the patients' expectation of function and the ability to stay in work after the illness[33].

The employment rate for ischemic stroke patients in our study was high even though the prevalence of cognitive impairment was high at 12 months. One explanation may be that our study have used cognitive tests that are too sensitive and demonstrate findings with little impact on employment. Our finding is in contrast to another study[6] where only 41 % of patients had returned to work after six months, even though the NIHSS at discharge was low (NIHSS 1 compared to 0.8 in our study).

An unpublished subgroup analysis of seven of our ischemic stroke patients showed that patients returning to work had less demanding tasks or less responsibility in their work than before the stroke[34]. This may also explain the high employment rate. The prevalence of unemployment in ischemic stroke patients in our study increased between three and 12 months. Some of the employed patients at three months may still have been on sick leave. At 12 months some of these patients may have converted to disability benefits due to a more clarified health status which may explain the increase in unemployment.

Prevalence of anxiety and depressive symptoms were higher in unemployed stroke patients at 12 months, but not at three months. This correlates with the findings in another study which found significant differences in depression in employed and unemployed patients[30]. Since the prevalence of cognitive impairment was unchanged from three to 12 months, the increasing prevalence of anxiety and depression may be the main cause for the increased unemployment rate. However, our study does not answer whether the depression causes the

unemployment or if the unemployment causes the depression. Further studies are needed to clarify this interaction. A study from 2008 found that psychiatric comorbidity 28 days after a stroke was a predictor of not returning to work[35].

*Strengths and weaknesses*

The main strength of this study is a long follow-up time with repeated testing of the ischemic stroke patients and the case-control design. The sample size is also large. Nevertheless, the case-control method was a challenge because of difficulties recruiting control patients.

A weakness is that NSTEMI patients did not undergo a cerebral MRI.

According to the power analysis we did not reach the number of patients we wanted. A lower number of patients may influence the results of the analyses.

## Conclusion

The current study found that the majority of patients employed at baseline retained their employment 12 months after an ischemic stroke. We found that the main factors influencing the ability to stay in work after a minor stroke are lower age, higher education and lack of affective symptoms e.g. anxiety and depression. Significantly more NSTEMI patients were employed after 12 months even though they had the same prevalence of cognitive impairment as the stroke group. The study suggests that to identify stroke patients with emotional symptoms is important since affective manifestations might contribute to employment.

## Declaration of Competing Interest

None

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## Informed consent

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

## Ethical approval

The ethics committee of Rogaland, Hordaland and Sogn and Fjordane (REC west) approved this study (REC number: 2012/1708).

## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Contributorship

HN is the main supervisor. He has been involved in protocol development, gaining ethical approval, data analysis and the first draft of the manuscript. HE is a co-supervisor and has been involved in protocol development and advice in the study period. AG is a neuropsychologist and has been involved in protocol development, especially the selection of cognitive tests and data analysis and interpretation. MTR is a neuropsychologist and has been involved in data analysis and interpretation. RM is a co-supervisor and has been involved in protocol development. SBS has been involved in the protocol development, especially the selection of cognitive tests. EJ has been involved in the protocol development with focus on anxiety and depression tests. All authors reviewed and edited the manuscript and approved the final version of the manuscript

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