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Prevalence, Pathogenesis and Prediction of Function

Doctoral thesis

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of Philosophiae Doctor
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Kombinert svikt i kognisjon og fysisk funksjon etter hjerneslag – årsaksmekanismer, forekomst og konsekvenser for videre funksjon

Svikt i både kognitive og fysiske funksjoner samtidig øker risikoen for demenssykdom, fall og funksjonssvikt. Hos personer som har gjennomgått hjerneslag har kognitiv og fysisk funksjon vanligvis vært studert, diagnostiser og behandlet separat. Økt kunnskap om underliggende mekanismer vil kunne bidra til mer målrettet oppfølging en stor pasientgruppe. Hovedhensikten med prosjektet har vært å undersøke samspillet mellom fysisk funksjon og kognisjon etter hjerneslag og studere sammenhenger med endringer i selvstendighet i hverdagsaktivitet og hjernepatologi.

Prosjektet er en del av studien The Norwegian Cognitive Impairment After Stroke (Nor-COAST), en prospektiv multisenter kohortstudie med 815 deltaker rekruttert fra fem ulike norske sykehus i perioden mai 2015 til mars 2017. Deltakerne gjennomført kognitive og fysiske tester ved sykehusinnleggelsen og tre måneder senere. I tillegg ble funksjonsnivå kartlagt ved tre og 18 måneder etter hjerneslaget. Et mindre utvalg ble inkludert i en substudie der MR-bilder ble tatt for å vurdere hjernehelse.

Studien avdekket kombinert svikt i kognisjon og fysisk funksjon ved 3 måneder hos 10-23% av deltakerne, avhengig av hvilke måleinstrumenter som ble brukt. I tillegg fant vi at både global kognisjon, eksekutiv funksjon og hukommelse var assosiert med fysisk funksjon. Kombinasjonen av mål på fysisk funksjon og kognisjon ved tre måneder var bedre enn separat vurdering for å forutsi endring i mestring av hverdagsaktiviteter over de neste 15 månedene. Vi fant at fysisk funksjon og kognisjon ved tre måneder var avgjørende for hvilket funksjonsnivå deltakerne stabiliserte seg på 18 måneder etter hjerneslaget. Analyser av MR-bilder i akuttfasen etter hjerneslag viste at størrelsen på hjerneslaget var assosiert med å ha kombinert svikt i kognisjon og fysisk funksjon under sykehusinnleggelsen.

Oppsummert har denne studien bidratt til å øke kunnskapen rundt betydningen av å se kognisjon og fysisk funksjon i sammenheng i oppfølging av personer som har hatt hjerneslag, hvilke konsekvenser en kombinert svikt har for langtidsfunksjon, og sammenhengen med patologiske forandringer i hjernen.

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List of papers

Paper 1

Einstad, MS; Saltvedt, I; Lydersen, S; Ursin, MH; Munthe-Kaas, R; Ihle-Hansen, H; Knapskog, AB; Askim, T; Beyer, MK; Næss, H, Seljeseth, YM; Ellekjær, H; Thingstad, P. **Associations between post-stroke motor and cognitive function: a cross-sectional study.** *BMC Geriatrics.* 2021;21(1):103.

Paper 2

Einstad, MS; Thingstad, P; Lydersen, S; Gunnes, M; Saltvedt, I; Askim, T. **Physical performance and cognition as predictors of instrumental activities of daily living after stroke: a prospective multicenter cohort study.** Accepted for publication in *Archives of Physical Medicine and Rehabilitation*, 2022.

Paper 3

Einstad, MS; Schellhorn, T; Thingstad, P; Lydersen, S; Aamodt, EB; Beyer, MK; Saltvedt, I; Askim, T. **Neuroimaging markers of dual impairment in cognition and physical performance following stroke: The Nor-COAST study.** Submitted for publication, 2022.

Summary

Dual impairment of physical performance and cognition has been reported to increase the risk of dementia, falls, and functional dependency. However, this coexistence of impairments has to a little extent been explored in stroke populations; instead, these impairments have been studied, diagnosed, and treated as distinct entities. As a result, further knowledge is needed to delineate the underlying pathological mechanisms of dual impairment and their consequences for long-term function in stroke survivors.

The overall aim of this thesis was to investigate both the synergistic relationship between physical performance and cognition after stroke and the associations between functional outcomes and brain pathology. This thesis was based on data from baseline and 3- and 18-month follow-ups of the Norwegian Cognitive Impairment After Stroke (Nor-COAST) study, a prospective multicenter cohort study including 815 participants admitted to stroke units with acute stroke in five Norwegian hospitals between May 2015 and March 2017.

Performance-based assessments included the Montreal Cognitive Assessment (MoCA) and Short Physical Performance Battery (SPPB) at baseline and 3-month follow-up. In addition, executive function, memory, grip strength, and dual task cost were assessed at 3-month follow-up. Instrumental activities of daily living (IADL) were assessed at 3- and 18-month follow-up with the Nottingham Extended ADL (NEADL) questionnaire. Approximately half of the Nor-COAST participants were included in an MRI sub-study in which information was obtained on markers of cerebrovascular and neurodegenerative pathology, as well as on stroke lesion location and volume.

Results from Paper 1 showed that every third participant in our sample showed impairment in either cognitive or physical function at 3 months post-stroke, with rates of concurrent impairment ranging from 10% to 23%, depending on which combination of assessments was applied. Impairments in physical performance and grip strength

were associated with impaired global cognition, executive dysfunction, and impaired memory. Higher dual-task cost was only associated with executive dysfunction.

In Paper 2, combining measures of physical performance and cognition was found to be superior to assessing one domain exclusively in the prediction of change in IADL from 3 to 18 months post-stroke; however, cognition appeared to be a stronger predictor than physical performance when applied in combination within the same model. Overall, a stable level of IADL function was found among participants, but high scores on measures of both physical performance and cognition at 3 months post-stroke were associated with a statistically significant improvement in function over the ensuing 15 months.

Results from Paper 3 showed that a larger stroke lesion volume was associated with dual impairment in cognition and physical performance at the time of stroke. Pre-existing pathology was found in two-thirds of the participants; however, associations with dual impairment were not significant when adjusting for age, whereas the association with stroke lesion volume remained significant. Participants with dual impairment were older, had poorer pre-stroke function, and suffered more severe stroke, on average, than participants with only one or no impaired domain.

To summarize, this thesis found that impairments in cognition and physical performance are observed in a substantial number of stroke patients, and that performance-based testing of dual impairment at 3 months post-stroke is useful for predicting IADL function at 18 months. These results contribute to increased knowledge of the interplay between post-stroke cognition and physical performance, their associations with brain pathology at the time of stroke, and their role in the prediction of long-term function. The identification of dual impairments at 3 months post-stroke may be relevant for preventing functional decline and supports the adoption of a holistic treatment approach for this patient group. Further research is needed to refine the methods for identifying risk profiles and developing personalized rehabilitation that targets especially vulnerable populations following stroke.

Abbreviations

10WLR	10-Word List Recall
AD	Alzheimer's Disease
ADL	Activities of daily living
DALYs	Disability-adjusted life years
DTC	Dual task cost
IADL	Instrumental activities of daily living
MCI	Mild cognitive impairment
MCR	Motoric Cognitive Risk syndrome
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
MTA	Medial temporal lobe atrophy
NEADL	Nottingham Extended Activities of Daily Living
NIHSS	National Institutes of Health Stroke Scale
Nor-COAST	Norwegian cognitive impairment after stroke
PSCI	Post-stroke cognitive impairment
SCI	Subjective cognitive impairment
SD	Standard deviation
SPPB	Short Physical Performance Battery
SVD	Small Vessel Disease
TIA	Transient ischemic attack
TMT-B	Trail Making Test Part B
WMH	White matter hyperintensities

1 Introduction

Stroke is the second most common cause of death and a leading cause of disability worldwide. Throughout the past decade, advances in acute treatment and improved secondary prevention have led to an increase in the number of persons living with stroke sequelae, and with an aging population, this number is expected to continue rising. Stroke survivors constitute a heterogeneous group in terms of both pre-stroke function and stroke severity. As a result, a wide range of impairments may be observed following stroke that could affect activities of daily living (ADL) in the short and long term.

Cognition and physical performance have often been studied, diagnosed, and treated as distinct entities. However, there is reason to believe that these two domains should be addressed together to yield a more accurate assessment of overall function. Recently described phenotypes, including impairments in both cognition and physical performance, have been associated with increased risk of dementia and functional dependency in the general older population. Little is known about this construct of dual impairment in stroke samples; thus, additional data are needed about its associations with underlying brain pathology and consequences for long-term function. Emerging evidence indicates that a combination of performance-based measures of physical and cognitive function supplements traditional risk factors in the prediction of long-term prognosis of ADL-function, which may be relevant in the identification of individuals who could benefit from more targeted rehabilitation and more personalized long-term follow-up after stroke.

2 Background

2.1 Cognitive and physical impairments during aging

Both age-related processes and intercurrent disease contribute to impairments and deterioration of function in older adults. Impairments in cognition and physical function might cause dementia and falls, respectively, which again in many cases lead to disability and dependency in ADL (Clouston et al., 2013). The population worldwide is aging and will continue to do so in the coming years, and consequently, conditions more prevalent in older age, such as dementia and physical disabilities are expected to rise in numbers (Nichols et al., 2019; Verghese et al., 2006). Several years may pass between when impairments in physical and cognitive abilities are first detected and when a diagnosis of dementia is reached or a fall causes a hip fracture, resulting in an extended period of time during which preventative measures can be implemented (Clouston et al., 2013).

Cognitive and physical performance are both indicators of biological aging. Impairments in these domains may be caused by underlying biological age-related processes and intercurrent disease, which lead to increasing vulnerability to pathology and functional limitations (Clouston et al., 2013). Cognition changes from midlife onward as a result of normal aging (Singh-Manoux et al., 2012); however, pathological processes such as neurodegeneration and cerebrovascular disease may interfere and yield cognitive changes beyond what is considered normal within the context of normal aging (Singh-Manoux et al., 2012). Cognitive impairment might be seen as a continuum from subjective cognitive complaints to mild cognitive impairment (MCI), with objectively measured impairments in cognition, but not so severe as to interfere with ADL (Petersen, 2004), to dementia with severe impairments which interfere with ADL (American Psychiatric Association, 2013).

Changes to the musculoskeletal system and neurological abnormalities that are caused either by normal aging or disease may contribute to declines in physical performance as age increases (Cooper et al., 2011; Rosso et al., 2013). Physical performance—especially gait speed—has for the last decade been regarded as a feasible predictor of overall

health, including risk of hospitalization and dependency in ADL (Fritz & Lusardi, 2009; Studenski et al., 2011). Accumulating evidence indicates that assessments of balance and muscle strength may also predict onset of ADL dependency (Wennie Huang et al., 2010). Impaired physical performance is included as part of the at-risk concept of frailty, which describes a state of reduced reserve capacity, and which is also associated with cognitive impairment (Fried et al., 2001). Thus, impaired physical performance, regardless of etiology, may be considered a sign of reduced resilience (Rosso et al., 2013).

2.2 Motor-cognitive interaction

The notion of cognition and physical performance being related, and that combining measures of these two in some way would make up a relevant clinical assessment, was first put forward by Lundin-Olsson and colleagues 25 years ago (Lundin-Olsson et al., 1997). They observed that a subset of older adults who stopped walking when they began talking also had an increased risk of falling throughout the following 6 months (Lundin-Olsson et al., 1997). Their paper constitutes the first scientific paper describing motor-cognitive interaction, which can be measured by performance-based tests that capture both cognitive abilities and physical performance (Montero-Odasso et al., 2018a).

The paradigm of viewing impairments in cognition and physical performance as domains regulated by shared neural resources and in equal parts affected by aging and neurodegeneration has gained increasing attention over the last decade. As a result, the need for suitable assessment tools to increase comparability across studies has been emphasized. In 2018, the Canadian Consortium on Neurodegeneration in Aging (CCNA) proposed a set of performance-based tests for the combined assessment of mobility and cognition to identify preclinical stages of decline in physical and cognitive performance (Montero-Odasso et al., 2018a). The consortium defined a core set of performance-based tests that were feasible in clinical and research settings, had adequate prognostic and diagnostic outcome measures, and that assessed motor-cognitive interaction

suitably. They focused on including tests for the cognitive domains of global cognition, memory, executive function, and processing speed, which are reported to be more strongly associated with physical performance than, for instance, visuospatial abilities or verbal fluency (Demnitz et al., 2016). As for physical performance, the most appropriate assessments proposed were those of gait speed, dual-task gait, and tests incorporating measures of gait, balance, and muscle strength (Montero-Odasso et al., 2018a).

The dual-task concept can be viewed as a direct extension of the "stops walking when talking" phenomenon (Montero-Odasso et al., 2012b). And, in addition to being a predictor of falls, reduction of gait speed while performing a cognitive task has been reported as a risk factor for dementia (Montero-Odasso et al., 2017). Consequently, dual-task cost is regarded as an expression of a motor-cognitive interaction (Al-Yahya et al., 2011).

Physical performance (e.g., gait speed) alone has also been reported as a relevant measure of the motor-cognitive interaction (Montero-Odasso et al., 2018a). Gait speed, both alone and as part of a physical performance battery, is a feasible measure in clinical settings that has favorable measuring properties (Studenski et al., 2011; Studenski et al., 2003).

2.3 Dual impairment in cognition and physical performance

During the past two decades, various concepts have been introduced, including impairments in physical performance and cognition, with a variety of names applied to label them. Among the most discussed are motoric cognitive risk syndrome (MCR), cognitive frailty, and dual decline, which will be described further in this chapter. For the purposes of this thesis, the co-occurrence of any impairments in cognition and physical performance will be referred to as dual impairment.

Physical performance, including slow gait speed, is a well-established predictor of cognitive impairment and dementia (Beauchet et al., 2016b; Kueper et al., 2017; Mielke

et al., 2013; Verghese et al., 2002) and has been reported to predict MCI and dementia up to 10 years prior to diagnosis (Buracchio et al., 2010; Chou et al., 2019). Further, Waite and colleagues observed that, in addition to reduced gait speed, individuals with cognitive complaints were at an even higher risk of dementia. Therefore, they proposed the incorporation of gait measures into definitions of preclinical dementia states (Waite et al., 2005).

Cognitive impairment is more likely to progress to dementia when accompanied by reduced physical performance, and impaired physical performance is more likely to result in falls and fractures when accompanied by cognitive impairment, suggesting common underlying mechanisms (Montero-Odasso et al., 2018a). Furthermore, these findings highlight the importance of identifying individuals with dual impairment, who are at increased risk of adverse outcomes.

2.3.1 Motoric cognitive risk syndrome

Observations about the relevance of adding measures of physical performance when assessing cognitive status led to an investigation of gait abnormalities in MCI (Verghese et al., 2008), which ultimately led to combining measures of the two domains to describe a new phenotype. MCR was first described by Verghese et al. and is defined by the combination of cognitive symptoms and gait speed (Verghese et al., 2013). More precisely, the criteria are: 1) cognitive complaints identified by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) questionnaire; 2) slow gait speed, defined as 1 SD below age- and sex-adjusted mean values; 3) preserved ADL; and 4) absence of dementia (Verghese et al., 2013). The criterion of cognitive complaints has since been broadened to include criteria from other standardized questionnaires (e.g., Clinical Dementia Rating [CDR], Geriatric Depression Scale [GDS], or AD8) (Allali et al., 2016). However, as highlighted by Rabin et al., there is a substantial heterogeneity in the assessment of subjective cognitive impairment (SCI), and memory was reported as the cognitive domain most frequently assessed (Rabin et al., 2015).

By applying these criteria, the prevalence of MCR has been reported among various populations. A multinational study including participants from 17 countries reported an overall pooled prevalence of 9.7%, with numbers ranging from 2% in cohorts from the United Kingdom and Australia to 18% in a French study sample (Verghese et al., 2014). Stroke has been reported as a risk factor of MCR (Allali et al., 2016); however, to our knowledge MCR has not been formally investigated in stroke cohorts.

Although the definition of cognitive complaints varies between the screening tools or questionnaires applied, MCR has only included subjective cognitive complaints, because the thought was that this classification would not call for objective cognitive assessments.

Physical performance has previously been thought to be more closely associated with vascular dementia—in which executive dysfunction is a common symptom—than with Alzheimer's disease (AD), in which memory deficits are typically the predominant symptom (Verghese et al., 2002). Therefore, MCR was originally deemed a more accurate predictor of vascular dementia than was AD (Verghese et al., 2013). However, this argument has been challenged by diverging findings. For instance, Verghese et al. found that participants with MCR had a 3-fold risk of developing dementia (HR = 3.27) compared to participants without MCR. Further, they found that MCR was a strong predictor of vascular dementia (HR = 12.81), but not of AD (HR = 0.66) (Verghese et al., 2013). On the other hand, Bennett et al. reported that MCI and the presence of motor impairments increased the risk of developing AD (Bennett et al., 2012). Nonetheless, MCR has been reported as a stronger risk factor for incident dementia relative to MCI (Verghese et al., 2014).

Maintaining an adequate level of physical performance requires an effective interplay between motor, cognitive, and psychological functions; when this interaction is perturbed, the risk of experiencing falls increases (Clouston et al., 2013). And, given that several cognitive domains are important for physical performance (e.g., executive functioning, attention, processing speed, and memory), it is reasonable to assume that MCR is a sensitive predictor of falls in older adults. A study combining five cohorts of

older people showed that MCR at baseline yielded a 44% increase in the risk of future falls, which was higher than for slow gait alone (Callisaya et al., 2016).

Regarding MCR as a predictor of mortality, a study including nearly 12,000 community-dwelling older adults without dementia found that MCR was associated with increased 2-year mortality (adjusted OR 1.89) (Ayers & Verghese, 2016). Because their study included generally healthy individuals who were, at minimum, able to live at home, it is reasonable to suspect that mortality rates would have been higher had individuals living in institutions also been included.

2.3.2 Cognitive frailty

Cognitive frailty is described as the simultaneous presence of frailty and cognitive symptoms (Kelaiditi et al., 2013). While the concept of MCR was adapted from the dementia-oriented MCI state, cognitive frailty originated from the more physically oriented frailty concept, commonly defined by the criteria proposed by Fried et al.: 1) unintentional weight loss; 2) weakness; 3) poor endurance and low energy; 4) reduced gait speed; and 5) low physical activity level. The original definition of cognitive frailty was: 1) presence of physical frailty; 2) cognitive impairment defined by a Clinical Dementia Rating [CDR] score of 0.5; and 3) exclusion of concurrent AD dementia or other dementias (Kelaiditi et al., 2013).

Despite the fact that this phenotype has been defined for years, there remain variations in which measures are applied to classify cognitive frailty. Hence, the prevalence rates vary depending on the measure applied. A recent meta-analysis reported prevalence rates between 2.5–50% over follow-up periods ranging from 2–14 years (Bu et al., 2021).

Cognitive frailty has been reported as a sensitive predictor of dementia, disability, and mortality (Feng et al., 2017; Shimada et al., 2016; Solfrizzi et al., 2017; Tsutsumimoto et al., 2020), and meta-analyses by Bu et al. found that all-cause mortality was 1.93 times higher (HR = 1.93, 95% CI 1.67–2.23) for individuals with cognitive frailty than for healthy older adults. They also found the risk of dementia to be 3.66 times higher (HR = 3.66, 95% CI 2.86–4.70) than for robust older adults without cognitive frailty (Bu et al., 2021).

However, the definition of physical frailty includes more than just physical performance, which has led to discussions about subtypes within the frailty phenotype. Liu et al. proposed that frailty could be divided into the following subgroups: 1) mobility type, dominated by slowness of gait and muscle weakness; 2) non-mobility type, dominated by exhaustion and weight loss; and 3) low physical activity type (Liu et al., 2017). On the basis of this classification, the individuals falling within the mobility type of frailty were found to be more cognitively impaired and to have lower survival and poorer overall health, suggesting that performance-based assessments identify individuals who are at high risk for functional decline (Liu et al., 2017).

2.3.4 Dual decline

While MCR and cognitive frailty are concepts that describe the simultaneous presence of impaired cognitive and physical performance, dual decline, which was first described by Montero-Odasso et al., comprises the concurrent decline of gait speed and cognition over time (Montero-Odasso et al., 2020). The Gait and Brain Study found that this temporal relationship between gait speed and cognitive scores was associated with an increased risk of dementia in those with concurrent declines in cognition and physical performance (Montero-Odasso et al., 2018b). In this study gait speed and the Montreal Cognitive Assessment (MoCA) were used as the physical and cognitive components, respectively (Montero-Odasso et al., 2018b; Nasreddine et al., 2005). A recent publication investigating physical performance across the cognitive spectrum that ranges from subjective cognitive complaint to dementia found that physical performance declined with increasing cognitive impairment (Sverdrup et al., 2021), supporting the temporal relationship described by Montero-Odasso and colleagues.

2.3.5 Performance-based approach to dual impairments

Although significant efforts have been made in the last decade towards harmonizing the various definitions of dual impairment, there remains a lack of consensus on the best definition for this phenotype of dual impairment. Regarding cognitive function, SCI has

been of main concern in MCR, while various screening tools for global cognition have been applied to identify cognitive frailty. A Physio-Cognitive Decline Syndrome (PCDS) has also recently been defined as the "concomitant presentation of mobility component of frailty—i.e., slowness or weakness, and early declines in any cognitive domains (1.5 SD below the matched norm)" (Chen & Arai, 2020). Arguments have been made for the benefits of objective measures over subjective measures of both cognitive and physical performance, as the former may enable a more standardized assessment, with opportunity for comparisons to normative data (Ruan et al., 2021). Regardless of how dual impairment is measured, a consensus has been reached in the current literature that the phenotype is broadly characterized by a state of enhanced risk of adverse events and outcomes as falls, fractures, dementia, and disability (Bu et al., 2021; Merchant et al., 2021).

Table 1. Overview of concepts describing dual impairment in cognition and physical performance

Concept of dual impairment	Cognitive component	Physical component
Motoric cognitive risk syndrome (Verghese et al., 2013)	Cognitive complaints identified applying the 15-item CERAD questionnaire, a yes/no rating scale of current functioning in several cognitive complaints	Gait speed ≥1 SD below age- and sex-appropriate mean values established in the same cohort
Cognitive frailty (Kelaiditi et al., 2013)	Clinical Dementia Rating = 0.5	Presence of physical frailty[a]
Dual decline (Montero-Odasso et al., 2020)	Decrease of ≥2 points in MoCA score between baseline and final assessment	Reduction of ≥10 cm/s in gait speed between baseline and final assessment
Physio-Cognitive Decline Syndrome (Chen & Arai, 2020)	≥1.5 SD below age/sex/education-matched norms in any cognitive function domain	Reduced gait speed and/or reduced grip strength

CERAD, The Consortium to Establish a Registry for Alzheimer's Disease; MoCA, Montreal Cognitive Assessment
[a]Physical frailty according to criteria defined by Fried et al. (2001)

2.4 Stroke

The incidence of stroke increases with age and is primarily seen in adults from midlife and onwards (Vangen-Lonne et al., 2015). However, the stroke population is heterogeneous, with a large range seen in pre-stroke function and stroke severity as well as in cognitive function and physical performance status (Dhamoon et al., 2017; Schellhorn et al., 2021a). The World Health Organization (WHO) defines stroke as *"rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin"* (Hatano, 1976). However, this classification of stroke mainly focuses on clinical presentation and fails to consider neuroimaging findings, which have become widely available in the decades following the proposal of the definition. As a result, the American Heart Association and American Stroke Association have proposed

an updated definition that includes clinical symptoms as well as pathological or neuroimaging findings of infarction: *"CNS infarction is 1) brain, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or 2) clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded"* (Sacco et al., 2013).

Symptoms lasting fewer than 24 h and without evidence of infarction by neuroimaging are defined as a transitory ischemic attack (TIA) (Sacco et al., 2013). Approximately 10–20% of all strokes are of hemorrhagic origin, and the remaining ischemic strokes are caused by cardioembolism, large artery atherosclerosis, small artery occlusion, or an undetermined cause, with approximately 25% of cases per category (Ornello et al., 2018; Pinho et al., 2019).

2.4.1 Consequences of stroke

According to the Global Burden of Diseases, Injuries and Risk Factors Study, stroke is the second most common cause of death (Naghavi et al., 2017) and the third most common cause of disability-adjusted life years (DALYs) (Hay et al., 2017) worldwide. Mortality rates have declined significantly the last decade, with a 25% reduction, from 59 to 44 deaths per 100,000 (Kvåle, 2018). This increase in survival rate is likely to result in more people living with stroke-related impairments for extended periods, which highlights the importance of high-quality long-term follow-up after stroke.

Traditionally, the focus of stroke rehabilitation has focused on regaining motor function in affected body functions; however, recent years has seen increased focus on hidden impairments after stroke, which include cognitive impairments, pain, depression, and changes to personality. These impairments are even reported to be present in stroke patients whose stroke, according to well-established stroke severity scales, was considered minor (Kapoor et al., 2017).

Post-stroke cognitive impairment (PSCI) includes any cognitive impairment that develops within six months after stroke, and incudes MCI and dementia (Iadecola et al.,

2019). There are discrepancies in how the prevalence of MCI and dementia post-stroke are classified, and rates appear to vary from 14–29% and 11–42%, respectively, 3 months post-stroke, depending on the method used to define PSCI (Munthe-Kaas et al., 2020). A hospital-based systematic review reported a PSCI prevalence rate of 53%, whereas 36% were classified as MCI (Barbay et al., 2018). In a meta-analysis including both community-based and hospital-based studies, Sexton et al. reported an MCI prevalence rate of 38% in the first year after stroke (Sexton et al., 2019). PSCI is even reported to be prevalent in individuals who underwent successful clinical recovery, as defined by a modified Rankin Scale (mRS) score of ≤2 (Jokinen et al., 2015).

Falls are common among stroke survivors, and a systematic review and meta-analysis (Xu et al., 2018) reported that proportions of fallers ranged from 23–55% in community-dwelling stroke survivors. Mobility and balance were the factors most associated with increased risk of falling, and a Swedish cohort found that the score on the Short Physical Performance Battery (SPPB) was associated with fear of falling (Vahlberg et al., 2013; Xu et al., 2018). Further, performance-based assessments of physical performance have been reported to be predictors of quality of life and disability (Vahlberg et al., 2013). It is also worth noting that individuals who had suffered from minor stroke or TIA had a slower gait speed and a poorer performance on assessments of physical performance relative to stroke-free individuals (Li et al., 2021). These results imply that performance-based testing, applied even in stroke survivors with little or no neurologic sequelae, may be of relevance.

Stroke survivors have been found to have a considerably steeper decline in ADL after stroke compared to their pre-stroke baseline (Dhamoon et al., 2017). On the other hand, many stroke survivors show a significant improvement in function, especially during the first 3 months post-stroke, and 60% of Norwegian stroke survivors were independent in their ADL, as assessed by the mRS at 3 months post-stroke (Fjærtoft, 2021; Langhorne et al., 2009). Nonetheless, only 20% of stroke patients reported an absence of symptoms or functional limitations, and approximately one-fifth of stroke patients experienced stroke-related disability 3 months post-stroke (Ullberg et al., 2015). After the initial 3–6

months, stroke survivors are considered to have entered the chronic post-stroke phase (Kwakkel & Kollen, 2013). Although fewer changes are expected in functional status after this time point, the duration of the transition period between ADL independency and dependency has been reported to be as high as 5 years post-stroke (Rejno et al., 2019).

Factors such as higher age, greater stroke severity, and impaired pre-stroke function are well-known predictors of post-stroke functional decline (Hankey et al., 2007; Reid et al., 2010). Verstraeten et al. reported that stroke patients had reduced physical, cognitive, and IADL function 3 months post-incident compared to healthy controls; they also reported a tendency for performance-based tests to be more accurate than rating scales at detecting post-stroke impairments (Verstraeten et al., 2020). This tendency is supported by findings that incorporating physical performance into a prediction model-based cognitive status improved the prediction of IADL function up to 6 months post-stroke (Bertolin et al., 2018).

2.4.2 Dual impairment after stroke

In recent years, the interplay between motor and cognitive functions has become a topic of interest in stroke populations as well (Chen et al., 2013). Especially executive function has been reported to be associated with physical performance and falls after stroke (Hayes et al., 2016; Tuena et al., 2020). However, global cognitive measures have also been linked to physical performance. Balance and Timed Up and Go (TUG) predicted global cognition, assessed by Mini Mental State Examination (MMSE) at one-year post-stroke in a Norwegian stroke sample, and 10-m walk test at baseline predicted MoCA score 1-year post-stroke (Sagnier et al., 2017; Ursin et al., 2015). Decline in TUG-score has been reported as a predictor of cognitive impairment at two years post-stroke (Ben Assayag et al., 2015). In the same study, both baseline MoCA score and time to complete TUG were reported as predictors of cognitive status at 6 months post-stroke, further they showed that the two assessments correlated moderately ($r = –0.425$) (Ben Assayag et al., 2015). and colleagues suggested that impaired physical performance in stroke

patients could be regarded as a “red flag”, as a corresponding cognitive impairment should be considered (Verstraeten et al., 2020). This view is supported by a review by VanGilder et al., who concluded that cognitive status was decisive of responsiveness to rehabilitation, which is an argument for considering the motor-cognitive interaction in stroke patients (Lingo VanGilder et al., 2020).

Studies on post-stroke cognition and physical performance vary in quality, especially regarding sample size and inclusion criteria, and there are large differences in which assessment tools which have been applied (Table 2). Several studies have investigated physical performance measures as predictors of cognition but concurrent impairments in cognitive and physical performance have to a little extent been explored beyond correlation analyses (Ben Assayag et al., 2015; Sagnier et al., 2017; Ursin et al., 2015).

Notably, some of the studies in Table 2 are hampered by weaknesses in study design as low sample size and heterogeneity in assessment tools. Other studies, such as those by Ben Assayag et al., Sagnier et al., and Ursin et al. had more robust study designs and more power analyses (Ben Assayag et al., 2015; Sagnier et al., 2017; Ursin et al., 2015). For instance, Ben Assayag et al. included well-known assessments of cognition and physical performance, and information about neuroimaging (e.g., pre-existing pathology and stroke lesion volume), and they carried out both cross-sectional and longitudinal analyses (Ben Assayag et al., 2015). Thus, their conclusion that physical performance are risk markers of post-stroke cognitive impairment up to 2 years after stroke appears to be valid (Ben Assayag et al., 2015).

Of the studies presented in Table 2, only the publications by Ben Assayag et al., Sagnier et al., and Verstraeten et al. included more than 200 participants (Ben Assayag et al., 2015; Sagnier et al., 2017; Verstraeten et al., 2020). However, in all three studies the mean age of the included participants were ≥10 years below the mean age of the general Norwegian stroke population (Fjærtoft, 2021). On the other hand, they found significant associations between the cognitive and physical performance tests they applied. This implies that despite the lower average age of their stroke samples, there is evidence of a strong motor-cognitive interaction among this population. Neither MCR or any of the

other dual impairment definitions described in Table 1, nor other combinations of performance-based assessments have, to our knowledge, previously been investigated in stroke samples. Consequently, further investigation of the motor-cognitive interaction and dual impairment in stroke patients is warranted.

Table 2. Selected studies on associations between cognition and physical performance in stroke populations.

Study, country	N	Mean age, years (SD)	Stroke severity	Population	Exclusion criteria	Study design	Cognitive measure	Measure of physical performance	Main findings
Arsic et al. (2015), Serbia	100	69.9 (7.7)	Not reported	Stroke patients (n=50) undergoing early rehabilitation and age and gender matched controls (n=50) without neurological disease	<50 or <80 years of age and not having hemiplegia caused by stroke	Cross-sectional case-control study during early rehabilitation	MMSE, TMT A&B	Gait speed, stride length, step frequency, STEP test	MMSE score was correlated with gait parameters in stroke patients. Cognitive and physical performance were more highly correlated in the controls. Stroke patients had lower scores on all cognitive and physical measures compared to controls.

Study, country	N	Mean age, years (SD)	Stroke severity	Population	Exclusion criteria	Study design	Cognitive measure	Measure of physical performance	Main findings
Ben Assayag et al. (2015), Israel	298	66.7 (9.6)	Median (IQR) NIHSS score: 2 (0–3) Mean (SE) infarct volume, mm^3: 2047.4 (4.9)	Mild to moderate first-ever acute ischemic stroke or transient ischemic attack (TIA)	Hemorrhagic stroke, stroke resulting from trauma or invasive procedures, severe aphasia, CD/dementia, or unlikely to be discharged from hospital	Prospective cohort with follow-up from 6 to 24 months post-stroke	MoCA, NeuroTrax computerized cognitive test battery	Single task preferred gait speed Dual task Timed up and Go (TUG) Berg Balance Scale (BBS)	At 6 months post-stroke MoCA score correlated with TUG score (r = –0.425) and usual gait speed (r = 0.509), and at 12 months r = –0-40 (TUG and r = 0.47 (gait speed) p < 0.001 for all correlations 15.4% developed cognitive impairment from 6–24 months after stroke and they had longer TUG times, lower gait speed and lower BBS scores.

Study, country	N	Mean age, years (SD)	Stroke severity	Population	Exclusion criteria	Study design	Cognitive measure	Measure of physical performance	Main findings
Hayes et al. (2016), Ireland	100	Not reported, range 31 to 98 years	Median (IQR) SSS score: 48 (12)	First-ever ischemic or hemorrhagic stroke	Pre-stroke cognitive impairment, aphasia, too medically unstable to participate or visual or hearing impairments that would interfere with assessments	Cross-sectional within 6 months post-stroke	MMSE, the Behavioral Assessment of the Dysexecutive Syndrome (BADS)	BBS	Participants with executive dysfunction had significantly lower scores on BBS.
Lin et al. (2021), United States	50	60.9 (12.3)	Median (IQR) NIHSS score: 6 (4–9)	Stroke patients with unilateral upper extremity weakness	Visual or hearing impairments limiting ability to participate in test procedures	Prospective cohort with inclusion within 1 week after stroke and follow-up at 6 and 12 weeks	Cog-4	Grip strength, Box & Blocks Test (BBT)	Participants with cognitive impairment performed significantly worse on both affected and unaffected extremity in BBT at baseline but not at follow-ups. Cognitive status was not associated with grip strength at any time point.

Study, country	N	Mean age, years (SD)	Stroke severity	Population	Exclusion criteria	Study design	Cognitive measure	Measure of physical performance	Main findings
Sagnier et al. (2017), France	212	64 (13)	Mean (SD) NIHSS score: 3.7 (3.3)	Supratentorial ischemic stroke	mRS ≥ 1, pre-stroke dementia or psychiatric disorder, or incapacity to perform tests, including severe hemiplegia or aphasia	Prospective cohort with follow-up at 3 and 12 months	MoCA	Fugl-Meyer motor assessment (FMMA) and 10-m walking test (10-MWT)	Changes in 10-MWT were independently associated with changes in MoCA scores. The cognitive domains of executive function and memory were the most associated with changes in gait speed.
Toglia et al. (2011), United States	72	70 (17)	Median (range) NIHSS score: 4 (0–13)	Stroke patients admitted to a rehabilitation unit	Not having completed the FIM assessment	Retrospective design	MoCA, MMSE	Motor sub-score of the Functional Independence Measure (mFIM)	MoCA scores at admission had marginally stronger correlations with mFIM scores at discharge than MMSE scores. Of the MoCA subdomains, visuoexecutive, recall, naming and orientation were associated with mFIM scores.

Ursin et al. (2015), Norway	180	72.1 (12.2)	Mean (SD) NIHSS score: 4.3 (6.5)	First-ever acute ischemic stroke or transient ischemic attack (TIA)	Pre-stroke cognitive impairment, or life-expectancy of <1 year	Prospective cohort with follow-up at 1-year post-stroke	MMSE, Clock Drawing Test, TMT A&B, 10-word test	BBS, Figure of Eight (Fig8), Timed Up and Go (TUG)	Participants who performed well on BBS and Fig8 had significantly lower risk of developing cognitive impairment. Fig8 was the strongest predictor of cognitive impairment 1-year post-stroke. TUG was not a significant predictor of cognitive impairment.
Verstraeten et al. (2020), The Netherlands	287	61.7 (10.7)	Mean (SD) NIHSS: 4.0 (3.8)	First or recurrent ischemic or hemorrhagic stroke (n=142). Controls (n=135) matched on age, sex, and estimated level of pre-stroke intellectual functioning	Pre-existent health problems interfering with cognitive functioning, or severe communication difficulties	Cross-sectional case-control at 3 months post-stroke	MMSE, Stroop test, Digit Span Forward & Backward, Word Fluency Test, Rule Cards Shift 2 from the Behavioral Assessment of the Dysexecutive Syndrome	Purdue Pegboard Test (PPT), total score and motor sub-scores of Barthel Index (BI) and Frenchay Activities Index (FAI)	Performance on PPT correlated significantly with all cognitive measures. Stroke patients performed worse than controls on all cognitive measures.

Cog-4, Cognitive assessment based on NIHSS items for orientation, executive function, language, and inattention; IQR, Interquartile range; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; SD, Standard deviation; TMT A&B, Trail Making Test A&B

2.5 Neuroimaging

Several brain abnormalities are caused by the natural aging process or by disease, which might lead to disturbances in cognition and physical performance (Clouston et al., 2013). Microstructural changes in normal-appearing white and gray matter and white matter hyperintensities (WMH) detected by magnetic resonance imaging (MRI) have been reported to be associated with long-term cognitive outcomes (Jokinen et al., 2013). Small vessel disease (SVD) is regarded as the main etiology of WMH, and together with stroke lesions constitute the most important cerebrovascular pathology seen in older adults (Thijs et al., 2000; Wardlaw et al., 2019). Medial temporal lobe atrophy (MTA), including hippocampal atrophy, is another important pathological marker that has been closely linked to neurodegeneration (e.g., AD) (Scheltens et al., 1992).

Impairments in physical performance has been reported to be associated with the presence of WMH, MTA, and gray matter atrophy (Baezner et al., 2008; Callisaya et al., 2015; Pinter et al., 2017). A progression of WMH increased risk of multiple falls (RR 1.30, 95% CI 1.00–1.70) independent of age and sex in a population of community-dwelling older adults (Callisaya et al., 2015). Furthermore, Rosano et al. reported that individuals who had suffered subclinical brain infarcts—especially in the basal ganglia—were more likely to develop gait disturbances (Rosano et al., 2007).

2.5.1 Neuroimaging and dual impairment

The coexistence of impairments in cognition and physical performance has been linked to common underlying central nervous pathology (Chhetri et al., 2017). Even structural changes that do not meet the criteria for neurological diseases, such as covert white matter lesions or small gray matter volume differences, have been found to be associated with slower gait speed and executive dysfunction (Smith et al., 2015). The hippocampus and prefrontal cortex have been reported as areas important to both cognition and physical performance (Montero-Odasso & Hachinski, 2014). This is in line

with findings of increased WMH and decreased gray matter volume and hippocampal volume being associated both with impaired physical performance and poorer scores on cognitive assessments (Nadkarni et al., 2014; Smith et al., 2015).

Associations between MCR and brain abnormalities are complex and remain to be fully elucidated. A systematic review and meta-analysis by Sekhon and colleagues concluded that MCR was significantly associated with low gray matter volume, mainly in the prefrontal and premotor cortex (Sekhon et al., 2019b). Although they reported no significant associations with burden of WMH, one study included in the systematic review found that individuals with MCR had a significantly higher prevalence of lacunar frontal lesions than did those without MCR (Wang et al., 2016). MCR has previously been reported as a stronger predictor of vascular dementia than AD, which makes atrophy the findings of Sekhon et al. regarding gray matter atrophy somewhat surprising. However, there is reason to believe that neurodegenerative pathology, and at least some types of vascular pathology, particularly in prefrontal and frontal cortex regions, contribute to MCR (Beauchet et al., 2016a; Blumen et al., 2019; Blumen et al., 2021; Mergeche et al., 2016; Wang et al., 2016).

In a population with SVD, both WMH and gray matter volumes were reported as factors associated with global cognition, executive function, processing speed, and physical performance, implying that these pathological brain changes are important for dual impairment (Jokinen et al., 2021).

In stroke survivors, the thalamus, angular gyrus, hippocampus, parahippocampal gyrus, and several basal ganglia structures have been considered important regions for increased risk of developing PSCI (Munsch et al., 2016; Zhao et al., 2018). Further, hippocampal volume correlated with global cognition in an Israeli stroke cohort (Kliper et al., 2016). In the Nor-COAST cohort, the presence of pathological WMH and MTA were reported as the most important predictors of PSCI at 3 months post-stroke, suggesting the involvement of both neurodegenerative and vascular pathogeneses (Schellhorn et al., 2021b). Among the SVD markers, the WMH score is the only marker found to be associated with post-stroke cognitive performance (Molad et al., 2017). The role of

WMH in PSCI is corroborated by several publications, including a systematic review by Georgakis et al., which reported that moderate to severe WMH at the time of stroke was associated with a relative risk for dementia of 2.17 (95% CI 1.72–2.73) and for cognitive impairment of 2.29 (95% CI 1.48–3.54) (Georgakis et al., 2019; Kang et al., 2013; Khan et al., 2019; Kliper et al., 2014).

Regarding physical performance, stroke lesion volume was reported to be associated with balance and gait, and basal ganglia involvement seems to be a negative factor for gait speed 1-year post-stroke (Genthon et al., 2008; Nadeau et al., 2016). WMH has been reported as the type of brain pathology most associated with post-stroke physical impairment (Dai et al., 2022; Sagnier et al., 2020). On the other hand, Nadeau et al. found no association between severity of WMH and physical performance (Nadeau et al., 2016). This finding has been supported by Khan et al., who concluded that WMH was only associated with cognition (Khan et al., 2019). Conversely, Auriat et al. reported that both cognitive and physical outcomes were associated with WMH (Auriat et al., 2019).

Although previous publications report somewhat diverging results, WMH, stroke lesion volume, and MTA seem to be important factors in the development of post-stroke impairments in cognition and physical performance. The roles of WMH and neurodegeneration in these studies on stroke patients are comparable to findings from population-based and SVD studies, and it would be reasonable to hypothesize that pathological brain markers of dual impairment could also overlap (Jokinen et al., 2021; Sekhon et al., 2019b).

2.6 Summary and rationale of thesis

In summary, according to population-based and dementia-orientated studies, there is evidence that dual impairment in cognition and physical performance is common in older adults. This phenotype describes individuals with increased risk of adverse health outcomes, including dementia and hospital admissions, and may be considered an at-risk state. However, this coexistence of impairments has not been studied to date in stroke populations. Furthermore, even in stroke survivors who have few or no neurological stroke sequelae, reduced cognition and physical performance interfering with ADL may be predictors of adverse outcomes, similar to what has been reported in MCR and cognitive frailty studies. Hence, further knowledge on the prevalence of dual impairment, its impact on long-term function, and its associations with structural brain changes would be useful in the understanding and advancement of post-stroke rehabilitation and follow-up.

Although previous research has found evidence of a motor-cognitive interaction in stroke patients, how and to what degree different cognitive measures are associated with physical performance have yet to be fully explored. The presence of impairments in cognitive or physical performance has been described in a substantial part of the stroke population. Thus, applying measures of cognitive and physical function after stroke would increase our knowledge base about the interplay between cognitive and physical performance and would help identify individuals with dual impairment.

Recovery after stroke is heterogeneous and identifying predictors of long-term ADL could contribute to improvements in follow-up after stroke. Measures of cognition and physical performance have been individually described as such predictors, but whether combining these measures is superior to assessing the measures separately remains unclear.

In studies describing dual impairment, divergent evidence regarding the associations with specific pathological markers have been reported. However, WMH and MTA seem to be important markers, and stroke lesion characteristics are reported as significant predictors in studies regarding stroke outcome. Stroke patients have both chronic brain pathology and stroke-related pathology, which has been associated with reduction in both cognition and physical performance. Therefore, investigating associations between neuroimaging markers and dual impairment in the acute post-stroke phase stroke will yield new insights into the etiology of post-stroke impairments in cognition and physical performance.

3 Aims

The overall aim of the thesis was to investigate the synergistic relationship between physical performance and cognition after stroke and the associations between dual impairment and both functional outcome and brain pathology.

The specific aims were as follows:

Paper 1

1. To describe concurrent impairment in cognition and motor performance.
2. To explore how motor performance was related to global cognition, executive function, and memory 3 months post-stroke.

Paper 2

1. To investigate whether measures of cognition and physical performance, separately or in combination, at 3 months post-stroke can predict changes in IADL function 15 months later.
2. To explore whether different paths of IADL could be identified by different scenarios, as defined by combinations of high and low scores on measures of physical performance and cognition.

Paper 3

1. To investigate to what extent pre-stroke cerebral pathology (neurodegeneration, cerebrovascular disease, or mixed pathology) was associated with post-stroke impairments in cognition and motor function.
2. To examine more specifically the association between white matter hyperintensity and medial temporal lobe atrophy and outcomes of cognitive and motor function, in addition to the associations between stroke lesion characteristics (lesion volume and location) and post-stroke impairment groups.

4 Methods

4.1 Study design and participants

This thesis was based on data from the Norwegian Cognitive Impairment after Stroke (Nor-COAST) study, a multicenter prospective cohort study with 815 participants recruited between May 2015 and March 2017 from five hospitals in Norway: St. Olavs hospital, Trondheim University Hospital; Ålesund Hospital; Haukeland University Hospital; Bærum Hospital, Vestre Viken Hospital Trust; and Oslo University Hospital, Ullevål (Thingstad et al., 2018). Participants were included in the Nor-COAST study if they were diagnosed with stroke according to the established WHO criteria (WHO, 1988) or findings on MRI compatible with intracerebral hemorrhage or infarction, symptom onset within 1 week before hospital admission, being ≥18 years of age, fluency in a Scandinavian language, and living in the catchment area of the participating hospitals. The only exclusion criterion was life expectancy of <3 months. Patients were screened for inclusion during the index stay, with follow-up assessments at 3, 18, and 36 months at the participating hospitals' outpatient clinics. Mean (SD) time from inclusion to 3-month follow-up was 3.8 (0.94) months and mean (SD) time from inclusion to 18-month follow-up was 18.7 (3.8) months. Papers 1 and 3 were cross-sectional in design and relied on data from the 3-month follow-up and baseline, respectively, whereas the study in Paper 2 was longitudinal in nature and relied on data from the 3- and 18-month follow-ups.

4.1.1 Study samples

A total of 2505 patients were admitted to stroke units at the participating hospitals during the inclusion period (Kuvås et al., 2020). Of those, 559 failed to meet the eligibility criteria, 753 were not screened for inclusion due to staff unavailability, and 143 were not included for other reasons. Ultimately, a total of 815 participants were included in the Nor-COAST study (Figure 1).

Of the 700 participants followed up at 3 months, 133 were excluded from Paper 1 due to missing data on performance-based assessments. In Paper 2, 156 participants of those assessed at the 3-month follow-up were excluded. Of the 544 included participants in Paper 2, 480 had been assessed with relevant measures at the 18-month follow-up. In Paper 3, data from participants included in the MRI sub-study of the Nor-COAST study were used. In addition to the 347 participants with study-specific MRIs, 63 participants had clinical MRI data available for visual scoring, resulting in a total of 410 participants with MRIs available for analyses. Of these participants, 62 were excluded from Paper 3 due to missing data on performance-based assessments at baseline.

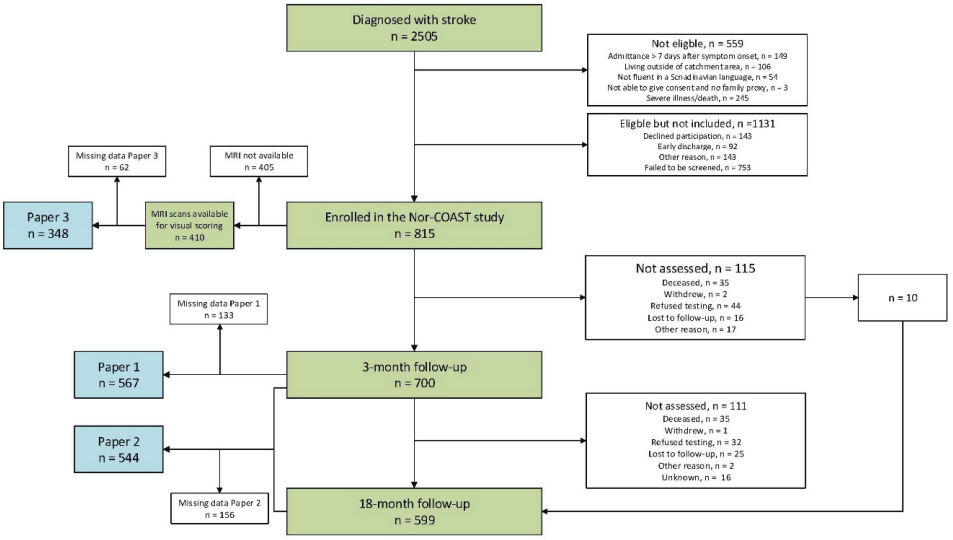

Figure 1. Flowchart of participants included in the papers.

Table 3. Demographic and clinical characteristics of participants

Characteristics	Paper 1 n=567	Paper 2 n=544	Paper 3 n=348
Age, mean (SD)	72.2 (11.7)	71.4 (11.8)	72.3 (11.3)
Women, n (%)	242 (42.7)	235 (43.2)	148 (42.5)
Education (years), mean (SD)	12.5 (3.8)	12.6 (3.8)	12.3 (3.8)
Living alone, n (%)	195 (34.6)	184 (34.1)	126 (36.5)
Infarction, n (%)	517 (91.2)	497 (91.4)	327 (91.4)
Hemorrhage, n (%)	51 (9.0)	47 (8.6)	21 (6.0%)
TOAST classification			
Large artery disease	53 (10.6)	51 (10.6)	34 (10.8)
Cardial emboli	116 (23.2)	112 (23.3)	71 (22.5)
Small vessel disease	121 (24.2)	116 (24.1)	82 (26.0)
Other etiology	11 (2.2)	9 (1.9)	6 (1.9)
Undetermined etiology	200 (39.9)	193 (40.1)	122 (38.7)
NIHSS at admittance, mean (SD)	3.7 (4.7)	3.7 (4.7)	3.8 (4.5)
NIHSS 0–4, n (%)	416 (75.2)	407 (74.8)	251 (72.1)
NIHSS >4, n (%)	137 (24.2)	135 (24.8)	93 (26.7)
Vascular risk factors			
Previous stroke, n (%)	121 (21.3)	120 (22.1)	80 (23.0)
Coronary heart disease, n (%)	96 (16.9)	90 (16.5)	57 (16.4)
Diabetes mellitus, n (%)	106 (18.7)	100 (18.4)	74 (21.3)
Atrial fibrillation, n (%)	129 (22.8)	121 (22.3)	77 (22.1)
Hypertension, n (%)	308 (54.3)	298 (54.8)	189 (54.3)
Hypercholesterolemia, n (%)	289 (51.0)	277 (50.9)	166 (47.7)
Current cigarette smoking, n (%)	111 (19.6)	109 (20.0)	68 (19.5)
BMI (kg/m^2), mean (SD)	26.1 (4.1)	26.2 (4.1)	26.1 (4.0)
Charlson Comorbidity Index, mean (SD)	3.9 (1.9)	3.8 (1.9)	3.9 (1.9)
Prestroke mRS, mean (SD)	0.7 (0.9)	0.7 (0.9)	0.8 (1.0)
mRS >2, n (%)	35 (6.2)	29 (5.3)	27 (7.8)
mRS at discharge, mean (SD)	2.0 (1.2)	2.0 (1.3)	2.1 (1.3)
mRS >2, n (%)	190 (33.5)	180 (33.1)	120 (34.5)

mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale

4.2 Measures

Table 4. Overview of timepoints for data collection for the three papers.

	Paper 1	Paper 2	Paper 3
Baseline			
Participant characteristics	X	X	X
MRI			X
NIHSS at admittance	X	X	X
Prestroke mRS	X	X	X
mRS at discharge			X
SPPB			X
MoCA			X
3-month follow-up			
mRS	X	X	
MoCA	X	X	
TMT-B	X		
10WLR	X		
SPPB	X	X	
Grip strength	X		
Dual task cost	X		
NEADL	X	X	
18-month follow-up			
NEADL		X	

10WLR, 10-Word List Recall; mRS, modified Rankin Scale; MoCA, Montreal Cognitive Assessment; NIHSS, National Institute of Health Stroke Scale; NEADL, Nottingham Extended Activities of Daily Living; SPPB, Short Physical Performance Battery; TMT-B, Trail Making Test B

4.2.1 Baseline assessments

Baseline characteristics such as age, sex, education, living conditions, vascular risk factors, and stroke characteristics were obtained by interviewing the participants or their next of kin during the initial hospital stay or by retrieval from medical records.

4.2.2 Performance-based assessments

Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA), a screening tool for MCI, was used to assess global cognition (Nasreddine et al., 2005). The MoCA has been reported to be superior to the MMSE when used in stroke patients, due to fewer ceiling effects in the memory tasks and better assessment of the cognitive domains of executive function and attention (Folstein et al., 1975; Pendlebury et al., 2010). The test comprises 10 sections that assess eight cognitive domains: short-term memory recall, visuospatial abilities, executive function, attention, concentration, working memory, language, and orientation. For participants with fewer than 12 years of education, one extra point is added to the sum score, as recommended by Nasreddine et al. The maximum score is 30 points, and in the original paper a cut-off of <26 points was recommended to indicate cognitive impairment. However, this threshold has been criticized for being too rigid, with a lower cut-off being proposed as likely more useful for optimal diagnostic accuracy of the MoCA for dementia (Davis et al., 2021). In the present work, the cut-off for cognitive impairment was set at <24, as based on normative data (Borland et al., 2017) (Papers 1 and 3).

Trail Making Test B

For the assessment of executive function, the Trail Making Test B (TMT-B) was applied (Sachdev et al., 2017). In this assessment, the numbers 1 to 13 and the letters A to L are enclosed within circles that are scattered across two pages, and participants are asked to draw lines that connect the circles, alternating between numbers and letters in their correct order, as quickly as possible and without errors (Reitan, 1958). For participants who were unable to complete the test or who required longer than 5 min to complete the test, the recorded time was set at 300 sec (Teuschl et al., 2018), and we did not account for errors made. Requiring longer than 167 sec (1 SD below normative mean for the age group 75–77 years) (Ivnik et al., 1996) to complete the test was defined as executive dysfunction (Paper 1).

10-Word List Recall

The delayed recall component of the 10-Word List Learning and Recall from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery was applied to assess memory (Morris et al., 1989). The participant is shown a list of 10 unrelated words and asked to read this list aloud; this process is repeated three consecutive times. The order of the words changes from trial to trial, and approximately 5 min afterwards, participants are asked to recall these words, which was recorded in the recall test (Morris et al., 1989). The cut-off for an impaired score was set at <5 words, which is at the 5th percentile of the 70–74-year age group with an education of ≥12 years in the normative material; this cut-off is commonly used in memory clinics in Norway (Beeri et al., 2006; Ulstein, 2008). The mean age of the study population lies in this range; thus, this cut-off was chosen (Paper 1).

Short Physical Performance Battery

The Short Physical Performance Battery (SPPB) is an assessment of physical performance that comprises three timed tasks: gait speed, as assessed by 4-meter timed trials; balance, as assessed by the ability to stand for 10 seco with feet placed in three positions (side-by-side, semi-tandem, and tandem); and leg strength, as measured by the time required for five sit-to-stand movements from a chair (Guralnik et al., 1994). Each subtask is scored on a 4-point scale based on the timing, with the total score ranging from 0–12, with higher scores indicating better function (Guralnik et al., 1994). A cut-off at 10 points on the SPPB has been shown to predict frailty, functional decline, and adverse health-related outcomes (da Camara et al., 2013; Guralnik et al., 1995; Verghese & Xue, 2010) and is widely used in research and clinical settings. Thus, the cut-off score indicating impairment was set at <10 points (Paper 1 and 3).

SPPB, and especially the gait speed component, is likely the most well-documented screening test for predicting adverse health outcomes in older individuals (Guralnik et al., 2000; Volpato et al., 2011; Wennie Huang et al., 2010). Due to the high reliability of the gait speed component, the use of gait speed exclusively rather than the use of the

entire SPPB has been discussed. However, previous findings suggest that the SPPB may be more sensitive to functional decline than to gait speed alone (Guralnik et al., 2000; Verghese & Xue, 2010). The Norwegian version of the SPPB is reported to have good test–retest reliability for use in older people with and without dementia (Olsen & Bergland, 2017) (Table 5).

Dual task cost

To assess dual task cost (DTC), the participants were first asked to walk 10 m in their preferred gait speed (single task), and then to walk the same distance while counting backwards (dual task) (Montero-Odasso et al., 2012b). Both the single and dual task were repeated twice, and the mean gait speed (m/s) was calculated and used as the score. In cases in which one of the two measurements were missing, the available time was used. DTC was calculated using the formula: *(Single task gait speed – dual task gait speed)/single task gait speed × 100)* (Montero-Odasso et al., 2012a). A reduction of ≥20% in gait speed under dual task compared to single task conditions was defined as impairment (Montero-Odasso et al., 2017) (Paper 1). Regarding minimal clinically important changes, a cut-off is yet to be defined (Montero-Odasso et al., 2018a). DTC has been reported as an adequate measure of the motor-cognitive interaction in community-dwelling older adults (Montero-Odasso et al., 2012a).

Grip strength

Grip strength was chosen as a supplement to SPPB to measure overall function, as it is a simple, inexpensive expression of overall muscle strength and a valid predictor of disability (Rantanen et al., 1999). Given its ease of applicability, there is reason to believe that it is less prone to differences in test-retest reliability. In addition, a longitudinal relationship between grip strength and cognition has been reported (Praetorius Bjork et al., 2016; Sternang et al., 2016).

To measure grip strength, a Jamar Hydraulic Hand Dynamometer® was used (Mathiowetz et al., 1985). Participants were seated with their elbow in a 90-degree position and their forearm and wrist in a neutral position. Three trials were performed with each hand, and the mean score of the three trials with the participant's dominant

hand was applied in the analyses. Scores <21 kg and <37 kg were defined as impairment for women and men, respectively (Sallinen et al., 2010) (Paper 1).

4.2.3 Functional measures

Modified Rankin Scale

The modified Rankin Scale (mRS) is an updated version of the original Rankin scale (van Swieten et al., 1988), which was constructed to assess outcomes after stroke and which is recommended as an outcome measure in stroke research (Lees et al., 2012; Rankin, 1957). The mRS is an ordinal scale ranging from 0 to 5, with 0 indicating "no symptoms" and 5 indicating "severe disability". A seventh category worth 6 points is often added that indicates "dead". As a result, lower numbers (0–2) indicate independency in daily activities, while higher numbers (3–5) indicate dependency. The mRS is widely used to assess functional outcome in stroke patients in research and in clinical setting (Lees et al., 2012; Sennfalt et al., 2018), and was used to assess functional level before stroke, at the time of hospital discharge, and at the 3- and 18-month follow-ups.

Nottingham Extended Activities of Daily Living

ADL are commonly applied to describe individuals' everyday functioning. IADL comprise tasks that are important to live independently within a community. Such tasks include shopping, managing personal finances, completing domestic chores, and using public transport (Lawton & Brody, 1969). IADL require more higher-level thinking operations involving various cognitive domains, including attention, memory, executive function, and visuospatial abilities (Bruderer-Hofstetter et al., 2020; Royall et al., 2007). Limitations in IADL are regarded as early signs of functional decline, and in the development of cognitive impairment, struggles with performing IADL are often seen as the first sign of functional decline as a result of reduced cognitive abilities (Reppermund et al., 2011). However, a certain level of physical performance is also required to be able to perform both IADL and more basic ADL tasks (Bruderer-Hofstetter et al., 2020).

IADL were assessed with Nottingham Extended Activities of Daily Living (NEADL) scale, a 0–66-point scale in which higher scores indicate more independence (Gladman et al., 1993). The scale consists of 22 questions that address mobility and kitchen, domestic, and leisure activities. Participants are asked whether they have completed the indicated activity within the last 2 weeks. The choices of answers are completed "alone without problem", "alone with problem", "with help", and "not at all". In stroke patients, the minimal clinically important difference is reported to be between 2.4–6.1 points (Wu et al., 2011). NEADL is shown to have few floor- or ceiling-effects (Sarker et al., 2012), making it suitable for a heterogeneous stroke population; therefore, the NEADL was set as the primary endpoint in Paper 2.

4.2.4. Stroke severity

The National Institutes of Health Stroke Scale (NIHSS) is a 15-item assessment scale used to objectively quantify neurologic impairment after stroke (Brott et al., 1989). The scale assesses cognitive functions including awareness, orientation, and response to commands; motor/neurological function through gaze; visual fields; facial palsy; strength; coordination; sensory functions; language, speech, and neglect. The summarized score ranges from 0–42, where 0 indicates no impairment and 42 indicates severe impairment, thereby yielding an impression of stroke severity. The NIHSS is reported to be an adequate tool for predicting post-stroke outcomes (Feigin et al., 2010; Shi et al., 2014).

4.2.5 Definition of dual impairment

As illustrated in Table 1, various definitions of dual impairment have been described. Accordingly, knowledge about assessments of cognition and physical performance that are used alone, the available assessments in the Nor-COAST study, and three cognitive and three physical performance assessments were applied to describe nine scenarios of dual impairment in Paper 1. Paper 3 we elaborated on the results from Paper 1; thus,

the outcome variable in Paper 3 was a four-category variable based on cross-tabulation of dichotomized scores on the MoCA and SPPB, as previously described. Participants were classified as having either 1) no impairments; 2) impaired cognition; 3) impaired physical performance; or 4) dual impairment.

4.3 Neuroimaging

4.3.1 Nor-COAST MRI sub-study

A sub-sample of the Nor-COAST participants underwent a study-specific MRI protocol at one of the five participating hospitals within the first week after stroke symptom onset. The study protocol included a 3D T1-weighted sequence, axial T2, 3D fluid attenuated inversion recovery (FLAIR), diffusion weighted imaging, and susceptibility weighted imaging. Further details about the study protocol are described by Schellhorn et al. (Schellhorn et al., 2021a). In addition to the 347 participants with study-specific MRI scans, 63 participants had clinical MRIs suitable for visual scoring, resulting in a total of 410 participants with MRIs available for visual scoring of pre-stroke pathological markers.

4.3.2 Image analysis

4.3.2.1 Visual rating of MRI scans

Validated visual rating scales were used to analyze brain changes unrelated to the acute stroke. STRIVE—STandards for ReportIng Vascular changes on nEuroimaging—recommendations were applied for rating SVD features (Wardlaw et al., 2013); for neurodegenerative disease, validated visual rating scales were used (Ferreira et al., 2015).

Cerebrovascular changes

White matter hyperintensities (WMHs) of presumed vascular origin were classified applying the widely used Fazekas scale (Fazekas et al., 1987) and classified as normal or pathological by combining score and age (Vernooij & Smits, 2012). The presence of

lacunes of presumed vascular origin assessed on the 3D FLAIR was invariably regarded as pathological (Donnan & Norrving, 2008). Microbleeds were classified as present when ≥2 hypointense lesions were found on susceptibility weighted imaging (Cordonnier et al., 2009; Poels et al., 2011), and old infarcts were classified as present when there was parenchymal defect with significant loss of volume without corresponding diffusion restriction.

Neurodegenerative changes

Medial temporal lobe atrophy (MTA) was assessed according to the established MTA scale (Scheltens et al., 1992), and scored as normal or pathological according to reference values adjusted for age (Ferreira et al., 2015). Posterior atrophy (PA) was assessed with the posterior atrophy scale (Koedam et al., 2011), and a value of ≥2 was considered pathological in participants <95 years of age (Ferreira et al., 2015). Ventricular enlargement, which is regarded as an expression of global atrophy, was measured by the Evans Index (EI) (Evans, 1942) and classified as normal or pathological by applying sex- and age-dependent reference values (Brix et al., 2017).

Grouping of pre-existing pathology

Participants were sorted into four groups according to the presence of pathological MRI markers: one group with normal findings and three groups defined according to the pathology present: 1) no pathological scores on visually rated brain MRI; 2) neurodegeneration (pathological markers of MTA, PA, or EI and no pathological markers of cerebrovascular disease); 3) cerebrovascular disease (pathological scoring of WMH, lacunes, or microbleeds and no pathological markers of neurodegeneration); and 4) mixed pathology (presence of pathological scores of both neurodegeneration and cerebrovascular disease).

4.3.2.2 Stroke lesion volume

Stroke lesion masks were created for participants with visible diffusion restrictions on diffusion weighted imaging. Stroke lesion volume was defined as equivalent to the

ischemic core, which represents the amount of irreversibly destroyed brain parenchyma, identified as diffusion restriction on the diffusion weighted imaging sequence. The ITK "Insight Segmentation and Registration Toolkit-Snap" (ITK-snap) snake tool (v. 3.8.0) (Yushkevich et al., 2006) was used to semi-automatically label acute infarcts to create lesion masks. Stroke lesion masks were created for all participants who had visible diffusion restriction on diffusion weighted imaging. The masked stroke volume in mm^3 was automatically measured by ITK-snap and converted to milliliters (mL) after being exported to a comma-separated values file.

4.3.2.3 Stroke localization

Localization of the acute stroke identified by using the coordinates of the stroke lesion masks to find the corresponding anatomical structure in the Talairach brain atlases (Lancaster et al., 2000). Gyri, thalami, and nuclei were classified as gray matter, and subgyral and extra-nuclear spaces were classified as white matter. Cerebellar structures were classified as cerebellum. In participants with multiple lesions in more than one region, gray matter was set as location if at least one lesion had this location, while white matter was set as location if the lesions were situated in either white matter or cerebellum, and cerebellum was set as location if no lesion was found in the other two locations. Due to the scarcity of participants classified with only a cerebellar lesion, participants with this location were excluded from the regression analyses.

4.4 Statistical procedures

Descriptive statistics were summarized using means and standard deviations or frequencies and percentages. Baseline characteristics were compared between participants included and those lost to follow-up. Independent samples *t*-test was used to test for differences in continuous variables that were approximately normally distributed, and Pearson's chi squared test was used for categorical variables. On a general note, a two-sided p-value <0.05 was regarded as statistically significant.

Statistical analyses were performed using IBM SPSS Statistics v.25.0 (Paper 1 and 2) and Stata/MP v.16 (Paper 2) and v.17 (Paper 3).

Paper 1: Available case analysis was carried out. For analyses of prevalence, scores on cognitive (MoCA, TMT-B, and 10WLR) and motor (SPPB, DTC, and grip strength) tests were dichotomized based on predefined cut-offs and investigated with cross tabulations between each of the motor and cognitive tests. Associations between performance-based tests of motor and cognitive function were studied using linear regression, with the continuous variables of the cognitive tests used as dependent variables and the motor measures used as covariates. The normality of residuals was confirmed by visual inspection of quantile-quantile (Q-Q) plots. First, regression analyses were performed for each combination of motor and cognitive assessments. Second, analyses for each of the cognitive tests were conducted one at a time—including all three motor assessments—as independent variables. All regression analyses were adjusted for age, sex, education, and baseline NIHSS score, all of which had been pre-indicated as plausible confounders.

Paper 2: Single mean imputation was carried out in cases with single items missing on the NEADL at 3 months (n=13) and 18 months (n=7) and on the MoCA (n=4). Cases in which >50% of the items were missing were excluded from the analyses. Missing scores on the SPPB were not imputed due to too few variables being part of the total score.

A mixed-effects model is usually considered a better statistical approach than ordinary regression analyses when investigating repeated measures and change over time. Further, this statistical model was preferred because of its appropriate handling of missing data under the missing-at-random assumption, thereby minimizing bias (Thoresen, 2012, p. 285).

We used mixed-effects linear regression models with the NEADL score as the dependent variable in three different models. The main covariates of interest were the MoCA and SPPB score at 3 months. All three regression models included the known risk factors of age, sex, stroke severity (NIHSS), and prestroke functional dependency (prestroke mRS)

as covariates, and patient as random effect. Further, we included timepoint (i.e., 18 vs 3 months) and either the MoCA score (Model A), the SPPB score (Model B), or both scores combined (Model C) and their interactions with the studied timepoints. The interaction between time and the MoCA and/or SPPB score(s) was examined to investigate the impact of the clinical measures on change over time. Normality of residuals was confirmed by visual inspection of Q–Q plots. The pre-stroke mRS score was treated as a categorical variable in the mixed models analyses, due to its non-linear association with NEADL score. Due to few participants with an mRS score of 4 or 5, participants with a score of 3 (n=27), 4 (n=1), or 5 (n=1) were collapsed into the score range category of 3–5 in the regression analyses. The model fit was compared between the models by likelihood ratio tests, with Model C defined as the reference model.

To investigate whether different paths of IADL could be identified by different combination of scores on the MoCA and SPPB, we presented the estimated level of NEADL score over time for four scenarios, based on the model with combined assessment, namely for SPPB scores of 8 and 12, and for MoCA scores of 22 and 28. These corresponded to the lower and upper quartiles, respectively, of the SPPB and MoCA scores in our data set, which were obtained by using the following variables in the analyses: SPPB score minus 8, SPPB score minus 12, MoCA score minus 22, and MoCA score minus 28. The four scenarios were then defined by combining the MoCA score upper quartile with the SPPB score lower and upper quartile and the MoCA score lower quartile with the SPPB score upper and lower quartile in the linear mixed-effects model.

Paper 3: Pearson's chi squared test was also applied for dichotomous and nominal variables for comparisons between the four impairment groups in Paper 3, and the Kruskal–Wallis test was applied for ordinal and continuous variables. Mean imputation was carried out in cases in which single items were missing on the MoCA or NIHSS. Cases in which >50% of the items were missing were excluded from analyses. Missing scores on the SPPB were not imputed due to too few variables being part of the total score. For comparisons of baseline characteristics between impairment groups, Pearson's chi

squared test was used for dichotomous and nominal categorical variables, and the Kruskal–Wallis test was used for ordinal and continuous variables. We used multinominal logistic regression models with the impairment group as the dependent variable and with the type of brain pathology (neurodegeneration, cerebrovascular disease, or mixed pathology), stroke volume, stroke location (right hemisphere and white matter as reference variables), WMH, and MTA as covariates. In the secondary analyses with only WMH or MTA included as covariates, the Fazekas scale was used as an ordinal variable in its original form, with scores ranging from 0–3, and the MTA scale was used as an ordinal variable (range 0–4), where the mean of the score in the left and right hemisphere was applied. Analyses were carried out with and without adjustment for age and sex. Level of statistical significance was set at two-tailed $p < 0.05$ in the regression analyses and at $p < 0.01$ in the comparisons between clinical characteristics, due to multiple hypotheses.

4.5 Ethical considerations

The Nor-COAST study, which includes the work presented in this thesis, was carried out according to the Declaration of Helsinki. Participation was voluntary and based on written informed consent from the participant or, in cases in which participants were unable to provide consent themselves, from their proxy. The study was approved by the Regional Committee for Medical and Health Research Ethics (REC) (2015/171 REK North and REC Central 194265) and registered in ClinicalTrials.gov (NCT02650531).

5 Results

5.1 Paper 1

Associations between post-stroke motor and cognitive function: a cross-sectional study

Of the total Nor-COAST study sample (n=815), 700 were assessed at the 3-month follow-up, and of these, 567 completed at least one motor and one cognitive assessment. The mean (SD) age of the study participants was 72.2 (11.7) years, 242 (43%) were women, and 460 (82%) were diagnosed with ischemic stroke. Baseline mean (SD) NIHSS score was 3.7 (4.7), and 416 (75%) of the participants had NIHSS scores ≤4. Compared to the included participants, those lost to follow-up were significantly older (mean [SD] age 78.5 [10.6], $p < 0.001$) and had suffered more severe strokes (mean [SD] NIHSS score 6.9 [7.8], $p < 0.001$).

The prevalence of concurrent motor and cognitive impairment ranged from 9.5% for DTC and 10WLR to 22.9% for grip strength and TMT-B (Figure 2). Regression analyses showed that SPPB was associated with the scores on the MoCA (regression coefficient B = 0.465, 95% CI 0.352–0.578, $p < 0.001$), TMT-B (B = –9.494, 95% CI –11.726 to –7.925, $p < 0.001$), and 10WLR (B = 0.132, 95% CI 0.054–0.211, $p = 0.001$). Grip strength was associated with MoCA (B = 0.075, 95% CI 0.039–0.112, $p < 0.001$), TMT-B (B = –1.972, 95% CI –2.672 to –1.272, $p < 0.001$) and 10WLR (B = 0.041, 95% CI 0.016–0.066, $p = 0.001$). Higher DTC was only associated with more time needed to complete the TMT-B (B = 0.475, 95% CI 0.075–0.875, $p = 0.005$). The associations remained statistically significant in the models including all three physical performance measures and adjustment for age, sex, and stroke severity.

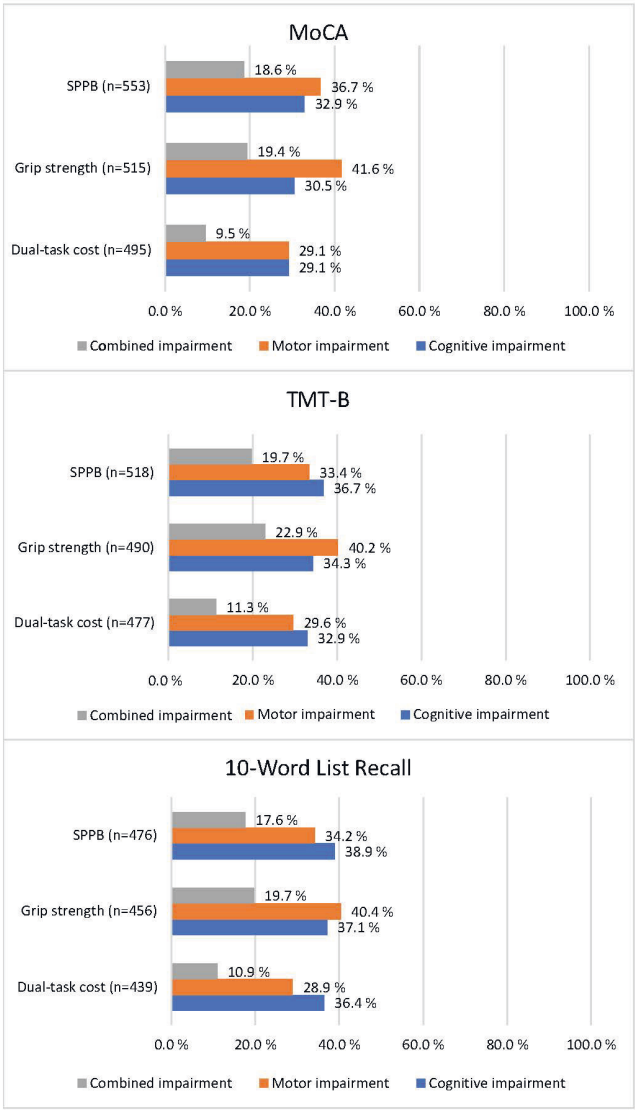

Figure 2. Prevalence of reduced scores on cognitive and motor measures.

Percentages of participants with cognitive impairment only (MoCA <24p, TMT-B >167 sec, 10-Word List Recall <4 words), motor impairment only (SPPB <10p, grip strength <21/37 kg, dual task cost >20%) or combined impairment. MoCA, Montreal Cognitive Assessment; SPPB, Short Physical Performance Battery; TMT-B, Trail Making Test B.

5.2 Paper 2

Physical performance and cognition as predictors of instrumental activities of daily living after stroke: a prospective multicenter cohort study

At the 3-month follow-up of the Nor-COAST study, 700 participants were assessed. Of those, 156 were excluded due to missing data, resulting in a total of 544 participants being included in the present study. Those excluded were significantly older (mean [SD] age 77.1 [10.7] vs 71.4 [11.8] years, $p < 0.001$) and had suffered more severe strokes (mean [SD] NIHSS score 5.7 [6.4] vs 3.7 [4.7], $p < 0.001$). Of the included participants, 235 (43.2%) were females and 29 (5.3%) had a pre-stroke mRS score of >2. Mean (SD) NEADL score was 51.4 (14.1) at 3 months and 52.3 (14.8) at 18 months.

Mixed-effects linear regression analyses showed that in the model that only included the MoCA as a performance-based measure, the interaction between the MoCA score and time was significant, with a coefficient of 0.268 (95% CI 0.086–0.449, $p = 0.004$), indicating that the MoCA score affected the change observed in the NEADL score between 3 and 18 months. In the model that included the SPPB instead of the MoCA score, a significant interaction was found between SPPB score and time (coeff. 0.331, 95% CI 0.042–0.619, $p = 0.025$). In the model that combined the SPPB and MoCA scores in the regression coefficient, the interaction with time was significant for MoCA (0.238, 95% CI 0.030–0.445, $p = 0.025$), but not for SPPB. The model that included both the MoCA and SPPB scores was significantly better than either of the two non-combinatorial models (likelihood ratio $p < 0.001$).

Figure 3 illustrates the change in NEADL score over time for the four predefined scenarios. The combination of SPPB and MoCA scores in the upper quartile at 3 months was associated with improved IADL over time (coeff. 1.396, 95% CI 0.252–2.540, $p = 0.017$).

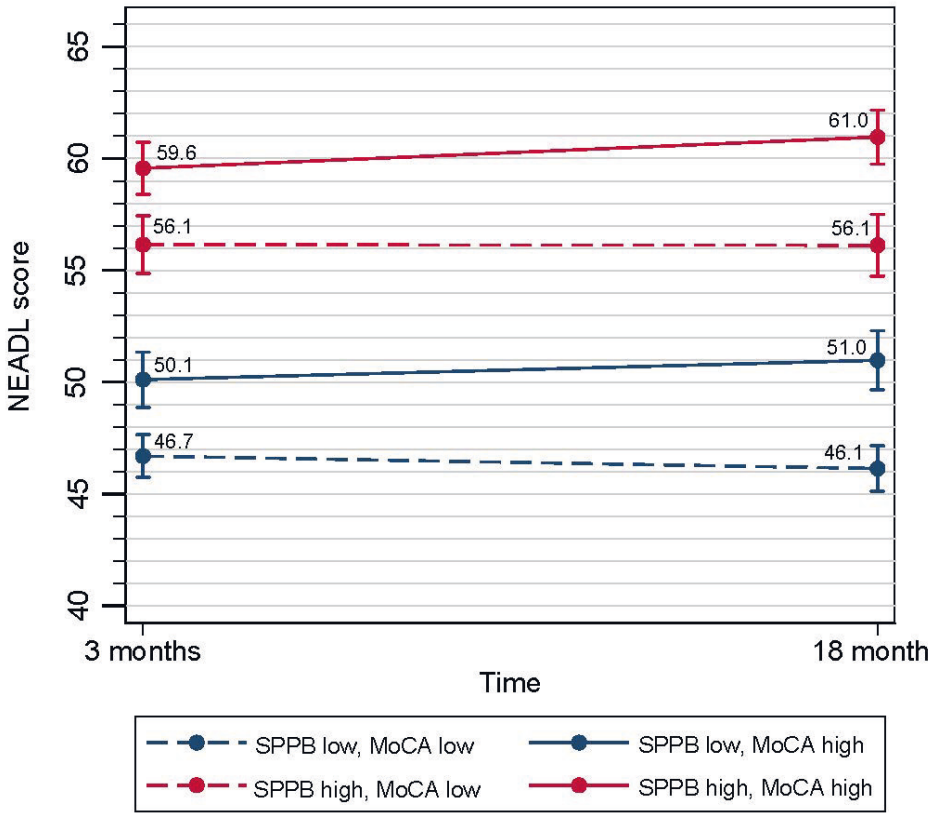

Figure 3. Predictive margin plot of the model including both MoCA and SPPB, with MoCA and SPPB centered on quartiles. SPPB low = 8p; SPPB high = 12p; MoCA low = 22p; MoCA high = 28p. NEADL, Nottingham Extended Activities of Daily Living; MoCA, Montreal Cognitive Assessment; SPPB, Short Physical Performance Battery.

5.3 Paper 3

Neuroimaging markers of dual impairment in cognition and physical performance following stroke: The Nor-COAST study

Of the 410 participants included in the MRI sub-study of the Nor-COAST study, 348 had available clinical assessments and were included in the present study (Figure 1). Those not included were significantly older (mean [SD] age 74.4 [12.0] vs 72.3 [11.3] years, $p = 0.012$), had poorer pre-stroke function (mean [SD] mRS score 1.1 [1.3] vs 0.8 [1.0], $p < 0.001$), and suffered more severe strokes (mean [SD] NIHSS score 5.4 [6.9] vs 3.6 [4.5], $p < 0.001$).

Within the final sample, 235 (43.2%) were female and 324 (93.9%) had suffered from an infarction. The mean (SD) MoCA score was 24.1 (4.9) and the mean (SD) SPPB score was 7.9 (3.7). Regarding the classification of impairments, 117 (33.6%) had normal scores on the MoCA and SPPB, 27 (7.8%) and 105 (30.2%) participants had reduced score on only the MoCA or SPPB, respectively, while 99 (28.4%) participants had dual impairment with reduced scores on both the MoCA and SPPB. Participants with dual impairment were significantly older, had fewer years of education, more severe stroke according to NIHSS score, more comorbidities, a higher prevalence of hypertension and cardiovascular disease, and higher pre-stroke mRS scores.

One or more pathological imaging markers were found in 234 (67.2%) of the participants. Percentages of impairment within the neuropathology groups are displayed in Figure 4.

Unadjusted binominal logistic regression analysis with MRI pathology groups as one categorical variable showed that cerebrovascular pathology and mixed pathology were associated with dual impairment, with OR 2.39 (95% CI 1.17–4.89, $p = 0.017$) and OR 2.18 (95% CI 1.05–4.53, $p = 0.036$), respectively. However, these associations became smaller and nonsignificant when adjusted for age and sex.

Secondary analyses showed that WMH and MTA were associated with dual impairment, with OR 2.28 (95%CI 1.65–3.15, p < 0.001) and OR 1.72 (95% CI 1.19–2.48, p = 0.004), respectively, in the unadjusted analyses, but not in the adjusted analyses. Stroke lesion volume became significantly associated with dual impairment after adjusting for age and sex (OR 1.03, 95% CI 1.00–1.05, p = 0.035).

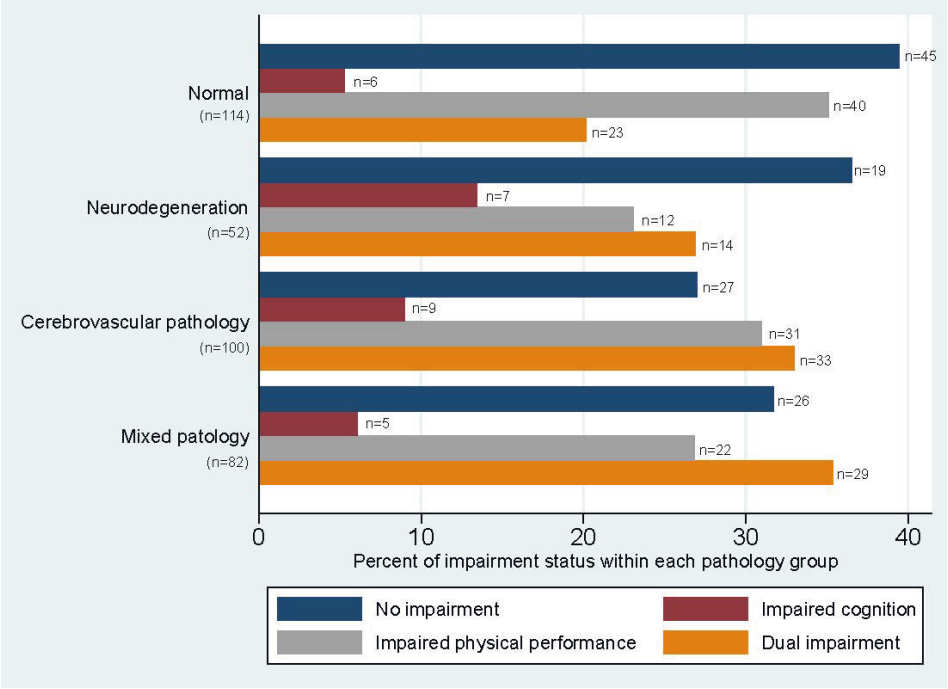

Figure 4. Distribution of impairment status within pathology groups.

6 Discussion

6.1 Main findings in this thesis

The main objective of this thesis was to investigate both the synergistic relationship between physical performance and cognition following stroke and the associations with functional outcomes and brain pathology. We found that one-third and one-fifth of participants had dual impairment in cognition and physical performance at baseline and the 3-month follow-up, respectively. In contrast to our expectations, no differences were found between how the cognitive domains were associated with physical performance at 3 months post-stroke. Further, DTC was, somewhat surprisingly, only associated with executive function. Results from longitudinal analyses showed that both global cognition and physical performance were predictive of long-term function. Poorer performance on the assessments was associated with poorer IADL at 18 months, even after adjusting for known risk factors for functional decline such as stroke severity, pre-stroke function, and age. Combining measures of cognition and physical performance was superior to assessing one domain exclusively at predicting functional change from 3 to 18 months. Contrary to our expectations, pre-existing pathology was not associated with dual impairment at the time of stroke incident. However, higher stroke lesion volume was identified as an important risk factor for dual impairment, with a 3% increase in risk of dual impairment per mL increase in stroke volume.

6.2 Discussion of main results

6.2.1 Dual impairment after stroke

Overall, the main findings from Paper 1 and 3 showed that dual impairment after stroke affects a substantial number of patients. By applying MoCA and SPPB as assessments of cognition and physical performance, respectively, we found a prevalence rate of dual impairment of 28.4% at baseline and 18.6% at the 3-month follow-up. In comparison, Verghese et al. reported a pooled prevalence for MCR of 9.7% in community-dwelling

older adults (Verghese et al., 2013). The higher prevalence found in our study sample was not surprising, as the stroke population are at greater risk of impairments than a community-dwelling sample, especially in the acute and subacute phase, which were studied in Paper 3 and 1, respectively. This is also supported by Allali et al., who found stroke to be a risk factor for MCR (Allali et al., 2016). However, studies on dual impairment in stroke patients are rare; thus, there is a lack of comparable findings in stroke samples.

For the present work, a pragmatic approach was chosen in which we applied scores and cut-offs for selected performance-based assessments of cognition and physical performance for the operationalization of dual impairment. These assessments and cut-offs are commonly used in clinical practice, which increases the clinical relevance of the results. However, the findings presented in this thesis are highly dependent on these choices, which is certainly the case for the prevalence of dual impairment reported in Paper 1, and the lack of expected findings in Paper 3 could also be a consequence of the loss of information due to dichotomization of variables. This should be considered in the discussion of the prevalence of dual impairment and comparisons to findings from other studies.

The definition of dual impairment applied in this thesis is based on objective assessments of cognition and physical performance. This differs notably from the definition of MCR, which is based on the presence of SCI rather than on an objective assessment of cognition (Verghese et al., 2013). A recent publication reporting the prevalence of MCR, PCDS, and cognitive frailty in the same population (n=509) found a prevalence rate of 13.6% for MCR, 18.8% for PCDS, while prevalence of cognitive frailty ranged from 8.8% to 28.7% depending on definition applied (reversible or potentially reversible) (48). Assessments at the 3-month follow-up could be representative of stable function, which would make the findings from Paper 1 comparable to the prevalence of PCDS found by Merchant et al. (Merchant et al., 2021). This is also the only definition presented in Table 1 that is based on performance-based assessments of both cognition and physical performance. The prevalence in this population does not deviate much

from the results found in population-based samples, despite differences in definitions. To further investigate whether there actually is a higher prevalence among stroke survivors than among the general population, comparisons with an age- and sex-matched reference population would be of great interest.

In Paper 1, we aimed to investigate whether global cognition, executive functioning, and memory were differently associated with physical performance. The hypothesis was that executive functioning is more strongly associated than memory, as has previously been reported (Verghese et al., 2002). Conversely, we found no differences between the three cognitive domains, a finding that is supported by those of Verstraeten et al., namely that all measures of separate cognitive domains were significantly correlated with motor function (Verstraeten et al., 2020). Equally, both Ben Assayag et al. and Sagnier et al. reported that global cognition was associated with several assessments of physical performance, including gait speed and Timed Up and Go (TUG) score (Ben Assayag et al., 2015; Sagnier et al., 2017), corroborating our findings. Ursin et al., on the other hand, reported that baseline TUG score was not a significant predictor of cognitive impairment at 1-year post-stroke, and suggested the use of more complex measures of physical performance (Ursin et al., 2015). However, these discrepancies may be at least partly due to methodological differences, such as the inclusion of variables for stroke severity, age, pre-stroke function, and educational level, and to the use of clinical diagnosis of cognitive impairment as the outcome variable.

6.2.2 Performance-based assessments to identify the risk of post-stroke functional decline

The results from Paper 2 demonstrated that MoCA and SPPB scores were both predictors of IADL function, and they remained independent predictors after adjusting for known risk factors for ADL dependency such as stroke severity, pre-stroke function, and age. Previous studies have shown that physical performance (assessed mostly by gait speed) and cognitive function are independently predictive of post-stroke outcome (Bertolin et al., 2018; Jokinen et al., 2015), and our results suggest that combining these

two tests yields an even more precise prediction. A synergistic effect of physical performance and cognition on IADL performance has been found in a population of individuals with SVD, which highlights the complex interplay between these domains and the relevance of the motor-cognitive interaction in IADL performance (Jokinen et al., 2021). These results align with our findings of the superiority of combining assessments of cognition and physical performance over using any one assessment in isolation.

Furthermore, we found in Paper 2 that if made to choose between a cognitive and physical performance assessment, the former is the better option. This conclusion is supported by a Delphi study in which cognition was found to be the most important factor for maintaining independence in IADL, while physical functions including gait, balance, and grip strength have also been noted as influential (Bruderer-Hofstetter et al., 2020).

Stroke severity (NIHSS) and pre-stroke function (mRS) were adjusted for in the analyses in Paper 2. Independently of the scores on these two widely used assessments, marked differences were found between the pre-defined scenarios based on upper- and lower median scores of the MoCA and SPPB scores. This finding implicates an additional value of applying performance-based assessments of cognition and physical performance when identifying post-stroke impairments. This is in line with findings from Jokinen and colleagues, who reported that even in participants with no apparent functional disability, as measured by an mRS score <2, cognitive impairment was widespread (Jokinen et al., 2015). Kapoor et al. found no significant differences in MoCA score between participants with good outcome (mRS 0–1) and poor outcome (mRS 2–5) (Kapoor et al., 2017). Further, they argued that scales incorporating measures of participation, cognition, mobility, and ADL abilities should be applied to better discern between functional impairments in stroke patients (Kapoor et al., 2017). The inclusion of cognitive screening as part of routine follow-up after stroke has already been debated. Though it should not be considered as a substitute for clinical diagnostic assessment, recently published guidelines regarding post-stroke cognitive impairment

recommended the MoCA as an initial screening assessment (Quinn et al., 2021). As a result, findings from Paper 2 add to the body of evidence in support of incorporating performance-based assessments to compliment the traditional assessments of neurological sequelae and overall functional level.

The findings of cognition and physical performance being associated with each other and stable IADL at the 3-month follow-up lend credence to the arguments in favor of identifying cognitive impairment after stroke, as such identification could impact rehabilitative potential. Increased awareness of cognitive difficulties following stroke and how they can accompany physical impairments could lead to more personalized follow-up and higher success rates in rehabilitation. This sentiment is shared by VanGilder et al., who reported in their review that cognitive impairments impacted responsiveness to physical rehabilitation (Lingo VanGilder et al., 2020). Accordingly, they recommended that health care professionals consider this fact when planning rehabilitation programs, as cognitively impaired individuals are likely to require more personalized follow-up to complete the rehabilitation successfully (Lingo VanGilder et al., 2020).

Our aim in Paper 2 was to investigate whether cognition and physical performance could predict changes in IADL over 15 months. By exploring this, we hoped to identify adequate predictors for functional decline, as individuals with impaired cognitive and physical performance have been reported to have a higher risk of disability and mortality, especially in the short term, compared to individuals with impairments in only one domain or no impairment at all (Grande et al., 2020). The results in Paper 2 were not based on the classification of dual impairment, which was applied in Paper 1 and 3. However, the differences in IADL levels that were identified based on assessment scores are nonetheless supported by Doi et al., who reported that MCR was an independent predictor of disability in community-dwelling older adults (Doi et al., 2017).

6.2.3 Functional trajectories after stroke

Stroke patients constitute a heterogeneous group, both in terms of age, pre-stroke function, and functional trajectory after stroke. The findings of distinct functional paths in Paper 2 and the differences in age and pre-stroke function depending on dual impairment status found in Paper 3 corroborate this statement. Although some stroke patients will have a diagnosis of dementia or other severe illness resulting in functional dependency before the stroke, a stroke might be regarded as a catalyst for functional decline for other individuals (Dhamoon et al., 2017; Pendlebury & Rothwell, 2009).

Low scores on both cognitive and physical measures gave an increased risk of stabilization at a lower IADL level in Paper 2. This is in line with findings from Buvarp et al., who reported stable IADL levels in patients with mild stroke (Buvarp et al., 2020). However, the same study also found a decline in function among patients with moderate stroke, which is an argument in support of prolonged rehabilitation in some patients (Buvarp et al., 2020). Further, Blomgren et al. found that reduced IADL levels may persist up to 7 years after stroke (Blomgren et al., 2018), which, together with results from Paper 2, highlight the importance of early rehabilitation in order to stabilize at the best possible level of function. The stabilization of function also implies that the window from stroke incident to 3 months is important for regaining function; it is also the time frame in which most of the rehabilitation occurs (Hankey et al., 2007). Thus, identifying individuals with dual impairment during the hospital stay may aid in identifying individuals in need of more personalized rehabilitation, which is especially the case with pre-stroke cognitive impairment (Lingo VanGilder et al., 2020).

While the results from Paper 2 showed no significant change in IADL over the 3-to-18-month course, Wæhler et al. reported that Nor-COAST participants classified as frail during hospital admission deteriorated in quality of life, especially self-care and mobility, during the same period of time (Wæhler et al., 2021). This identification of frailty as a predictor of post-stroke outcome is an argument in favor of further exploration of combining performance-based assessments and frailty in prediction of post-stroke function (Herdman et al., 2011). Frail stroke patients experiencing minor strokes are

more likely to experience a larger deterioration in function than patients who are not frail, which might manifest in a functional dependency without recovery to pre-stroke function (Clegg et al., 2013).

6.2.4 Associations between MRI markers of neuropathology and dual impairment

In contrast to previous findings, results from Paper 3 showed no significant associations between pre-stroke MRI markers and dual impairment after adjusting for age and sex. These findings were somewhat surprising, as pre-stroke pathological changes in brain structure, including MTA and WMH, are associated with post-stroke cognition and physical performance (Dai et al., 2022; Georgakis et al., 2019; Pohjasvaara et al., 2007). Further, associations between pre-existing pathology and development of PSCI in the Nor-COAST population have been reported (Schellhorn et al., 2021b). However, Schellhorn et al. used cognitive measures from 3-month follow-ups, whereas in Paper 3, data from baseline were used, meaning that cognitive status could have changed between the assessment dates. In addition, some methodological differences (further discussed under sections 6.3.1.5 and 6.3.2) may have played a role.

Given the substantial burden of pathological brain changes prior to stroke, it might be assumed that many stroke patients are at risk of dual impairment already before the stroke incident (Schellhorn et al., 2021b). However, in MCR populations the importance of WMH has been disputed to some extent, and a systematic review concluded that gray matter atrophy was more important than WMH. Despite the fact that this result is more in line with our findings, the results from Paper 3 regarding pre-existing pathology may have been exposed to some methodological challenges (further discussed in section 6.3.1). Other publications have suggested an interplay between gray and white matter changes. For example, Jokinen et al. found that both pathological processes were associated with dual impairment (Jokinen et al., 2021; Sekhon et al., 2019b). Considering this, WMH has repeatedly been found to be important for post-stroke function and, to various extents, with dual impairment, but application of different classifications and measuring techniques may render the results less comparable.

Stroke lesion volume was the only MRI marker associated with post-stroke dual impairment in Paper 3. This finding is supported by previous studies reporting stroke lesion volume as a predictor of post-stroke outcome (Hawe et al., 2018; Zaidi et al., 2012). However, these studies did not include pre-stroke pathological markers; thus, comparing the impact of the various structural changes was not possible.

Blumen et al. reported that both WMH and neurodegeneration seem to be important in the development of dual impairment, while Jokinen et al. concluded that a combined measure including assessment of hippocampal atrophy, gray matter volume, and WMH could be used as an imaging marker associated with vascular cognitive impairment in a SVD population (Blumen et al., 2019; Jokinen et al., 2020). Combining this knowledge about chronic brain pathology with measures of stroke lesion (both volume and location) may be an ideal approach to increase our knowledge base about the importance of chronic and acute brain pathology in stroke patients and the risk of dual impairment.

6.3 Methodological considerations

In the following section are discussed methodological aspects regarding the internal and external validity of the results from this thesis.

6.3.1 Internal validity of the study

In observational studies, internal validity refers to whether the study measures what it has set out; if the "exposure" (independent variable) is responsible for observed changes, not any other possible causes (Carlson & Morrison, 2009). If internal validity is compromised, the results from the study will be less trustworthy. Study design, study sample, and assessment properties are of importance to the precision and validity of the study.

6.3.1.1 Study design

Studies with an observational design follow a population or a group over a given time span without interventions (Portney & Watkins, 2009). Such studies are suitable to describe population characteristics and to investigate associations. The present thesis is based on observational data from baseline and at 3- and 18-month follow-up of the Nor-COAST study. The major strengths of the study are its large sample size and multicenter design. However, due to its observational nature, no conclusion can be drawn on causality, and the results may only be used to identify associations. Nevertheless, this design is suitable to describe a patient group and generate new research questions based on those observations.

6.3.1.2 Performance-based assessments

The Nor-COAST test battery for cognition and physical performance was extensive and comprehensives, including a greater number of tests than was applied in the studies comprising this thesis. To improve the reliability of the assessments, all health care personnel involved in data collection underwent standardized training. Thus, it is reasonable to assume that the inter-rater reliability of the tests was compromised to a small extent. In Paper 1, three cognitive and three physical tests were included. The test battery in the present study was chosen to capture the heterogeneity of the population and to detect preclinical impairments. In addition, the applicability of tests as screening tools in clinical settings was emphasized. Of the selected tests, the SPPB, DTC, MoCA and TMT-B were included in the core battery of shared measures of mobility and cognition proposed by Montero-Odasso et al. (Montero-Odasso et al., 2018a). The test battery was performed in a standardized order, with the cognitive tests always being performed before the physical ones—this constitutes a strength of the study. The MoCA and SPPB were the first of the cognitive and physical tests to be performed, respectively, to reduce selection bias on the two tests which had been regarded as the most global assessments. Hence, the higher completion rates observed for these tests were expected.

In Paper 2 and 3, the MoCA and SPPB were the main concern, a decision which was influenced by the current focus in the literature, especially the recommendations by Montero-Odasso and colleagues (Montero-Odasso et al., 2018a), and the fact that they had been exposed to less selection bias than other tests. In line with recommendations from the Canadian Consortium on Neurodegeneration and Aging (Montero-Odasso et al., 2018a), we selected cut-offs with high sensitivity for impairments in order to capture both subtle and clinical impairments, and as the purpose was to describe prevalence of an at-risk condition rather than reach a diagnosis, we found the chosen cut-offs to be adequate. Regression analyses were adjusted for known risk factors such as age, sex, education, and stroke severity (Paper 1); however, an obvious limitation in Paper 3 is the lack of adjustment for education in the regression analyses, as educational level is known to influence cognition, which may have led to an overestimation of associations and challenged the internal validity (Ihle-Hansen et al., 2017). This is further discussed under section *6.3.2 statistical considerations*.

Cognitive assessments

Cognition and different levels of cognitive impairment can be regarded as falling on a continuum. Consequently, introducing fixed, dichotomic cut-offs will lead to a less nuanced picture and loss of statistical power. We applied cut-offs based on normative data commonly applied in Norwegian memory clinics for TMT-B and 10WLR and based on the mean age of the participants (Strobel et al., 2018; Ulstein, 2008). However, the cut-offs were not adjusted for age, sex, or education on an individual level, and a substantial proportion of the participants were older than the age groups the cut-offs were based on. Hence, the use of this cut-off could have led to an overestimation of impairment. For MoCA, the cut-off for cognitive impairment in the original publication was set at <26 points (Nasreddine et al., 2005). However, after careful discussion, we opted for a cut-off at <24 points. This decision was supported by a recent publication based on approximately 300 community-dwelling Norwegian adults >70 years, in which the mean MoCA score in men was 24 (Engedal et al., 2021). In the Nor-COAST population, a cut-off of <26 points was reported to yield a sensitivity of 0.71 and a

specificity of 0.73 for cognitive impairment; however, more than half of the included population scored <26 points (Munthe-Kaas et al., 2021). Godefroy et al. Godefroy et al. (2011) reported that lowering the cut-off to <24 points improved the sensitivity to 0.92, but reduced the specificity to 0.58 in their stroke sample (Godefroy et al., 2011). In such matters, it is ultimately and invariably a question of increasing specificity at the cost of sensitivity, or vice versa (Lydersen, 2017).

Physical performance assessments

SPPB was chosen for the assessment of physical performance because it is much-used, well-documented for prediction of adverse health outcomes, and supplies information beyond just gait speed (Guralnik et al., 1995). Another strength of the SPPB is the possibility of receiving a score despite being unable to walk, which reduces the risk of selection bias due to missing data.

Regarding the SPPB, the 10-point cut-off is widely used for identifying individuals at risk of poor balance, gait difficulties, and increased risk of falls, and the application of this cut-off was regarded as adequate in the study populations (Papers 1 and 3) in this thesis (Guralnik et al., 1995). For grip strength, we used age-normative cut-offs split by sex, as recommended by the normative data published by Sallinen et al. (2010). However, the population in Sallinen's study had a lower mean age than that of the population included in Paper 1. As a result, it is reasonable to suspect that the sensitivity and specificity is somewhat skewed in our population compared to that of Sallinen et al.

As with the cognitive assessments, the use of such dichotomized cut-offs will always introduce a risk of misclassification and loss of statistical power. However, to answer the research questions of this thesis, we believe the application of such cut-offs were justified.

DTC is somewhat different than the two other physical assessments, because it is considered more a measure of the motor-cognitive interaction rather than a test of physical performance (Montero-Odasso et al., 2012b). Thus, we expected DTC to be equally or more strongly associated with cognitive measures than with grip strength and SPPB. However, our standardized protocol with counting backwards was likely

insufficiently challenging for a high percentage of the participants, and other studies applying cognitive tasks—such as subtraction by threes or sevens—have reported better sensitivity for assessing the motor-cognitive interaction in older adults (Muir et al., 2012). Individual adjustments of the cognitive task have been recommended to improve the sensitivity of the test (Muir et al., 2012; Patel & Bhatt, 2014), but this is challenging in large multicenter studies such as Nor-COAST. As prioritization of either the cognitive or physical component will influence the performance, standardized protocols with clear guidelines on this matter are required. The test may be better suited for smaller intervention studies than multicenter or epidemiological studies, in which robust simple tests are required. DTC as an assessment of brain resilience may be relevant in clinical settings to get an overall impression of patients at risk of cognitive decline. Nonetheless, as a formal assessment with standardized cut-off values, the test—in the format applied in this thesis—was inferior to the other tests included.

6.3.1.3 Defining dual impairment

In this thesis, dual impairment was detected by combining assessments of cognition and physical performance, and its purpose was to identify individuals with simultaneous impairments in cognition and physical performance. DTC, on the other hand, is the assessment of the capacity of carrying out two tasks simultaneously (Annweiler et al., 2013). Reduced dual task capability could be regarded as an expression of reduced brain resilience, which perhaps at some point manifests as dual impairment, as it is challenged by performance-based assessments. For instance, gait is a complex movement, and several cognitive tasks (such as some included in the MoCA) require the combination of thinking and movement, such as the figure-copying task (Montero-Odasso et al., 2012b; Nasreddine et al., 2005). It is important to recognize the consequences of reduced dual task capacity in clinical settings; for instance, by allowing patients to perform one task before giving instructions for the next, or by avoiding talking and walking simultaneously to reduce the risk of falling. However, objectively assessing dual task capacity requires tailoring the assessment at the individual level. Thus, applying one cognitive and one

physical assessment with standardized performance and available normative data to describe the state of dual impairment, which, by proxy, could imply a reduced brain resilience, may be superior to dual task assessments in clinical settings.

The methodology behind the classification of dual impairment in the study samples included in this thesis have several shortcomings, including the lack of adjustments for age and education. However, the concept of dual impairment has only been highlighted in recent years and has to a small extent been described in stroke populations. Thus, we think the somewhat exploratory approach in this work is considered a justification of the classification based on raw scores of performance-based assessments.

In Paper 1, nine combinations were used to describe single and dual impairment 3 months after stroke. This was done in order to investigate whether there were differences between the cognitive domains in regard to associations with physical performance measures. In Paper 2 and 3, we aimed to further explore dual impairment by applying only one definition. In the Nor-COAST population, a substantially larger part of the total study sample had completed the SPPB and MoCA compared to the other assessments, meaning that these two has the lowest risks of selection bias. Hence, these two assessments were chosen for further investigation of dual impairment.

A criterion for MCR and cognitive frailty is the absence of dementia. In the studies constituting this thesis, however, participants with pre-stroke cognitive impairment were not excluded (n=64 with GDS >2) (Kelaiditi et al., 2013; Verghese et al., 2013). Strictly, this would mean that the individuals with MCR and cognitive frailty should have normal scores on cognitive assessments. However, as reported by Merchant et al., average scores on cognitive assessments such as the MMSE and the MoCA fell below the cut-off for normal cognition in both individuals with cognitive frailty and MCR (Merchant et al., 2021). This is supported by the frequent overlap found between MCR and MCI (Sekhon et al., 2018). Hence, the cognitive status of the dual impairment population in our studies may not differ substantially from MCR and cognitive frailty populations. Nonetheless, the number of participants with pre-stroke dementia

included in this thesis (n=21 with GDS score >3) was low due to completion of the performance-based tests being a criterion for inclusion in all three papers.

In MCR, the cognitive criterion is based on the presence of SCI (Verghese et al., 2013). Although asking the patient or caregiver about SCI is a simple screening tool easily implemented in clinical practice, there are some limitations to the application of this criterion. For instance, prevalence may be influenced by depression and cultural variations (Caramelli & Beato, 2008; Sekhon et al., 2019a). On the other hand, attention deficits, executive dysfunction, and behavioral changes may not necessarily present themselves as cognitive difficulties, but rather as psychiatric symptoms in the form of anxiety and depression (Verdelho et al., 2021). As such, depression and SCI may, in fact, constitute early symptoms of cognitive impairment. Hence, an objective assessment of multiple cognitive domains is arguably superior to SCI when identifying dual impairment in stroke patients (Facal et al., 2019).

Regarding the physical criterion, MCR applies gait speed, while various definitions of frailty incorporating gait and grip strength have been used to define cognitive frailty (Kelaiditi et al., 2013; Verghese et al., 2013). Sekhon and colleagues found that by applying gait speed or the time taken to complete five sit-to-stand movements as the physical criterion of MCR, different participant samples were classified with MCR (Sekhon et al., 2018). The same publication concluded that the prevalence of MCR was higher when gait speed was used as a criterion (Sekhon et al., 2018). Gait speed and duration to complete five sit-to-stand movements are both components of the SPPB, and based on these findings, applying a composite score incorporating both gait speed and five times sit to stand appears to be an adequate approach.

In contrast to the definitions of MCR and cognitive frailty, but in line with the newly described PCDS (Table 1), we applied performance-based assessments to define dual impairment. This decision was mainly based on the recommendations from the Canadian Consortium on Neurodegeneration in Aging (Montero-Odasso et al., 2018a). The MoCA and SPPB are well-known assessments in clinical and research settings, and combining these assessments is feasible to incorporate in clinical practice. Nevertheless,

a consensus on definitions regarding interpretation of scores are needed before clinical implementation can be achieved. Although the results based on this definition of dual impairments are considered valid, it is important to bear in mind that the classification applied in the present thesis could have led to risk of misclassification bias.

6.3.1.4 Assessment of IADL

The total NEADL score was used to assess IADL in Paper 2 (Nouri & Lincoln, 1987). The use of the total score in analyses has been discussed, given that the four subcategories of questions are not unidimensional, and reduced score in one category (e.g., household work) may not hold the same clinical relevance as does a reduced score in the mobility category (das Nair et al., 2011). To remedy this to some extent, the scores were reported descriptively within the sub-categories. Furthermore, there are some known gender biases, especially in the kitchen and domestic categories, and some of the questions in the leisure activities category are influenced by season (broadly speaking, individuals are more active during the summer) and residential situation.

The NEADL includes more questions that rely heavily on physical performance, while cognitively demanding tasks are mainly limited to the question about managing finances and using the telephone. For instance, in the IADL scale by Lawton and Brody or the Frenchay Activities Index, more items requiring a higher level of cognitive abilities are included (Lawton & Brody, 1969; Schuling et al., 1993). On the other hand, Sarker et al. found that NEADL had fewer floor effects than did the Frenchay Activities Index in a stroke population (Sarker et al., 2012). This, in addition to the results from Paper 2 showing that cognition was the best predictor of changes in IADL, indicates that the NEADL should be regarded as an appropriate measure of IADL in this population after all.

6.3.1.5 Neuroimaging variables

For pathology existing prior to the incident stroke, visually rated scales were applied for classification of brain MRI markers (Ferreira et al., 2015; Wardlaw et al., 2013). These scales, especially the Fazekas scale for WMH and Scheltens scale for MTA, are widely used in clinical settings (Fazekas et al., 1987; Scheltens et al., 1992). As a result, findings from Paper 3 based on these visually rated scales may be directly transferable to clinical practice, which is an advantage. However, the cut-offs applied that dichotomized these scales as indicating either the presence or absence of pathology are based on age-adjusted cut-offs (Vernooij & Smits, 2012). Particularly in the older age groups, this is not entirely without limitations; for instance, the presence of some WMH is regarded as within the normal range for certain age groups (Vernooij & Smits, 2012). However, it is possible that even pathological changes regarded as within the normal range could cause dual impairment (Smith et al., 2015). Analyses in Paper 3 were also performed with the raw scores of WMH and MTA rating scales, and the associations with dual impairment status became insignificant when adjusted for age and sex. The scales are ordinal, with 0–3 (WMH) and 0–4 (MTA) as ranges, and more sensitive quantification methods (e.g., as applied by Aamodt et al.) may have led to findings of significant associations with the use of continuous variables as covariates (Aamodt et al., 2021). Considering this, an underestimation of associations between the presence of pre-stroke pathological brain MRI markers and dual impairment may be the case in Paper 3. Nonetheless, an advantage of applying visual rating scales is the robustness against reduced image quality, and more detailed volumetric tools may have reduced the number of participants with MRIs available for analyses, which—again—would have reduced the statistical power of the results. Concerning stroke lesion characteristics, stroke lesion volume was treated as a continuous variable and was significantly associated with dual impairment. Furthermore, it can be argued that the results from the analyses with pre-stroke neurodegenerative and cerebrovascular pathology may have differed had similar volumetric scales been applied.

6.3.2 Statistical considerations

Handling of missing data

In Paper 1, available case analyses were performed for all variables, while in Paper 3, the MoCA score was imputed using a single mean imputation in cases in which <50% of the items were missing. In Paper 2, the MoCA, NEADL, and NIHSS scores were imputed with a single mean imputation in cases in which <50% of the items were missing in the sum score of each assessment. SPPB was regarded as not possible to imputate on, as too few items are included in the sum score. The decision to impute on MoCA, NEADL and NIHSS likely led to the inclusion of an additional number of participants in the analyses, thereby contributing to reduced selection bias in Papers 2 and 3. In contrast, no variables were imputated on in Paper 1, which could have resulted in differences in composition of participants for the nine regression analyses. Due to the variances in number of the included participants across the analyses in Paper 1, complete case analysis was chosen as the approach. Nonetheless, the analyses that included all three physical assessments as covariates yielded the same statistical significance, despite a lower number of included participants.

Confounders

Confounding refers to the mixing of effects when attempting to relate an exposure to an outcome, but actually measuring the effect of a third factor (Grimes & Schulz, 2002). As opposed to a mediator, a confounder is associated with the exposure and affects the outcome, but it is not a link in the causal chain between exposure and outcome (Hulley et al., 2007). If not accounted for, the associations observed between exposure and outcome may be partly explained by the confounder, thereby risking a Type I error and threatening the internal validity (Glasser, 2014). Age and stroke severity are factors known to be associated with post-stroke outcomes; thus, they were adjusted for in all three papers (Hankey et al., 2007). Education is associated with cognitive status and was, therefore, adjusted for in Paper 1. However, as a general rule of thumb, no more than n/10 variables should be included as covariates in the regression analyses to avoid making a Type I error (i.e., rejecting the null hypothesis) (Altman, 1990). In Paper 3, the

group with cognitive impairment only included 27 participants, which did not allow for >3 covariates in the regression analyses, despite the fact that education should ideally also have been included as a covariate. In Paper 2, we aimed to create a prediction model with as few predictors as possible, and after careful discussion, we opted not to include education. On the other hand, we adjusted for pre-stroke function, as we regarded that as a confounder that could affect cognition, physical performance, and IADL status.

Regression analyses

Papers 1 and 3 had a cross-sectional design, while Paper 2 was a prospective cohort study with a follow-up period of 15 months. In Papers 1 and 3, linear and multinominal logistic regression models were applied, respectively, whereas linear mixed model analysis was applied in Paper 2. Regression models are preferred because they allow for adjustments for different covariates. Nevertheless, multicollinearity becomes a concern when adding more covariates to a model. This phenomenon occurs when at ≥2 highly correlated variables are assessed simultaneously in a regression model (Vatcheva et al., 2016). Multicollinearity does not affect the overall fit of the model, but the p-values of the correlated variables will be affected, which could lead to flawed interpretation of results (Vatcheva et al., 2016). Collinearity was tested by obtaining the variance inflation factor (VIF) between variables included in the regression analyses of Papers 1 and 2, and none of the included covariates were considered as too highly correlated.

Available case analyses were performed in Papers 1 and 3, which resulted in different samples sizes, depending on which covariates were included. Although this may have limited direct comparison between analyses, the large variances in sample size for performance-based assessments (Paper 1) and MRI markers (Paper 3) meant that complete case analyses would have excluded a substantial portion of the included participants and introduced further selection bias.

In Paper 2, linear mixed model analysis was regarded as a suitable approach to examine the repeated measures. This allowed for inclusion of all participants—even those with NEADL at only one time point—resulting in a larger sample size, as 64 of the included

participants did not have a NEADL score at 18-months follow-up. Linear mixed models consider the covariance between measurements in an appropriate manner. Complete case analyses are unbiased only if data are missing completely at random (MCAR), but linear mixed model analyses are unbiased under the less restrictive missing at random (MAR) assumption (Laake et al., 2012).

Dichotomization of a variable will likely cause loss of information. However, we still opted to dichotomize scores on the MoCA and SPPB in order to create the four-category impairment status variable that was set as the dependent variable in Paper 3. It is also highly possible that some of the statistical power disappeared in the dichotomization of the two continuous variables (Altman & Royston, 2006). The raw scores on the MoCA and SPPB were used as a basis for the dependent variable. In retrospect, a better approach would have been to use cut-offs based on z-scores that are based on education-, age- and sex-adjusted normative material, as both cognition and physical performance change with aging, and cognition is associated with level of education (Bergland & Strand, 2019; Borland et al., 2017; Ihle-Hansen et al., 2017). The application of raw scores with the same cut-off for all participants may have resulted in an overestimation of impaired cognition and physical performance and, thereby, to an overestimation of dual impairment in Papers 1 and 3. For instance, Borland et al. reported that a MoCA score <22 fell 1.5 SD below the mean MoCA score for the age group 75–85 years with only primary school education (Borland et al., 2017). Likewise for the SPPB, where a score of 9.2 points fell 1 SD below the mean score for women aged 75 years (Bergland & Strand, 2019).

6.3.3 External validity of the study

External validity refers to the generalizability of the results from a given study; to which extent the results are applicable in other settings and for other populations than the ones investigated (Gold, 2012).

The Nor-COAST sample was recruited from five different hospitals, ranging from smaller size to large university hospitals, and representing three out of four health regions in Norway. However, stroke patients who suffered from a more severe stroke were excluded, due to the exclusion criteria of short life expectancy and severe pre-stroke ADL dependency in the Nor-COAST study (Thingstad et al., 2018).

It is well-known that selection bias is an omnipresent threat when recruiting stroke patients for study participation, and patients who are older, have impaired pre-stroke function, experienced a severe stroke, or who have higher comorbidity burdens are more likely to be excluded (Kuvås et al., 2020; Pendlebury & Rothwell, 2019). The Nor-COAST study had quite broad inclusion criteria, aiming to include a representative sample of the Norwegian stroke population. To minimize missing data, telephone interviews were conducted with participants or with their caregivers, or with appropriate nursing home staff in cases in which the participant was unable to attend the follow-up in person. In addition, the 3-month follow-up was to some extent coordinated with the routine assessment by a physician at the stroke unit, which may have increased follow-up rates.

Kuvås et al. investigated selection bias in the Nor-COAST study by comparing the sample to stroke patients registered in the Norwegian Stroke Registry but not included in the study (Kuvås et al., 2020). The Norwegian Stroke Registry has a 87% coverage and is regarded as representative of the Norwegian stroke population (Fjærtoft, 2021). Results from this comparison showed that the Nor-COAST participants were slightly heathier before the stroke and had experienced milder strokes (Kuvås et al., 2020). The included population did not differ significantly in age from the overall Norwegian stroke population, but factors such as living in an institution, cerebral hemorrhage, and recurrent stroke were associated with exclusion from the Nor-COAST study (Kuvås et al., 2020). Nonetheless, as participants in the Nor-COAST study were more similar to the general stroke population than those not included, Kuvås and colleagues concluded that the selection bias in the Nor-COAST study resulted in a study sample that is

representative of the majority of the stroke population, comprising individuals with high pre-stroke function who experienced a mild stroke (Kuvås et al., 2020).

As shown in Figure 1, 700 (87%) participants from the original study sample were followed up at 3 months. However, in Papers 1 and 2, having completed performance-based assessments at this timepoint was required for inclusion, resulting in a further selection of participants. Comparisons of participant characteristics showed that those excluded from analyses in Papers 1 and 2 were older and had experienced more severe stroke than the included participants. In Paper 3, the only additional inclusion criteria for the MRI sub-study at baseline were related to the practical execution of the procedure, as an effort to avoid systematic exclusion based on other characteristics. However, those not included had, on average, suffered from a more severe stroke than did the participants included in the MRI sub-study (Schellhorn et al., 2021a). Further, completion of performance-based assessments during the hospital stay was part of the inclusion criteria for Paper 3, and an exclusion of frailer and more cognitively impaired participants is to be expected.

As a result, the Nor-COAST participants are representative of patients with mild strokes admitted to a Norwegian stroke unit. Regarding generalizability, our results should be interpreted with some caution in the general stroke population, especially in patients living in nursing homes and those having suffered from severe stroke, who were not properly represented in the Nor-COAST sample (Kuvås et al., 2020). Nonetheless, the results from the Nor-COAST study are probably valid for stroke patients who suffered a minor to moderate stroke, which includes the majority of the Norwegian stroke population. Further, the results are to be regarded as valid for stroke patients having experienced mild strokes and being admitted to a stroke unit in high-income Western countries that follow stroke care guidelines similar to the Norwegian guidelines.

7 Conclusion

In conclusion, this work contributes to the body of knowledge about the close interactions between cognition and physical performance and suggests that this topic should be of interest in stroke rehabilitation and prevention of functional dependency after stroke.

The findings highlight the importance of identifying individuals with dual impairment to be able to provide more personalized rehabilitation after stroke. Assessments of global cognition and physical performance at 3 months post-stroke both predict IADL in the longer term after stroke, and a combination of the two seems to be superior to either one in isolation. Concurrent low scores on performance-based assessments of global cognition and physical performance increases stroke patients' risk of stabilizing at a lower functional level than stroke patients with normal scores, underlining the importance of early and ambitious rehabilitation in the subacute phase.

Regarding neuroimaging and dual impairment, findings from this work provide novel information about stroke lesion volume as a risk factor for dual impairment and could encourage further research on this topic. As this thesis comprises some of the first explorations of dual impairment in stroke patients, the results should be verified in other stroke samples, as well as with studies including age- and sex-matched healthy controls.

However, this work does not offer conclusions on which measurements and methodological approaches are most relevant for identification of risk profiles. Hence, further research concerning the performance-based assessments and risk profiles is warranted. Hopefully, this thesis will contribute to raising attention to the interplay between and concurrent presence of impairments in cognition and physical performance after stroke and stimulate further research regarding underlying etiology and consequences for long-term function.

8 Clinical implications

The number of individuals living with consequences of stroke is increasing, and they might live on for many years after the stroke incident. The results presented in this thesis contribute to the growing knowledge about the follow-up of stroke patients in both the short and long term. Stroke patients constitute a heterogeneous group, and identification of individuals at risk of functional decline would allow for more targeted treatment, which would be of great benefit to the patients, their relatives, and the health care system.

The stroke patients with dual impairment might comprise a distinct group of frail stroke patients, and the stroke could be regarded as a consequence and amplifier of extant processes related to reduced brain resilience. The results from this thesis argue for increased focus on identifying these individuals and tailoring rehabilitation to this target group. To achieve this, traditional post-stroke follow-up and rehabilitation should be expanded to incorporate knowledge from other areas of expertise, such as geriatrics.

By combining assessments of cognition and physical performance, distinct functional paths independent of stroke severity and pre-stroke function were identified. This highlights the valuable information on functional status and outcome that may be gained from concurrent assessment of cognition and physical performance in the acute and subacute phase after stroke. Further, stable function after 3 months implies that actions to improve function during the first 3 months should be prioritized, and rehabilitation goals should be ambitious to achieve improvement during this period. Further, the identification of dual impairment during hospital admission might aid in targeting stroke patients in need of more personalized rehabilitation and follow-up. In addition, the stabilization of function from 3 to 18 months may be an argument for performance-based assessments of cognition and physical performance (e.g., MoCA and SPPB) as part of the 3-month follow-up.

Although classified with criteria other than MCR and cognitive frailty, the prevalence of dual impairment found in this thesis and its associations with older age, poorer pre-stroke function, and higher risk of functional disability implies that these stroke patients constitute a particular phenotype with increased risk of adverse health outcomes. Results from this thesis support an approach that assesses overall functional level, as achieved by performance-based assessments, and not just the stroke sequalae, because these stroke patients may require a different type of follow-up to avoid functional deterioration in the aftermath of their stroke.

Overall, there was a considerable burden of pre-existing brain pathology in the sample included in Paper 3, and despite no significant associations with dual impairment status being found, there was a tendency towards WMH being of relevance. Such changes may be an expression of a vulnerable brain less able to compensate for the impact of a stroke lesion, corroborating the idea of a distinct phenotype. The visually rated MRI scales used in this thesis are widely implemented in clinical practice. Hence, findings of pre-existing pathology, especially in addition to stroke lesions of larger sizes, should lead to dual impairment risk assessment.

9 Suggestions for further research

A subset of the stroke population comprises older adults with comorbidity, cognitive impairment, and frailty before stroke, which is important to consider in during follow-up and rehabilitation. These patients are the most exposed to risk of experiencing a functional deterioration caused partly or entirely by the stroke. Thus, there is a need for further knowledge about this distinct phenotype in which individuals typically present with dual impairments after stroke.

Future research should aim to harmonize the definition and operationalization of dual impairment. Prevalence depends heavily on measures and cut-offs applied, and consensus on which criteria to use when classifying dual impairment must be reached to render studies more comparable across populations and countries. For instance, differences in prevalence of dual impairment and risk of adverse outcomes between the stroke population and population-based samples would be of interest.

Regarding identification of individuals at risk of functional decline after stroke, measures should be taken towards agreement on which performance-based assessments are best suited for application in the stroke population. This could include intervention studies that apply personalized measures and evaluation of rehabilitation programs with both patient-related outcome measures and clinical endpoints as outcomes.

We found that IADL function was overall stable up to 18 months post-stroke, but studies with longer follow-up and application of trajectory analyses would contribute to reducing this knowledge gap about functional trajectories in the long term after stroke.

Knowing that stroke patients seem, overall, to have a substantial burden of brain pathology prior to stroke, further research on brain pathology and dual impairment should include more sensitive methods for detecting cerebrovascular and neurodegenerative pathology. This could increase knowledge about etiology and contribute to the identification of possible targets for preventive measures.

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Paper 1

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RESEARCH ARTICLE Open Access

Associations between post-stroke motor and cognitive function: a cross-sectional study

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Abstract

Background: Motor and cognitive impairments are frequently observed following stroke, but are often managed as distinct entities, and there is little evidence regarding how they are related. The aim of this study was to describe the prevalence of concurrent motor and cognitive impairments 3 months after stroke and to examine how motor performance was associated with memory, executive function and global cognition.

Methods: The Norwegian Cognitive Impairment After Stroke (Nor-COAST) study is a prospective multicentre cohort study including patients hospitalized with acute stroke between May 2015 and March 2017. The National Institutes of Health Stroke Scale (NIHSS) was used to measure stroke severity at admission. Level of disability was assessed by the Modified Rankin Scale (mRS). Motor and cognitive functions were assessed 3 months post-stroke using the Montreal Cognitive Assessment (MoCA), Trail Making Test Part B (TMT-B), 10-Word List Recall (10WLR), Short Physical Performance Battery (SPPB), dual-task cost (DTC) and grip strength (Jamar®). Cut-offs were set according to current recommendations. Associations were examined using linear regression with cognitive tests as dependent variables and motor domains as covariates, adjusted for age, sex, education and stroke severity.

Results: Of 567 participants included, 242 (43%) were women, mean (SD) age was 72.2 (11.7) years, 416 (75%) had an NIHSS score ≤ 4 and 475 (84%) had an mRS score of ≤2. Prevalence of concurrent motor and cognitive impairment ranged from 9.5% for DTC and 10WLR to 22.9% for grip strength and TMT-B. SPPB was associated with MoCA (regression coefficient B = 0.465, 95%CI [0.352, 0.578]), TMT-B (B = -9.494, 95%CI [− 11.726, − 7.925]) and 10WLR (B = 0.132, 95%CI [0.054, 0.211]). Grip strength was associated with MoCA (B = 0.075, 95%CI [0.039, 0.112]), TMT-B (B = -1.972, 95%CI [− 2.672, − 1.272]) and 10WLR (B = 0.041, 95%CI [0.016, 0.066]). Higher DTC was associated with more time needed to complete TMT-B (B = 0.475, 95%CI [0.075, 0.875]) but not with MoCA or 10WLR.

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Conclusion: Three months after suffering mainly minor strokes, 30–40% of participants had motor or cognitive impairments, while 20% had concurrent impairments. Motor performance was associated with memory, executive function and global cognition. The identification of concurrent impairments could be relevant for preventing functional decline.

Trial registration: ClinicalTrials.gov Identifier: NCT02650531.

Keywords: Stroke, Cognitive function, Motor function, Function

Background

Stroke is reported to be the third-most common cause of disability-adjusted life years (DALYs) worldwide [1]. Post-stroke motor and cognitive impairments are prevalent, and even though function improve during the first 3 months after stroke [2], approximately one fifth of stroke patients experience stroke-related disability 3 months post-stroke [3], highlighting the need of early detection and prevention of further deterioration of function. Motor deficits leading to impaired gait, balance and general reduction in physical function are seen in almost 50% of stroke cases 3 months after stroke [4]. The prevalence of mild and major cognitive impairments appears to vary from 14 to 29% and 11 to 42%, respectively, 3 months post-stroke, depending on the method used to define post-stroke neurocognitive disorder [5]. In a study assessing stroke patients 3-6 months post-stroke, Sachdev et al. reported a prevalence of mild cognitive impairment and dementia of 37 and 21%, respectively [6], underlining the importance of addressing cognitive impairments following stroke.

Assessments of motor and cognitive functions have established roles in the follow-up of stroke patients but have traditionally been studied, diagnosed and managed as distinct entities [7]. However, the stroke lesion itself, comorbid cerebrovascular disease and neurodegeneration may all cause both cognitive and motor impairments [8].

It is well-documented that older people in the general population with concurrent impairments in motor and cognitive functions are at increased risk of developing dementia as well as being at risk for higher rates of hospital admissions, falls, dependency and mortality [7, 9, 10]. In population-based studies, the simultaneous presence of gait disturbances and memory complaints, called motoric cognitive risk (MCR) syndrome, has also been shown to increase risk of developing dementia [10]. Additionally, in the stroke population, impaired balance and gait post-stroke are significant risk factors for cognitive impairment [11, 12]. However, previous studies are few in number, and there is a need for additional knowledge about the relationship between motor and cognitive impairments based on multicentre studies of stroke populations.

Previous research has clearly indicated an association between cognitive and motor performance among older people. Vascular pathology appears to be related to motor impairments and executive dysfunction, while impaired memory is a typical symptom of neurodegeneration, especially Alzheimer's disease [13, 14]. Gait performance following stroke has been reported to be associated with global cognition, executive function and memory [11, 12, 15]. The inability to combine a cognitive task with a motor task like walking, assessed as dual-task cost, has been proposed as an early marker of dementia development [16]. However, studies of associations between motor function and different cognitive domains in older populations have found divergent results [10, 17–20], and there is little evidence in stroke populations. We hypothesized that motor performance would be more closely related to executive function than to memory in a stroke sample, reflecting vascular pathology. A recent consensus report recommended a minimum core battery for assessing the motor-cognitive interphase related to ageing and neurodegeneration in order to increase comparability across research studies, detect subtle or common reversible factors, and accelerate research on dementia, falls, and ageing-related disabilities [7]. This test battery included gait speed, dual-task cost of gait speed (DTC-speed), the Montreal Cognitive Assessment (MoCA) and the Trail Making Test Parts A & B (TMT-A & -B) [21–23].

The overall aim of this study was to describe concurrent impairment in cognition and motor performance and to explore how motor performance was related to global cognition, executive function and memory 3 months post-stroke.

Methods

The Nor-COAST study

The Norwegian Cognitive Impairment After Stroke (Nor-COAST) study is a prospective cohort study with participants recruited from five different hospitals in Norway between May 2015 and March 2017. The details of the study have been published elsewhere [24]. Inclusion criteria were as follows: a diagnosis of stroke according to the WHO criteria [25] or findings on magnetic resonance imaging (MRI) compatible with

intracerebral haemorrhage or infarction; symptom onset within 1 week of admission; age > 18 years; the ability to communicate in Norwegian; and residing within the catchment area of the participating hospitals. Patients with expected survival < 3 months were excluded. The present study is a cross-sectional sub-study of the Nor-COAST study, utilizing data from the three-month follow-up. In addition to the inclusion and exclusion criteria for the Nor-COAST, the participants included in the present study had to have completed at least one cognitive and one motor assessment at three-month follow-up.

Assessments

Participant characteristics

The National Institutes of Health Stroke Scale (NIHSS) [26] score at admission was used to measure stroke severity; possible scores range 0–42, with a higher score indicating a more severe stroke. Mild stroke was defined as NIHSS score 0–4 points, for moderate stroke 5–12 points, for moderate to severe stroke 16–20 points and for severe stroke > 20 points [4]. At three-moth follow-up, instrumental activities of daily living (IADL) were assessed with the Nottingham Extended Activities of Daily Living (NEADL), a 0–66-point scale where a higher score indicates greater independence [27], and the inability to walk 200 m was used as an indicator of physical frailty. Both assessments were based on information collected through interview of patient or caregiver. Functional dependency was measured with the Modified Rankin Scale (mRS) [28], which comprises six levels scored as 0–5 where 0 indicates no disability and 5 indicates severe disability; 6 is used to indicate death. Prestroke score on mRS was recorded at baseline though interview of caregivers, while status at 3 months was assessed by interview of patient or caregiver at the hospital outpatient clinic. The Charlson Comorbidity Index [29] was used as a descriptive measure to quantify comorbidity among the participants and was based on participant information and medical records collected at baseline.

Motor performance tests

The Short Physical Performance Battery (SPPB), an assessment of mobility, consists of three tasks: gait speed, assessed by 4-m timed trials; balance, assessed by the ability to stand for 10 s with the feet in three different positions; and leg strength, measured by the time required for five sit-to-stand movements from a chair. Each task is scored on a 4-point scale, with a total score ranging 0–12 and higher scores indicating better function [30]. The cut-off for a score indicating impairment was set at < 10 points [31]. To assess dual-task cost, the participants were first asked to walk 10 m at their preferred gait speed, and then walk the same distance while counting backwards [21]. Dual-task cost was calculated using the formula *([single-task gait speed – dual-task gait speed]/single-task gait speed × 100 = dual-task cost)* [16]; a reduction of more than 20% was characterized as impairment [16]. Grip strength was measured with a Jamar Hydraulic Hand Dynamometer® (Lafayette Instrument Europe, Loughborough, UK), and the highest score of three attempts using the stronger hand was applied in the analyses. Scores < 21 kg were characterized as impairment for women and < 37 kg for men [32].

Cognitive assessments

Global cognition was assessed with the Montreal Cognitive Assessment (MoCA) with possible scores ranging from 0 to 30 and higher scores indicating better cognition [23]. A cut-off for impairment was set at < 24 points, based on previous recommendations [33]. To assess executive function, the Trail Making Test Part B (TMT-B) [22] was applied. Taking more than 167 s (one standard deviation [SD] below normative mean for the age group 75–77 years) [34] to complete the test was defined as executive dysfunction. The 10-Word List Recall (10WLR), part of the 10-Word List Learning and Recall from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery was applied to assess memory; a score < 5 was defined as impairment, in line with age-adjusted normative data [35, 36].

Data collection

Baseline characteristics were retrieved from participants, their caregivers and medical records. Stroke diagnosis and NIHSS scores were assessed by stroke physicians during hospital stay. At three-month follow-up, participants were evaluated at a hospital outpatient clinic. Motor and cognitive assessments were performed by healthcare personnel who were trained to perform these tests and according to a standardized manual.

Statistics

Demographic and clinical characteristics were summarized using mean and SD for continuous variables and frequencies and percentages for categorical variables. For analyses of prevalence, the clinical variables were dichotomized based on predefined cut-offs and investigated with cross tabulations between each of the motor and cognitive tests. Associations were studied using linear regression with the continuous variables of the cognitive tests as dependent variables and the motor measures as independent variables. First, regression analyses were performed for each combination of motor and cognitive assessments. Second, we conducted analyses for each of the cognitive tests one at a time, including all three motor assessments, as independent

variables. All regression analyses were adjusted for age, sex, education and baseline NIHSS score, which had been pre-defined as plausible confounders. Residuals were checked for normality by visual inspection of Q-Q plots. Statistical significance was defined as two-sided *p*-value < 0.05, and 95% confidence intervals (CI) are reported where relevant. Data were analyzed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

Of 815 patients recruited to the Nor-COAST study, 700 were followed up at 3 months, and of these, 567 completed at least one motor and one cognitive assessment (Fig. 1). The mean (SD) age of the study participants was 72.2 (11.7) years; 242 (43%) were women; and 460 (82%) were diagnosed with ischemic stroke. Baseline mean (SD) NIHSS score was 3.7 (4.7), and 416 (75%) of the participants had NIHSS scores ≤4 points, indicating minor strokes (Table 1). The pre-stroke modified Rankin Scale (mRS) score was ≤2 in 533 (94%) of the participants, and after 3 months, 475 (84%) had an mRS score ≤ 2 (Table 1). As compared to study participants, those lost to follow-up were significantly older (mean [SD] age 78.5 [10.6], *p*-value < 0.001) and had suffered more severe strokes (mean [SD] NIHSS score 6.9 [7.8], *p*-value < 0.001), but there were no differences in sex.

Prevalence of motor and cognitive impairments

Scores for the motor and cognitive tests are presented in Table 2. SPPB scores < 10 points were found in 210 (37%) participants, indicating reduced mobility. DTC ≥ 20% was measured in 146 (29%) participants, indicating a clinically relevant reduction in dual task capacity, while grip strength was below cut-off in 97 (45%) of the women and 120 (39%) of the men, indicating a clinically relevant reduction of strength. On the cognitive tests, 185 (33%) scored below 24 points on the MoCA, indicating reduced global cognition; TMT-B > 167 s indicated impaired executive function in 194 (37%); and 10WLR score below five showed impairment in memory in 188 (39%) of the participants.

Regarding the prevalence of concurrent impairment, dual-task cost in combination with each of the cognitive tests showed a prevalence of approximately 10% (range 9.5–11.3%). The other combinations of tests resulted in reduced scores for both the cognitive and motor tests in about one-fifth of the participants (range 18.6–22.9%) (Fig. 2). Of the participants who scored below 24 points on the MoCA, 103 (57%) scored below 10 points on the SPPB, and of those who took more than 167 s to complete the TMT-B or could not complete it, 102 (54%) scored below 10 points on the SPPB (Fig. 2).

Associations between motor and cognitive function

As shown in Table 3, the regression analyses showed that both the SPPB score and grip strength were associated with scores on the MoCA ($p < 0.001$), TMT-B ($p < 0.001$) and 10WLR ($p = 0.001$). For example, the estimated regression coefficient B = 0.465 for SPPB with MoCA as dependent variable means that for two individuals with the same age, sex, education and stroke severity (NIHSS score at admission), and with one score

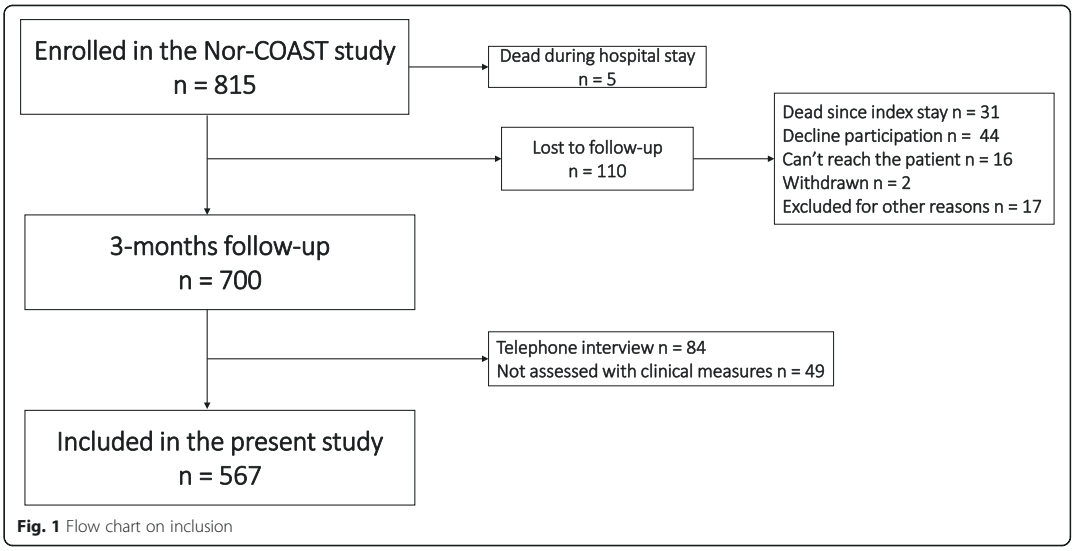

Fig. 1 Flow chart on inclusion

Table 1 Baseline characteristics

	n		
Demographics			
Age, years, mean (SD)	567	72.2	(11.7)
Females, n (%)	567	242	(42.7%)
Living alone, n (%)	564	195	(34.4%)
Education > 9 years, n (%)	567	424	(74.8%)
Stroke classification			
Infarction, n (%)	558	460	(82.4)
Haemorrhage, n (%)	558	51	(9.0%)
Not classified, n (%)	558	47	(8.3%)
NIHSS score at admittance (0–42), mean (SD)	553	3.7	(4.7)
NIHSS score at admittance			
Mild stroke (0–4), n (%)	553	416	(75.2%)
Moderate stroke (5–15), n (%)	553	113	(20.4%)
Moderate to severe stroke (16–20), n (%)	553	20	(3.5%)
Severe stroke (> 20), n (%)	553	4	(0.7%)
Charlson Comorbidity Index, baseline (0–24), mean (SD)	567	3.9	(1.9)
Antiplatelet treatment at discharge, n (%)	567	388	(68.4%)
Anticoagulation treatment at discharge, n (%)	567	166	(29.3%)
mRS (0–6), pre-stroke, mean (SD)	565	0.7	(0.9)

SD standard deviation, *NIHSS* National Institutes of Health Stroke Scale, (0-42p), *mRS* Modified Rankin Scale (0-6p)

Table 2 Assessments at three-month follow-up

	n		
Assessments of motor performance			
SPPB (0–12), mean (SD)	563	9.4	(3.1)
Dual-task cost, (%), mean (SD)	500	12.3	(16.2)
Grip strength (kg), mean (SD)			
Men	305	40.1	(11.7)
Women	216	21.7	(6.9)
Gait speed 4 m, (m/s), mean (SD)	550	1.0	(0.3)
Assessments of cognitive performance			
MoCA (0–30), mean (SD)	562	23.8	(4.7)
TMT-B (0–300), mean (SD)	525	154.7	(83.9)
10-Word List Recall (0–10), mean (SD)	484	5.2	(2.7)
Assessments of function			
Able to walk 200 m, 3 months, n (%)	527	485	(92.0%)
mRS (0–6), 3 months, mean (SD)	565	2.0	(1.3)
Nottingham EADL (0–66), 3 months, mean (SD)	553	49.0	(13.0)

SD standard deviation, *SPPB* Short Physical Performance Battery (0-12p), *Dual-task cost* ([single-task gait speed – dual-task gait speed]/single-task gait speed × 100) (0–100%), *MoCA* Montreal Cognitive Assessment (0-30p), *TMT-B* Trail Making Test Part B (0–300 s), *10-Word List Recall* the recall part of the 10-Word List Learning and Recall from the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) Battery (0–10 words), *mRS* Modified Rankin Scale, *Nottingham EADL* Nottingham Extended Activities of Daily Living scale (0-66p)

difference in SPPB, the expected difference in MOCA is 0.465. The DTC was associated only with the score on the TMT-B ($p = 0.005$). These associations remained statistically significant in the adjusted model (Table 4).

Discussion

In this cross-sectional study of survivors who had suffered mainly mild strokes, we found impairments in either cognitive function or motor function in about one-third of patients, while the prevalence of concurrent impairment ranged from 10 to 23%, depending on which combination of motor and cognitive domains were assessed. Impairments in mobility and grip strength were associated with impaired global cognition, executive dysfunction and impaired memory. Higher dual-task cost was associated only with executive dysfunction. The identification of concurrent impairments could be relevant for preventing functional decline and should encourage a holistic approach to this patient group.

The scores on post-stroke cognitive tests identifying impairment shown here are in line with the results of previous studies [37]. A trend of reduced mobility 3 months post-stroke, especially in patients having suffered from moderate stroke, has been described [38], and Vahlberg et al. [39] found SPPB scores in line with finding from the present study, which are lower than reported in the general population [40]. Motor function has been reported to be a significant predictor of

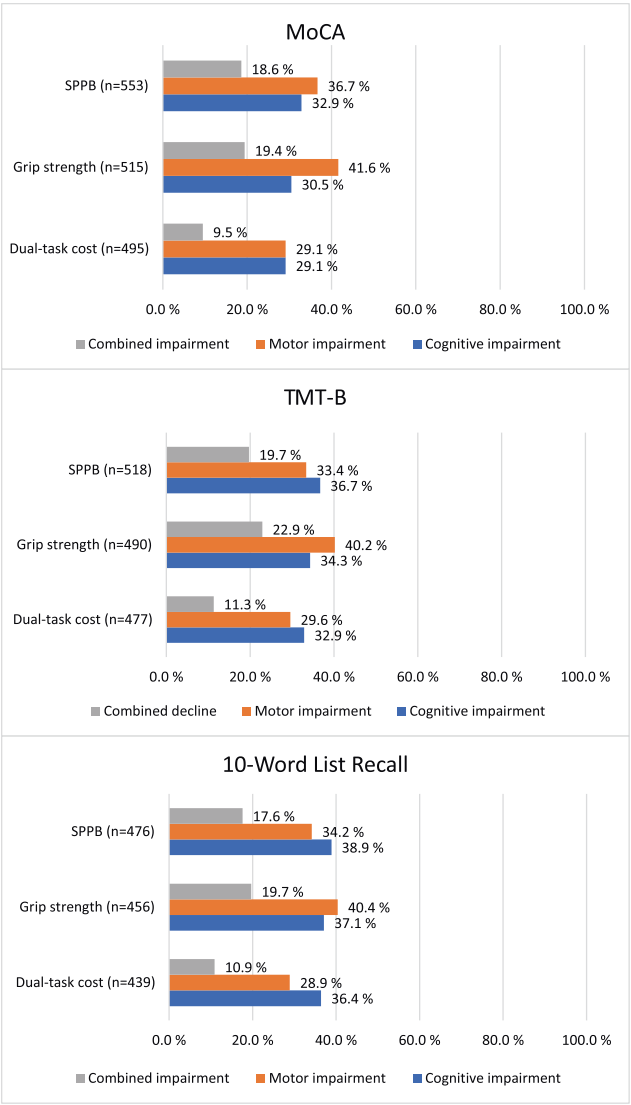

Fig. 2 Prevalence of motor and cognitive impairments. *MoCA* Montreal Cognitive Assessment; *SPPB* Short Physical Performance battery; *Dual-task cost* ([single-task gait speed – dual-task gait speed]/single-task gait speed × 100); *TMT-B* Trail Making Test Part B. Impaired performance was defined as: MoCA <24p, TMT-B > 167 s, 10-Word List Recall < 5 words, SPPB < 10 p, Dual-task cost > 20% and grip strength < 21 kg (women) and < 37 kg (men)

cognitive decline after stroke [12]. However, associations between motor performance and cognitive domains have not, to the best of our knowledge, been examined previously in stroke samples. The dual-task cost has been recommended as a valid measure of the motor-cognitive interphase [41] and found to predict incident dementia in individuals with mild cognitive impairment without previous history of stroke [16]. Several studies of elderly persons with cognitive impairment have shown a strong association between the dual-task test and global cognition [10, 19], but this was not supported by a study of patients with Parkinson's disease [42]. In the present study, dual-task cost was associated only with executive function.

Table 3 Regression analyses with one motor domain at a time as covariate[a]

	Regression coefficient			
	n	*B*	*p-value*	*95% CI*
MoCA				
SPPB	539	0.465	< 0.001	0.352, 0.578
Dual-task cost	485	−0.004	0.661	−0.023, 0.015
Grip strength	503	0.075	< 0.001	0.039, 0.112
TMT-B				
SPPB	507	−9.494	< 0.001	−11.726, −7.925
Dual-task cost	468	0.475	0.005	0.075, 0.875
Grip strength	479	−1.972	< 0.001	−2.672, − 1.272
10-Word List Recall				
SPPB	464	0.132	0.001	0.054, 0.211
Dual-task cost	430	0.000	0.951	−0.014, 0.015
Grip strength	446	0.041	0.001	0.016, 0.066

MoCA Montreal Cognitive Assessment, *SPPB* Short Physical Performance Battery, *Dual-task cost* ([single-task gait speed – dual-task gait speed]/single-task gait speed × 100), *TMT-B* Trail Making Test Part B
[a]adjusted for age, sex, education and stroke severity (NIHSS score at admission)

In the present study, we have demonstrated that, although the patients suffered mainly mild strokes with low NIHSS scores, cognitive and motor impairments as well as concurrent impairments are prevalent, as the majority of patients with impaired MoCA scores also had impaired SPPB scores and vice versa. Concurrent motor and cognitive impairments have been shown to predict poor prognosis as, for example, an increased risk of developing dementia in stroke-free populations [43, 44], and there is reason to believe that these impairments can impact recovery and everyday life [45]. Therefore, we believe that, as part of the routine follow-up protocol after stroke, assessments of cognition and global motor functions should be performed to gain more information that may be relevant for prognosis and may indicate a need for continued rehabilitation even 3 months after a stroke [45]. Further cognitive function is very important for planning and performing rehabilitation and cognitive impairment, such as impaired memory or executive dysfunction, might change responsiveness to motor rehabilitation, which should be taken into consideration when developing targeted interventions in stroke populations [46]. We did not find support for motor performance being more closely associated with specific cognitive domains, and we suggest using global tests like MoCA and SPPB in order to assess cognitive and motor function.

Table 4 Regression analyses with all motor domains as covariates in the same model[a]

	Regression coefficient		
	B	*p-value*	*95% CI*
MoCA ($n = 463$)			
SPPB	0.309	< 0.001	0.179, 0.438
Dual-task cost	−0.006	0.497	−0.025, 0.012
Grip strength	0.063	< 0.001	0.028, 0.097
TMT-B ($n = 448$)			
SPPB	−8.588	< 0.001	−11.204, −5.972
Dual-task cost	0.499	0.009	0.124, 0.873
Grip strength	−1.613	< 0.001	−2.296, −0.930
10-Word List Recall ($n = 417$)			
SPPB	0.099	0.048	0.001, 0.198
Dual-task cost	−0.002	0.786	−0.017, 0.013
Grip strength	0.036	0.010	0.010, 0.061

MoCA Montreal Cognitive Assessment, *SPPB* Short Physical Performance Battery, *Dual-task cost* ([single-task gait speed – dual-task gait speed]/single-task gait speed × 100), *TMT-B* Trail Making Test Part B
[a]adjusted for age, sex, education and stroke severity (NIHSS score at admission)

Shared underlying pathologies might explain concurrent impairment in cognition and motor performance, for which there is increasing evidence [9]. Theoretically, the impairments can be caused directly by the stroke lesion or by structural and functional impairments that appear at a distance from the stroke lesion, also known as diaschisis [47]. Previous studies have shown that stroke survivors have small-vessel disease and neurodegeneration in addition to focal stroke lesions [48, 49], and small-vessel disease and neurodegenerative disease are both reported to be associated with impairments in gait and balance as well as cognition [8, 50–52]. Consequently, the observed impairments in motor and cognitive functions may be a symptom of both focal and disseminated brain pathology. The lack of findings of distinct associations could support a hypothesis of mixed pathology, but further research, including neuroimaging, is needed to achieve better insight.

The strengths of this work are the multicentre design, a relatively large sample size, and the comprehensive test battery that has been performed in line with consensus guidelines [7]. It is also a strength that the Nor-COAST participants are shown to be representative of the majority of the Norwegian stroke population that suffers from mild strokes [53]. Compared to the Norwegian Stroke Registry, the participants included in this sub-study were slightly younger (72 vs 73 years) with a larger proportion suffering from minor impairments (75% vs 69%) measured by baseline NIHSS scores [4]. Despite relatively wide inclusion criteria, there was a selection bias towards younger stroke patients with milder strokes. As a result, this sub-sample probably comprises those individuals most likely to benefit from interventions designed to prevent further functional decline and may be generalized to this part of the stroke population. The

prevalence of impairments reported in this study is closely related to the choice of test battery and cut-off values, which are in line with current recommendations [7]. For MoCA, the cut-off for impairment was set at < 24 points, [33, 54] which should also detect patients with mild cognitive impairment in this population with elderly stroke patients. Because of the large scale of the study, we used a standardized protocol for dual-task cost with counting backwards. This could represent a methodological limitation in this heterogeneous sample, and individual adjustments such as applying more-complex cognitive tasks or motor performance tests could have resulted in other findings [55] but were deemed beyond the scope of this multicentre study. Lastly, the cross-sectional design of the study limits any conclusions in regard to causality.

Conclusion

We found subtle cognitive and motor impairments and combinations of these to be relatively common among stroke survivors despite high premorbid functioning and minor strokes. Motor performance was associated with memory, executive function and global cognition. Our findings add knowledge about post-stroke motor and cognitive function and highlight the need for awareness of motor and cognitive impairments in stroke populations. Further research is needed in regard to the prognostic significance of our findings, as well as their associations to underlying pathology. Concurrent impairments should be recognized both in a short- and long-term perspective in order to identify and target those patients in need of prolonged rehabilitation to prevent further functional decline.

Abbreviations

10WLR: 10-Word List Recall; ADL: Activities of daily living; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; DTC: Dual-task cost; MoCA: Montreal Cognitive Assessment; MRI: Magnetic Resonance Imaging; mRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; Nor-COAST: Norwegian Cognitive Impairment After Stroke; SPPB: Short Physical Performance Battery; TMT-B: Trail Making Test Part B

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Authors' contributions

MSE, IS and PT have been responsible for planning the present report and have been the major contributors in writing the manuscript. MHU contributed to the planning of the study. SL has been involved in planning and interpretation of statistical analyses, which were performed by SL and MSE. TA, RM-K, HI-H, ABK, MKB, HN, YMS and HE are members of the steering committee of the Nor-COAST study and have been involved in planning the design of the Nor-COAST study and in the recruitment and follow-up of participants in the present study. All authors have critically read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to Norwegian legal regulations. Requests to obtain anonymized study data can be addressed to the corresponding author.

Ethics approval and consent to participate

The present study was carried out according to the Declaration of Helsinki, and participation was voluntary and based on written informed consent from the participant, or, in cases where participants were not able to give consent themselves, by their proxy. The study has been approved by the Regional Committee for Medical and Health Research Ethics in North, REK Nord (REC number 2015/171). ClinicalTrials.gov Identifier: NCT02650531.

Consent for publication

Not applicable.

Competing interests

ABK and IS have been investigators in the drug trial Boehringer-Ingelheim 1346.0023, and ABK has also been an investigator for Roche BN29553. The remaining authors declare no conflicts interest.

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Paper 2

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Running title: **Predictors of post-stroke IADL**

Physical performance and cognition as predictors of instrumental activities of daily living after stroke: a prospective multicentre cohort study

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Clinical trial registration number: ClinicalTrials.gov NCT02650531

Abstract

Objective: To investigate if cognition and physical performance, both separately and combined, 3 months post-stroke predict change in instrumental activities of daily living (IADL) up to 18 months, and if different paths of IADL could be identified by different scenarios, defined by combinations of high and low scores on physical performance and cognition.

Design: The study is part of the Norwegian Cognitive Impairment after Stroke (Nor-COAST) study, a prospective multicentre cohort study including acute stroke patients.

Setting: Stroke outpatient clinics at 3 university hospitals and 2 local hospitals.

Participants: Adult stroke survivors (n=544) were followed up at 3 and 18 months after stroke. Participants' mean age was 72.6±11.8 years, 235±43.2 % were females.

Interventions: Not applicable.

Main outcome measures: The primary outcome was IADL as measured by Nottingham Extended Activities of Daily Living. At 3 months, Short Physical Performance Battery (SPPB) and Montreal Cognitive Assessment (MoCA) were used to assess physical performance and cognition, respectively.

Results: The model combining SPPB and MoCA was significantly better than separate models (Likelihood ratio $p<0.001$). Mixed-effects linear regression analyses showed that the regression coefficient (95% confidence interval (CI) for the interaction with time was significant for MoCA, 0.238 (CI, 0.030-0.445; $p=0.025$), but not for SPPB. A combination of

SPPB and MoCA score in the upper quartile at 3 months was associated with improved IADL 1.396 (CI, 0.252-2.540; p=0.017) over time.

Conclusions: Combining measures of cognition and physical performance gave the best prediction of change in IADL. Function at 3 months is decisive for long-term IADL status, which highlights the importance of targeted rehabilitation in the early and subacute phases after stroke.

Keywords: Stroke, recovery, cognition, mobility, rehabilitation

Abbreviations:

CI-Confidence interval

IADL-Instrumental activities of daily living

MoCA-Montreal Cognitive Assessment

mRS-modified Rankin scale

NEADL-Nottingham Extended Activities of Daily Living

NIHSS-National Institutes of Health Stroke Scale

SPPB- Short Physical Performance Battery

Stroke is a leading cause of disability-adjusted life-years worldwide (1), and 40% of stroke survivors have functional dependency in instrumental activities of daily living (IADL) 3 years after stroke (2). Furthermore, a significant proportion of stroke survivors without functional

dependency have been found to have problems with cognition and social participation up to 5 years post-stroke (3, 4).

Maintaining independence in IADL is important for quality of life, reduces risk of depression and anxiety, and is associated with better health outcomes (5, 6). In the stroke population, factors such as old age, severity of stroke, and impaired pre-stroke function are well-known predictors of post-stroke functional decline (7, 8). Verstraeten et al. reported that stroke patients had reduced physical, cognitive, and IADL function 3 months after the event compared to healthy controls, and a tendency towards performance-based tests being superior to rating scales in detection of post-stroke impairments (9).

Individuals with impairments in both physical performance and cognition have been described as a phenotype with higher risk of morbidity and progression to dementia (10), and a recent study reported that higher frequency of pre-stroke functional and cognitive impairment gave poorer prognosis post-stroke (10).

Post-stroke cognitive impairment (PSCI) is increasingly recognized as a frequent condition, with reported prevalence for mild cognitive impairment and dementia in stroke survivors ranging from 67% to 37% and 42% to 21%, respectively, depending on study design and diagnostic criteria (11, 12). Cognitive dysfunction, especially within the domains of executive function, memory, and attention, have been reported to be associated with poorer IADL-function after stroke (13, 14).

Reduced physical function is seen in almost 50% of stroke cases 3 months after stroke (15), and assessment of physical performance is an established part of follow-up and integrated in stroke rehabilitation (16). Nevertheless, associations between physical performance and IADL in the stroke population have been sparsely investigated and evidence is diverging. Some studies have reported ability as a predictor of IADL-function (17, 18), while others found no significant association between mobility in the acute phase and IADL 6 months later (19). Thus, more research is needed to determine the impact of physical performance on the prediction of IADL after stroke.

It has been shown that stroke patients reach a plateau phase in functional recovery 3 months after a stroke (8). However, studies have reported that recovery and transition between dependency and independency in ADL happen up to 12 months post-stroke (20, 21), indicating substantial heterogeneity between patients. Thus, it would also be of great value to identify the recovery paths beyond 3 months for subgroups of stroke survivors based on measures of cognition and physical performance.

The Norwegian Cognitive Impairment After Stroke (Nor-COAST) study previously reported that 103 (19%) of the participating stroke survivors (n=553) had concomitant impairments in mobility and global cognition 3 months after stroke (22), indicating that combining these measures might give a more precise prediction than applying one at a time.

The primary aim of this study was to investigate if measures of cognition and physical performance, separately or in combination, at 3 months after stroke can predict change in

IADL-function 15 months later. A secondary aim was to explore if different paths of IADL could be identified by different scenarios, defined by combinations of high and low scores on physical performance and cognition.

Methods

Study design and participants

The present study is part of Nor-COAST, a large multicentre prospective cohort study including participants from five different hospitals in Norway between May 2015 and March 2017 (23). Patients were screened for inclusion during the index stay with follow-up assessments at 3, 18, and 36 months. Inclusion criteria were: diagnosed with stroke according to the WHO criteria (24) or with findings on magnetic resonance imaging (MRI) compatible with intracerebral haemorrhage or infarction, symptom onset within one week before admission, being over 18 years of age, fluency in a Scandinavian language, and living in the catchment area of the participating hospitals. Patients with less than 3 months expected survival were excluded from the study. Further details were published in the protocol paper for the Nor-COAST study (23).

In the present study, participants who completed Nottingham Extended Activities of Daily Living (NEADL), Short Physical Performance Battery (SPPB), and Montreal Cognitive Assessment (MoCA) at 3-month follow-up were included (Figure 1).

Assessments

Baseline characteristics

Age and sex were registered at admission to hospital, and the Charlson Comorbidity Index (25) was retrieved from medical journals. The National Institutes of Health Stroke Scale (NIHSS) (26) score at admission was used to measure stroke severity, with a possible score range of 0-42, with a higher score indicating a more severe stroke. Functional dependency prior to the stroke was measured with Modified Rankin Scale (mRS) (27), ranging from 0 to 6, where a higher score indicates a greater degree of dependency and 6 denotes death.

Dependent variable

IADL at 3- and 18-month follow-up was assessed with the NEADL scale, a 0-66-point scale where a higher score indicates greater independence (28). The scale consists of 22 questions covering mobility, kitchen, domestic, and leisure activities.

Predictors

Global cognition was assessed with MoCA, a ten-item test covering eight cognitive domains, with possible scores ranging from 0 to 30, including one additional point for education < 12 years, and higher scores indicating better cognition (29). The SPPB is a measure of physical performance and consists of three tasks: four-meter preferred gait speed, balance, and sit-to-stand from chair five times, with four-point scales for each task and a summary score ranging from 0 to 12, with higher scores indicating better physical function (30, 31).

Data collection

Baseline characteristics were retrieved from participants, proxies, and medical records during hospital stay. At 3- and 18-month follow-up participants were assessed at a hospital outpatient clinic. NEADL score was collected by an interview of the participant or proxy. Clinical assessments were performed by trained health care personnel according to a standardized manual.

Ethical considerations

The present study was carried out according to the Declaration of Helsinki. Participation was voluntary and based on written informed consent from the participant, or, in cases where participants were not able to give consent, by their proxy. The study has been approved by the Regional Committee for Medical and Health Research Ethics (REC Central 194265) and registered in ClinicalTrials.gov (NCT02650531).

Statistical analyses

Demographic and clinical characteristics were summarized using means and standard deviations (SD) or frequencies and percentages. Single mean imputation was carried out in cases with single items missing on NEADL score at 3 months (n=13) and 18 months (n=7), and MoCA (n=4). Cases with more than 50% of the items missing were excluded from the analyses. Missing scores on SPPB were not imputed due to too few variables being part of the total score.

We used mixed-effects linear regression models with the NEADL score as the dependent variable in 3 different models. All three regression models included the known risk factors age, sex, stroke severity (NIHSS), and prestroke functional dependency (prestroke mRS) as covariates, and patient as random effect. Further, we included time point (i.e., 18 months versus 3 months) and either MoCA (Model A), SPPB (Model B), or both in combination (Model C), and their interactions with time. The interaction between time and MoCA and/or SPPB was examined to investigate the impact of the clinical measures on change over time. Normality of residuals was confirmed by visual inspection of quantile-quantile (Q-Q) plots. Prestroke mRS was treated as a categorical variable in the mixed models analyses due to its non-linear association with NEADL score. Due to few participants with an mRS score of 4 or 5, participants with a score of 3 (n=27), 4 (n=1), or 5 (n=1) were collapsed into score 3-5 in the regression analyses. The model fit was compared between the models by likelihood ratio tests, with Model C defined as the reference model.

To answer the secondary aim of the study we presented the estimated level of NEADL score over time for four scenarios based on the model with combined assessment, namely for SPPB scores of 8 and 12, and for MoCA scores of 22 and 28. These correspond to the lower and upper quartiles of SPPB and MoCA in our data set. These results were obtained by using the variables SPPB score minus 8, SPPB score minus 12, MoCA score minus 22, and MoCA score minus 28 in the analyses. The four scenarios were then defined by combining MoCA upper quartile with SPPB lower and upper quartile and MoCA lower quartile with SPPB upper and lower quartile in the linear mixed-effects model.

Statistical significance was defined as two-sided $p < 0.05$. Data were analysed using IMB SPSS version 25.0[a] and STATA 16[b].

Results

Participant characteristics

Seven hundred participants were assessed in the Nor-COAST study at 3 months; 156 of these were excluded due to missing data, giving 544 participants included in the present study (Figure 1). Those excluded were significantly older (mean (SD) age 77.1 (10.7) versus 71.4 (11.8) years, p<0.001) and had suffered from more severe strokes (mean (SD) NIHSS score 5.7 (6.4) versus 3.7 (4.7), p<0.001).

Of the participants, 235 (43.2%) were females and 29 (5.3%) had a prestroke mRS score > 2 (Table 1). Three months post-stroke mean (SD) SPPB score was 9.4 (3.1) and mean (SD) MoCA score was 24.4 (4.8) (Table 2). Mean (SD) NEADL score at 3 months was 51.4 (14.1) and at 18 months 52.3 (14.8), giving a non-significant change of 0.3 (9.8) points (p = 0.447) for the 480 participants with complete data on both occasions.

Prediction of change in IADL-function

In Model A the interaction between MoCA and time was significant with a coefficient of 0.268 (95% CI 0.086 to 0.449, p=0.004), indicating that MoCA had an impact on change in NEADL

score from 3 to 18 months. In Model B there was a significant interaction between SPPB and time (coeff. 0.331, 95% CI 0.042 to 0.619, p=0.025). In Model C the interaction between MoCA and time remained stable (coeff. 0.238, 95% CI 0.030 to 0.445, p=0.025), whereas the interaction between SPPB and time was no longer significant (p=0.431). Each model extension, that is, Model C vs Model A, and Model C vs Model B, was a statistically significant improvement of the model (Likelihood ratio test, all p <0.001). All the results from the mixed-effects regression analyses are displayed in Table 3.

Change in IADL based on 3-month cognition and physical performance

Figure 2 illustrates the change in NEADL score over time for the four scenarios. Only the combination of MoCA and SPPB score in the upper quartile gave a significant association between time and NEADL score (coeff. 1.396, 95% CI 0.252 to 2.540, p=0.017) (Table 4).

Discussion

In this longitudinal observational study of stroke survivors accessible for clinical assessments 3 months after stroke incident, we found that combining measures of physical performance and cognition was superior to only assessing one domain in order to predict change in IADL from 3 to 18 months post-stroke. However, cognition appeared to be a stronger predictor than physical performance when applied in the same model (Model C: Combined assessment). Overall, there was a stable IADL-function from three to 18 months for all four predefined scenarios. High scores on both cognition and physical performance were

associated with a statistically significant improvement in IADL over time. These results indicate that physical performance and cognitive status at 3 months post-stroke is determinative for IADL-function in the chronic phase after stroke.

Our main finding was that measures of physical performance and cognition in combination added value to the prediction of post-stroke IADL-function, even when adjusting for known risk factors of functional decline. This result highlights the need for clinical assessments of both cognition and global physical function in the subacute phase beyond application of traditional stroke severity scales and functional screening tools (3, 32, 33).

MoCA was the strongest predictor of change in IADL-function, a finding supported by previously published results, as even in a subgroup scoring zero points on NIHSS, cognitive dysfunction correlated with a decline in post-stroke IADL-function (13, 19). Impairments in several cognitive domains after stroke, including global cognition, have been reported (34). Executive function, memory, and attention, which are all incorporated domains in MoCA, are reported to be the most important for maintenance of IADL-function in stroke survivors (14, 29). MoCA is a sensitive screening tool for cognitive impairment in stroke patients, in addition to being more feasible in a clinical setting than extensive neuropsychological testing (35).

Singam et al. reported that physical performance was predictive of IADL-function 6 years after stroke (18). This is in line with results of the present study, which showed that physical performance may, when applied alone, be an important predictor of change in IADL-function. However, the prediction was better in combination with measures of cognition. This is

interesting because NEADL mainly includes tasks in which physical performance seems to be more important than cognition (36). Many of the motor tasks in NEADL might in fact challenge the dual task capacity and the motor-cognitive interphase in addition to physical performance, which is thought to be closely linked to cognition and cognitive reserves (37). Further, our results are in line with a recently published Delphi study regarding factors important for IADL-function, where cognition was listed as the most important feature, while physical performance was also reported as an essential factor (38).

We identified four distinct scenarios based on the model that included measures of both physical performance and cognition (Model C: Combined assessment) where adjustments were made for other known risk factors. Functional dependency at 3 months post-stroke, mainly reported as mRS, has been reported as a predictor of long-term function, both in terms of ADL-dependency, comorbidity, and death (39), and the present study shows that applying clinical tests at 3 months adds value to the prediction in addition to known risk factors for functional decline.

Three of the four scenarios had stable, non-significant changes in IADL-function from 3 three to 18 months, indicating that the vast majority of the participants did not change in IADL-function, which is also supported by the non-significant change in NEADL-score in the total study sample. This contrasts with the findings reported by Rejnö et al., who found that transition from ADL independency to dependency mainly happened during the first year after stroke (40). Further, Buvarp et al. found that patients with moderate stroke declined in functional mobility from 3 to 12 months post-stroke, which is an argument for prolonged

rehabilitation in a selected group of stroke patients (41). However, most studies show that patients reach a plateau phase in function between 3 and 6 months (8, 42). The fact that most functional recovery happens during the first 3 months after stroke, in which most of the rehabilitation also takes place (21), might explain why the IADL-function reaches a plateau after this.

Time was a statistically significant predictor of change in the scenario representing stroke survivors with the best scores on both physical performance and cognition. This scenario had an increase in NEADL score of 1.4, which is lower than the six points regarded as a clinically significant change (43). However, approximately 15 points on the NEADL differed between this scenario and the one with scores on both MoCA and SPPB in the lower quartiles, which implicates that the level on performance-based tests at 3 months is decisive for the level at which IADL-function stroke patients will stabilize in the long term. This finding highlights the importance of high-quality acute treatment and early rehabilitation in order to achieve best possible cognition and physical function the first months post-stroke (42).

To the best of our knowledge this is the first study to date addressing the role of physical performance and cognition in prediction of IADL-function, which is an important outcome, after stroke. The large sample size and the longitudinal multicentre design should also be considered a significant strength. The repeated measures allow us to identify predictors of change in IADL-function, and the mixed model statistical analyses use data from all participants, including those with partially missing data, thus avoiding loss of statistical power. NEADL is shown to have few floor or ceiling effects (44), making it applicable for a

heterogeneous stroke population, and MoCA and SPPB are widely used feasible clinical measures, and therefor easy to incorporate into clinical evaluations of stroke patients (45-49).

Study limitations

The cohort design of the study inhibits us concluding on causality, and there is a need for external validation in order to draw any conclusion on this prediction model outside of the present study sample. The study included 67% of the original Nor-COAST population, which has been shown to be representative of the majority of the general stroke population who suffers from mild to moderate strokes (50), and conclusions for individuals having suffered from severe stroke cannot be drawn. There are some known gender biases in the application of NEADL in which several of the questions favour women, which is why sex was adjusted for in the analyses. Furthermore, NEADL includes more mobility than cognitive questions compared to other IADL-tools, which might have led to an underestimation of associations with cognition. Another limitation is the lack of information on pre-stroke physical and cognitive function.

Conclusions

Being able to predict change in IADL-function after stroke is of great value to patients and health care providers. This is the first study to examine how the combination of cognition and physical performance in an early stage following a stroke predicts change in daily life activities over time. Combining measures of physical performance and cognition provided the best

prediction of change in IADL over time. Cognitive and physical function at 3 months post-stroke were determinative for IADL-function over the next 15 months, which highlights the importance of adequate acute treatment and targeted rehabilitation in the early and subacute phases. Further research should target how measures of physical and cognitive performance in the early stage can be used for identification of specific risk profiles and more personalized long-term rehabilitation.

Table 1. Baseline characteristics.

	Total sample n=544	Lost to follow-up n=156
Demographics		
Age, mean (SD)	71.4 (11.8)	77.1 (10.7)
Females, n (%)	235 (43.2)	66 (42.3)
Living alone, n (%)	184 (34.4)	62 (42.2)
Education > 9 years, n (%)	408 (75.0)	92 (59.0)
Stroke classification		
Infarction, n (%)	497 (91.4)	139 (89.1)
Hemorrhage, n (%)	47 (8.6)	17 (10.9)
Stroke severity		
NIHSS score at admission, mean (SD)	3.7 (4.7)	5.7 (6.4)
Charlson Comorbidity Index, mean (SD)	3.8 (1.9)	4.6 (1.9)
mRS score, prestroke, mean (SD)	0.7 (0.9)	1.6 (1.4)
mRS = 0, n (%)	291 (53.5)	48 (31.4)
mRS = 1, n (%)	147 (27.0)	27 (17.7)
mRS = 2, n (%)	77 (14.2)	27 (17.7)
mRS = 3, n (%)	27 (5.0)	33 (21.6)
mRS = 4, n (%)	1 (0.2)	17 (11.1)
mRS = 5, n (%)	1 (0.2)	1 (0.7)

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Table 2. Clinical assessments at three and 18 months.

	3 months n=544	18 months n=480
SPPB score (0-12), mean (SD)	9.4 (3.1)	N/A
MoCA score (0-30), mean (SD)	24.4 (4.8)	N/A
Nottingham E-ADL (0-66), mean (SD)	51.4 (14.1)	52.3 (14.8)
Mobility (0-18), mean (SD)	14.3 (4.7)	14.3 (4.8)
Kitchen (0-15), mean (SD)	13.5 (3.2)	13.5 (3.3)
Domestic activities (0-15), mean (SD)	10.7 (4.4)	10.9 (4.3)
Leisure activities (0-18), mean (SD)	12.9(4.2)	13.6 (4.6)

N/A-Not applicable

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Table 3. Results from linear mixed-effects models with Nottingham-EADL as dependent variable (n=544).

	Nottingham-EADL		
	Coef.	*95% CI*	*P-value*
Model A: Cognition			
MoCA	1.000	0.772 to 1.226	<0.001
Time	-6.225	-10.772 to -1.678	0.007
Time*MoCA	0.268	0.086 to 0.449	0.004
Age	-0.206	-0.289 to -0.122	<0.001
Female sex	-0.494	-2.196 to 1.208	0.569
NIHSS	-0.334	-0.514 to 0.154	<0.001
mRS prestroke, scores			
1	-3.482	5.504 to -1.460	0.001
2	-5.712	-8.339 to -3.085	<0.001
3-5	-16.375	-20.591 to -12.158	<0.001
Model B: Physical performance			
SPPB	2.571	2.271 to 2.871	<0.001
Time	-2.571	-5.798 to -0.005	0.050
Time*SPPB	0.331	0.042 to 0.619	0.025
Age	-0.164	-0.232 to -0.096	<0.001
Female sex	-2.386	-3.834 to -0.938	0.001
NIHSS	-0.209	-0.361 to -0.057	0.007
mRS prestroke, scores			
1	-2.362	4.072 to -0.652	0.007
2	-3.095	-5.337 to -0.854	0.007
3-5	-11.042	-14.657 to -7.426	<0.001
Model C: Combined assessment			
MoCA	0.570	0.369 to 0.770	<0.001
SPPB	2.364	2.058 to 2.671	<0.001
Time	-6.840	-11.394 to -2.285	0.003
Time*MoCA	0.238	0.030 to 0.445	0.025
Time*SPPB	0.132	-0.197 to 0.461	0.431
Age	-0.085	-0.154 to -0.017	0.015
Female sex	-2.220	-3.602 to -0.839	0.002
NIHSS	-0.162	-0.307 to -0.016	0.029
mRS prestroke, scores			
1	-2.230	-3.861 to -0.599	0.007
2	-2.755	-4.894 to -0.615	0.012
3-5	-7.972	-11.515 to -4.429	<0.001

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Table 4. Coefficients of time in Model C with MoCA and SPPB centered on quartiles.

	MoCA lower quartile			MoCA upper quartile		
	Coeff.	*95% CI*	*p-value*	*Coeff.*	*95% CI*	*p-value*
SPPB lower quartile	-0.558	-1.561 to 0.446	0.276	0.867	-0.508 to 2.243	0.216
SPPB upper quartile	-0.029	-1.462 to 1.404	0.968	1.396	0.252 to 2.540	0.017

SPPB: lower quartile = 8p, upper quartile=12p; MoCA: lower quartile = 22p, upper quartile=28p. Analyses are adjusted for age, sex, stroke severity and prestroke function.

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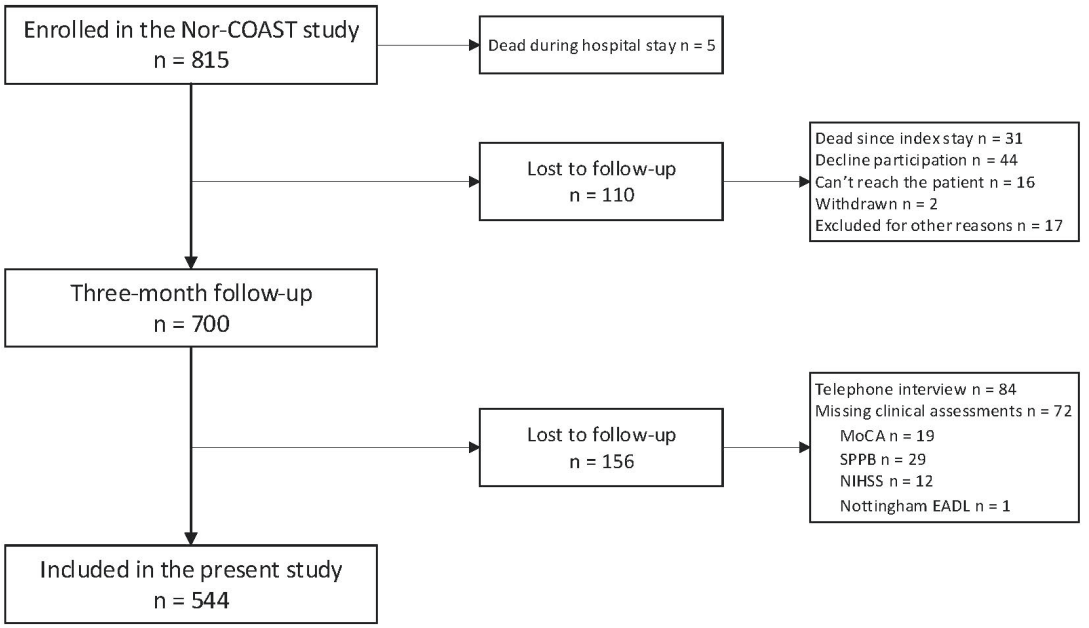
Figure 1. Flow chart on inclusion.



MoCA-Montreal Cognitive Assessment; *SPPB*-Short Physical Performance Battery; *NIHSS*-National Institutes of Health Stroke Scale; *NEADL*-Nottingham Extended Activities of Daily Living

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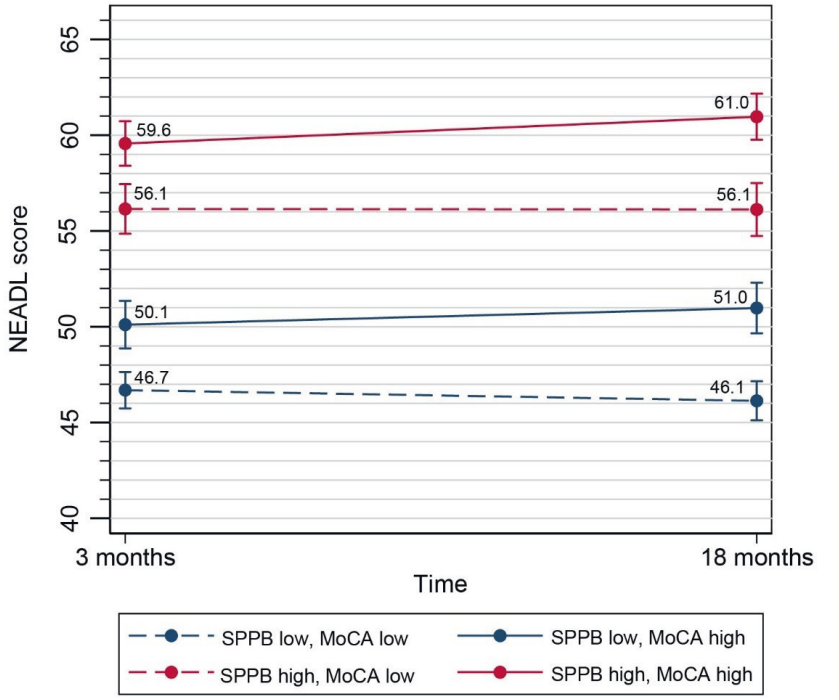
Figure 2. Predictive margins plot with 95% CI of Model C with MoCA and SPPB centered on quartiles.



NEADL-Nottingham Extended Activities of Daily Living (0-66); *SPPB*-Short Physical Performance Battery (0-12); *MoCA*-Montreal Cognitive Assessment (0-30); SPPB low=8p; SPPB high=12p; MoCA low=22p; MoCA high=28p

Suppliers

a. SPSS version 25; IMB

b. STATA version 16; StataCorp

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