Doctoral theses at NTNU, 2021:237

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Doctoral thesis

NTNU
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ISBN 978-82-326-6363-7 (printed ver.)
ISBN 978-82-326-5744-5 (electronic ver.)
ISSN 1503-8181 (printed ver.)
ISSN 2703-8084 (online ver.)

Doctoral theses at NTNU, 2021:237

Printed by NTNU Grafisk senter

Betydningen av klassifiseringsmetoder, type hjerneslag og hjerte-karsykdom for forløpet av kognitiv svikt etter hjerneslag

Forekomsten av hjerneslag og demens øker eksponentielt med alder. Grunnet økende antall eldre i befolkningen de nærmeste årene vil denne forekomsten øke betydelig. Behandlingen av hjerneslag har bedret seg de senere årene og det er derfor flere som overlever hjerneslag. Det er nå omkring 12 000 hjerneslag pr. år i Norge. På verdensbasis er hjerneslag den nest hyppigste årsaken til død og hjerneslag er også en av de hyppigste årsakene til funksjonsnedsettelse. Kognitiv svikt er en av hovedårsakene til funksjonsnedsettelse etter hjerneslag. Med kognitiv svikt menes problemer med å være orientert for tid og sted, gjenkalle hendelser, lære nye ting, tenke abstrakt, forstå det som blir sagt og uttrykke seg forståelig eller ha problemer med oppmerksomhet, bedømme rom-retning eller å planlegge og utføre praktiske handlinger. Kognitiv svikt spenner fra mild kognitiv svikt hvor dagliglivet i liten grad er påvirket til demens hvor den kognitive svikten påvirker dagliglivet i større grad. Tidligere studier har vist at omkring 50 % av pasienter som har gjennomgått hjerneslag har kognitiv etter hjerneslaget og at omkring 15 % av pasienter med hjerneslag har demens før hjerneslaget.

Hovedhensikten med prosjektet var å undersøke betydningen av klassifiseringsmetoder samt type hjerneslag og hjerte-karsykdom for forløpet av kognitiv svikt 3- og 18 måneder etter hjerneslag.

Prosjektet er et delprosjekt i studien Norwegian Cognitive Impairment After Stroke (Nor-COAST) som er en prospektiv multisenter kohortstudie som inkluderte 815 deltakere innlagt i sykehus med akutt hjerneslag i perioden mai 2015 til mars 2017. Deltakerne ble inkludert ved slagenhetene ved St. Olavs hospital, Oslo Universitetssykehus Ullevål, Vestre Viken HF Bærum sykehus, Haukeland universitetssjukehus og Ålesund sjukehus. 700 av deltakerne ble undersøkt 3 måneder etter hjerneslaget, 599 av deltakerne ble undersøkt 18 måneder etter hjerneslaget og 483 av deltakerne ble undersøkt 36 måneder etter hjerneslaget. I Nor-COAST ble deltakerne testet med kognitive tester og fysiske tester, og det ble tatt blodprøver samt billedundersøkelser av hjernen i form av MR.

Studien viste at andelen som klassifiseres med normal kognisjon, mild kognitiv svikt og demens 3 måneder etter hjerneslaget varierer med ulike klassifiseringsmetoder. Samsvaret mellom ulike klassifiseringsmetoder var dårligere for mild kognitiv svikt enn for demens. Kognitiv svikt etter hjerneslag er vanlig både 3 måneder og 18 måneder etter hjerneslaget for hele slagpopulasjonen, for de ulike typene hjerneslag og uavhengig av hjerte-karsykdom forut for hjerneslaget. Deltakere som hadde hjerneslag forårsaket av sykdom i hjernenes store kar hadde redusert oppmerksomhet sammenliknet med deltakere som hadde hjerneslag forårsaket av sykdom i hjernens små kar. Deltakere som hadde kransåresykdom, atrieflimmer eller tidligere hjerneslag, hadde dårligere kognitiv funksjon enn deltakere uten disse sykdommene. Deltakerne hadde stabil kognitiv funksjon fra 3 måneder til 18 måneder etter hjerneslaget, med unntak av at det tilkom noe bedring i språk, oppmerksomhet samt evnen til å planlegge og utføre handlinger.

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Finansieringskilde: Samarbeidsorganet Helse Midt-Norge RHF

Ovennevnte avhandling er funnet verdig til å forsvares offentlig for graden PhD i medisin.
Digital disputas finner sted torsdag 24. juni 2021, kl. 12.15.

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Acknowledgements

The work for this thesis was conducted at the Geriatrics, Movement Science and Stroke (GeMS) research group at the Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU) and funded by the Liaison Committee for Education, Research and Innovation in Central Norway. I am grateful to both for the opportunities they have given me.

First and foremost, my deepest gratitude to all **the participants and their relatives** who took part in the Nor-COAST study. Without you, none of this research would have been possible.

I would like to express my sincere gratitude to my main supervisor, **Professor Ingvild Saltvedt,** for giving me the opportunity to be a PhD student in your well-managed Nor-COAST project and for all your support and encouragement throughout the project. I admire your extensive knowledge and enthusiasm, and I am very thankful for the many hours you spent on this project and for your availability whenever I needed your expertise. Your supervision has been invaluable and extremely important to me, and I will be forever grateful.

I am deeply indebted to my co-supervisors, **Hege Ihle-Hansen** and **Anne-Brita Knapskog,** for your interest and all the knowledge you so generously shared. Thank you for always being available and willing to help me. Your constructive feedback has made an immense contribution to the quality of this work.

A warm thank you to **Associate Professor Brynjar Fure,** who guided me through the last paper of this PhD project. Your extensive knowledge was critical to its completion and has inspired my own learning. Thanks also for your calm demeanor and belief in me; both encouraged me and advanced the development of this work. I would be remiss if I failed to mention your prompt and well-considered responses to all my questions and concerns.

I am also very grateful to the head of GeMS, **Professor Torunn Askim.** Your knowledge and support, especially in challenging times, have been immensely important and valuable.

Thank you to all the **co-authors** not yet mentioned: **Mona K. Beyer, Marte Stine Einstad, Rannveig S. Eldholm, Hanne Ellekjær, Mari N. Gynnild, Professor Stian Lydersen, Ragnhild Munthe-Kaas, Halvor Næss, Professor Sarah T. Pendlebury, Yngve M. Seljeseth, Pernille Thingstad,** and **Professor Torgeir Bruun Wyller** for your scientific interest and your constructive feedback. A very special thank you to **Ragnhild Munthe-Kaas** for all the discussions and close collaboration as joint first authors of one of the papers. I am grateful for your enthusiasm and support, and I appreciate both. Even more important than research is life, and your support on a personal level throughout these years has been an invaluable gift. To **Professor Stian Lydersen,** thank you for your excellent statistical guidance and for sharing your extensive knowledge with me, as well as your enthusiastic approach to my statistical problems. This has been a highly

educational experience for me. You might have already realized, to your credit, that I found the statistical work to be among the most pleasant parts of this PhD project. A very special thank you to one of the most knowledgeable researchers on poststroke cognitive impairment in the world, **Professor Sarah T. Pendlebury,** with whom we were so fortunate to collaborate. Your expertise and interest in the work are truly appreciated, and your contributions have extended by education and my understanding. A special thank you also to **Mari N. Gynnild** and **Marte Stine Einstad** for enlightening discussions, continuing support, and the gift of friendship.

I owe my deepest gratitude to our expert panel: **Professor emeritus Knut Engedal, Professor Geir Selbæk,** and **Anne Rita Øksengård** for your valuable advice. To **Professor Geir Selbæk,** a special thank you for inviting me to work with you on dementia classification in the HUNT4 70+ study. Your extensive knowledge and enthusiasm have not only added immensely to my education but have also inspired me. I will always be grateful for your availability and your prompt and precise responses to my seemingly endless questions.

Thank you to all the members of **the Nor-COAST collaboration group** for including me in your scientific environment and to all **staff at the participating hospitals.** A special thank you to our project coordinator, **Nina Sjøgren,** for all the enthusiasm and assistance and for being so solution oriented. I am also very grateful to **Till Schellhorn** for the many fruitful discussions and for increasing my knowledge in the field of neuroradiology.

Thank you to my colleagues in GeMS for welcoming me into your scientific community. A special thank you to my office colleagues and fellow PhD students **Martina R. Bovim, Marte Stine Einstad, Rannveig S. Eldholm, Tor Ivar Gjellesvik, Mari Gunnes, Mari N. Gynnild, Ole Petter Norvang, Arnhild J. Nygård, Ailan Phan, Inga Røyset,** and **Roland Stock** for the countless discussions but also for abundant laughter. **Rannveig S. Eldholm,** thank you, as well, for all your helpful advice, your friendship, and for sharing your inexhaustible technological knowledge on any platform I could ever think of. **Mari Gunnes,** thank you for the many valuable methodological and statistical discussions and for the very special bond we built in Covid times during the write-up of our thesis. Your gift of friendship has been invaluable to me. I am also grateful to **Inga Røyset** for unflagging support through the good as well as the challenging days.

Thank you to my husband, **Professor Trygve Kristiansen,** and to his colleague **Associate Professor David Kristiansen** and to **Jonas R. Kildal** for your contributions to graphing in Python.

Thank you to my fellow PhD students: **Maria Ø. Nyhus** and **Malgorzata Isabella S. Magelssen** for always being there for me and, in addition, to **Maria Ø. Nyhus** for many productive and worthwhile discussions as fellow statistical students.

To my friend **Brage H. Amundsen,** many thanks for reading my thesis and giving me constructive feedback during challenging times. What other cardiologist in the world would read an entire thesis on poststroke cognitive impairment? I deeply appreciate your interest in this PhD project, and I value our friendship.

My sincere thanks to **Petter Quist-Paulsen** for valuable support throughout the whole PhD period.

Thank you to all my **colleagues in the Department of Geriatric Medicine at St. Olav's Hospital** for all the support. A warm thank you to **Professor emeritus Olav Sletvold,** the former head of the Department of Geriatric Medicine who introduced me to geriatrics in medical school. I remain ever grateful for your warm welcome when I started my work at your department, and I thank you for sharing your extensive knowledge with me throughout the period of my education as a geriatrician. Your positivism and enthusiasm have inspired me. Along with my main supervisor, **Professor Ingvild Saltvedt,** I credit you both for all my acquired skills in geriatrics. I am forever grateful to both of you.

Tom Christian Martinsen was the head of Clinic of Medicine at St. Olav's Hospital throughout most of the work of this PhD project. Thank you for the opportunity to take a leave for the project and for all your valuable support since I started my work at St. Olav's in 2006.

I am very grateful to **my family and good friends** for always being there for me. A warm thank you to my parents, **Tertit and Oddvar,** and to my sister and brother, **Mari and Sigbjørn,** for their unflagging support throughout my life and for your invaluable help with our children. Thank you also to my parents-in-law, **Tove and Arve,** my brothers- and sister-in-law **Thomas, Olav, and Marita,** and to my nieces and nephews **Johanne, Sverre, Maren, Sanna,** and **Sindre** for your love and support.

In the end – but above all – thank you to my husband **Trygve** and our three beloved children **Torstein, Synnøve, and Lovise** for your love, patience, and support.

Trondheim, March 2021

Stina Aam

List of papers

Paper 1

Munthe-Kaas, R, Aam, S, Ihle-Hansen, H, Lydersen, S, Knapskog, AB, Wyller, TB, Fure, B, Thingstad, P, Askim, T, Beyer, MK, Næss, H, Seljeseth, YM, Ellekjær, H, Pendlebury, ST, Saltvedt, I. *Impact of different methods defining poststroke neurocognitive disorder: The Nor-COAST study.* Alzheimer's Dement. 2020;6(1):e12000.

Paper 2

Aam, S, Einstad, MS, Munthe-Kaas, R, Lydersen, S, Ihle-Hansen, H, Knapskog, AB, Ellekjær, H, Seljeseth, YM, Saltvedt, I. *Poststroke Cognitive Impairment—Impact of Follow-Up Time and Stroke Subtype on Severity and Cognitive Profile: The Nor-COAST Study.* Front Neurol. 2020;11:699.

Paper 3

Aam, S, Gynnild, MN, Munthe-Kaas, R, Saltvedt, I, Lydersen, S, Knapskog, AB, Ihle-Hansen, H, Ellekjær, H, Eldholm, RS, Fure, B. *The impact of vascular risk factors on poststroke cognitive impairment: The Nor-COAST study*. (Revised version accepted for publication in Frontiers in Neurology)

Summary

Stroke is the second-largest cause of death and second-leading cause of disability-adjusted life-years worldwide. Poststroke cognitive impairment (PSCI) is common, yet evidence regarding cognitive symptom profiles, course over time, pathogenesis, and impact of vascular risk factors remains scarce. In studies of PSCI, classification according to criteria for poststroke neurocognitive disorders (NCD) is commonly used, and the reported prevalence of poststroke NCD varies according to different diagnostic criteria.

The overall aim of the thesis was to study the impact of different operational definitions of PSCI, its course over time, and the impact of stroke subtype and vascular risk factors on PSCI. It was based on the Nor-COAST study, a multicenter, prospective cohort study where 815 participants hospitalized with acute stroke in five Norwegian stroke units were recruited from May 2015 through March 2017.

At 3- and 18-month follow-ups, attention, executive function, memory, language, and perceptual-motor function were assessed. The Montreal Cognitive Assessment (MoCA) was administered and the Global Deterioration Scale (GDS) was assessed. Scores <-1.5 standard deviation (SD) were considered abnormal. NCD were classified according to the Diagnostic and Statistical Manual (DSM-5) criteria. Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS). Stroke subtype was categorized as intracerebral hemorrhage (ICH), large artery disease (LAD), cardioembolic stroke (CE), small vessel disease (SVD), or un-/other determined strokes (UD). Vascular risk factors were collected from patients' medical records during their hospital stays.

In Paper 1, we used three operational definitions of NCD to assess the prevalence of all poststroke NCD and, separately, mild and major NCD using cognitive assessment only (model A), DSM-5 criteria (cognitive assessment combined with instrumental activities of daily living) (model B), or the GDS (model C). Further, we explored agreement among these methods. In all, 599 participants were included. Mean age was 71.6 years (SD 11.8); 43% were females; and mean NIHSS was 3.7 (SD 4.7). The prevalence of poststroke NCD varied according to the operational definitions used to define cases. The

prevalence of mild NCD varied from 174 (29%) in model B to 83 (14%) in model C; the prevalence of major NCD varied from 249 (42%) in model A to 68 (11%) in model C. The poorest agreement was found between models defining mild NCD, whereas models for major NCD were more consistent.

In Paper 2, we investigated whether follow-up time and etiological stroke subtype had any impact on the probability of PSCI and its severity and cognitive symptom profile 3 and 18 months poststroke. Mixed-effects logistic or linear regression was applied with all poststroke NCD classified according to DSM-5 criteria, global z, MoCA z-score, and z-scores of the cognitive domains (attention, executive function, memory, language, perceptual-motor function) as dependent variables. Independent variables included time as well as stroke subtype and interaction between these. The analyses were adjusted for age, education, and sex. The effects of time and stroke subtype were analyzed by likelihood ratio tests (LR). In all, 617 participants were included. Mean age was 71.6 years (SD 11.8); 42% were females; and mean NIHSS score at admittance was 3.8 (SD 4.8). We showed that PSCI is common for the entire stroke population and for all stroke subtypes both short and long term after stroke. We found stability in cognitive function over the observation period. Exceptions were improvement in executive function and language in the entire stroke cohort and language in ICH. Attention was more impaired among patients with cortical stroke compared to those with small vessel disease.

In Paper 3, we explored the association between prestroke vascular risk factors and PSCI 3 and 18 months poststroke within global cognitive measures and different cognitive domains. We also studied the course of PSCI in patients with and without prestroke vascular risk factors. Mixed-effects linear regression was applied with global z, MoCA z-score, and z-scores of the cognitive domains (attention, executive function, memory, language) as dependent variables. Independent variables were vascular risk factors, time, and the interaction between these. The analyses were adjusted for age, education,

and sex. The effects of time and vascular risk factors were analyzed by LR. In all, 635 participants were included. Mean age was 71.6 years (SD 11.7); 42% were females; and mean NIHSS score at admittance was 3.8 (SD 4.8). We found no significant change in cognition over the observation period except for improvement in attention in patients without atrial fibrillation and in executive function in patients without coronary heart disease.

Overall, we provided evidence that more studies assessing the reliability of different diagnostic approaches are needed before a final consensus on the definition of poststroke NCD can be reached. Our findings of PSCI as common in all cognitive domains with some improvements in specific cognitive domains might contribute to individualizing follow-ups for stroke patients. The severely impaired global cognitive function we identified might indicate a focal stroke lesion initiating pathophysiological processes leading to global cognitive impairment, and our findings of differences across stroke subtypes may also offer new insights into underlying mechanisms.

Abbreviations

AD8	Ascertain Dementia 8-item Informant Questionnaire AD8
AF	atrial fibrillation
BI	Barthel Index
CE	cardioembolic stroke
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CHD	coronary heart disease
DSM	Diagnostic and Statistical Manual
GDS	Global Deterioration Scale
I-ADL	instrumental activities of daily living
ICD	International Classification of Diseases and Related Health Problems
ICH	intracerebral hemorrhage
LAD	large artery disease
mRS	modified Rankin Scale
MoCA	Montreal Cognitive Assessment
NCD	neurocognitive disorders
NIHSS	National Institutes of Health Stroke Scale
NINDS-AIREN	National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neurosciences
NINDS-CSN	National Institute of Neurological Disorders and Canadian Stroke Network
Nor-COAST	Norwegian Cognitive Impairment After Stroke
P-ADL	personal activities of daily living
PSCI	poststroke cognitive impairment
STROKOG	Stroke and Cognition consortium
SVD	small vessel disease
TIA	transient ischemic attack

TMT	Trail Making Test
TOAST	Trial of Org 10172 in Acute Stroke Treatment
UD	undetermined etiology
VASCOG	Vascular Cognitive and Behavioral Disorders criteria
VICCCS	Vascular Impairment of Cognition Classification Consensus Study

1 Introduction

Stroke is the second-largest cause of death globally and the second-leading cause of disability-adjusted life-years worldwide, with ischemic heart disease being the leading cause. Both incidence of stroke and stroke-related mortality have decreased over the last two decades. Nevertheless, the decrease in incidence has been less steep than the rate of stroke-related mortality, and in summary, due to the aging population worldwide, the numbers of stroke survivors are expected to increase (1, 2). Poststroke cognitive impairment (PSCI) is common among stroke survivors, and its prevalence has been reported to be 53.4% in a recent review and meta-analysis (3). In addition, recently published results from the Stroke and Cognition consortium (STROKOG) showed global impairment in 44% of patients within 6 months following a stroke, and 30% to 35% had impairments in all the cognitive domains assessed (4). Thus, the need for more knowledge about the prognosis for cognitive function among stroke survivors is significant.

Several factors influence the course of PSCI, including PSCI classification methods, stroke etiology, and prestroke vascular risk factors, among others. This thesis aimed to improve the knowledge in this field by exploring the impact of different classification methods of PSCI early after a stroke, its course from early to late poststroke, and the impact of stroke subtype and vascular risk factors early and late after a stroke.

2 Background

2.1 Definitions of stroke and transient ischemic attack

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 h or leading to death with no apparent cause other than that of vascular origin*" (5).

A transient ischemic attack (TIA) is defined *as "episodes of temporary and focal dysfunction of vascular origin, which are variable in duration, commonly lasting from 2 to 15 minutes, but occasionally lasting as long as a day (24 hours). They leave no persistent neurological deficit"* (6, 7).

These classic definitions of stroke and TIA are mainly clinical and depend on the duration of symptoms; they do not consider the advances in neuroimaging that have become generally available in recent decades. Therefore, the American Heart Association/American Stroke Association proposed new definitions of stroke and TIA based on both clinical evidence and evidence of infarction by pathology or imaging (7):

I. Definition of CNS infarction: "*CNS infarction is brain, spinal cord, or retinal cell death attributable to ischemia, based on*
    1. *pathological, imaging, or other objective evidence of cerebral, 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*." (7)

II. Definition of TIA: "*focal arterial ischemia with transient symptoms (lasting <24 hours) and without evidence of infarction by pathology or imaging.*" (7)

In line with these definitions, the forthcoming 11th revision of the International Classification of Diseases and Related Health Problems (ICD-11) defines TIA based on the exclusion of acute infarction (8).

About 10–20% of strokes are hemorrhagic, and the rest are ischemic strokes typically related to large artery disease (LAD), cardioembolic stroke (CE), or small vessel disease (SVD), often labeled lacunar infarction, with about 25% in each category (9-11).

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification is the most widely used system for classifying ischemic stroke etiology. It categorizes ischemic strokes according to five groups: LAD, CE, SVD, stroke of other determined etiology, and stroke of undetermined etiology (UD) (12, 13). LAD and CE strokes are often cortical strokes of large volume, while SVD strokes are subcortical and of small volume (12).

2.2 Definitions of poststroke cognitive impairment

PSCI is defined as any cognitive decline developing within six months after a stroke and includes mild cognitive impairment (MCI) and dementia (14). In updated criteria for cognitive impairment (fifth revision of the Diagnostic and Statistical Manual (DSM-5) and the Society for the Study of Vascular Cognitive and Behavioral Disorders (VASCOG) criteria), MCI and dementia are replaced by the terminology mild and major neurocognitive disorders (NCD), respectively, and these terms are used hereafter in this thesis (15, 16). Early-onset PSCI is cognitive decline manifested at least three–six months after a stroke, while delayed-onset PSCI is cognitive decline manifested beyond the early poststroke period (17). The etiology for PSCI can be vascular, neurodegenerative, or mixed etiology of vascular and any neurodegenerative etiology.

2.3 Prevalence of poststroke cognitive impairment

Pendlebury and Rothwell, in a systematic review of poststroke major NCD, reported rates ranging from 7.4% (95% confidence interval [CI] 4.8–10.0) in population-based studies of first-ever stroke excluding prestroke major NCD to 53% (95% CI 47–60) in hospital-based studies of recurrent stroke including participants with prestroke major NCD (18). In a recent review and meta-analysis of hospital-based studies, Barbay and colleagues (3) reported a prevalence of poststroke NCD of 53% whereof 36% (95% CI 29–44) represented mild NCD and 16.5% (95% CI 12–21) major NCD. Sexton and colleagues reported a prevalence of mild poststroke NCD of 38% (95% CI 32–43) in a recent review and meta-analysis of hospital-based and community-based studies (19).

2.4 Different methods of defining poststroke cognitive impairment

Diagnosing cognitive status according to criteria requirements for cognitive impairment that include both cognition and activities of daily living (ADL) is used in clinical practice and most commonly in research. However, diagnoses based solely on cognitive status are also used in research (3, 18, 19). When cognitive testing is not feasible, a clinical evaluation is recommended by DSM-5 criteria for mild and major NCD, and this method is utilized in clinical practice as well as research (15, 19). As cognitive impairment is considered to appear on a continuum, continuous measures of cognition rather than the diagnosis of PSCI are widely applied in the research context (4).

In the clinical setting, a diagnosis of PSCI is made by personnel who are trained in the clinical assessment of cognition and who evaluate the patient in person. Clinical diagnoses, in addition to diagnoses based on the information available from data sets, are used in research. For many large research studies, clinical diagnoses are not feasible due to the cost involved, and this emphasizes the need for more knowledge on comparisons of different research methods used to define PSCI.

2.5 The diagnoses of mild and major neurocognitive disorders

Major NCD is a clinical syndrome characterized by a cognitive decline severe enough to interfere with independence in ADL. Mild NCD is characterized by a cognitive decline that is not severe enough to fulfill the criteria for major NCD. The clinical process of diagnosing mild and major NCD is conducted in two steps where a syndromal diagnosis of mild or major NCD is made first and an etiological diagnosis of subtypes is made in a second step.

2.6 Impact of different operational definitions of poststroke neurocognitive disorders

When classifying cognitive status according to diagnostic criteria, the main operational decisions that have an impact on the results are 1) the classification criteria used; 2) the allocation of the different cognitive tests to the different cognitive domains; 3) the cut-off between normal cognition and NCD; 4) the number of tests per cognitive domain; 5) the normative data used; and 6) the measures for ADL (Figure 1).

In recent studies, the STROKOG and the Vascular Impairment of Cognition Classification Consensus Study (VICCCS) have highlighted the importance of standardizing methods for diagnosing vascular cognitive impairment in order to improve research quality (20, 21).

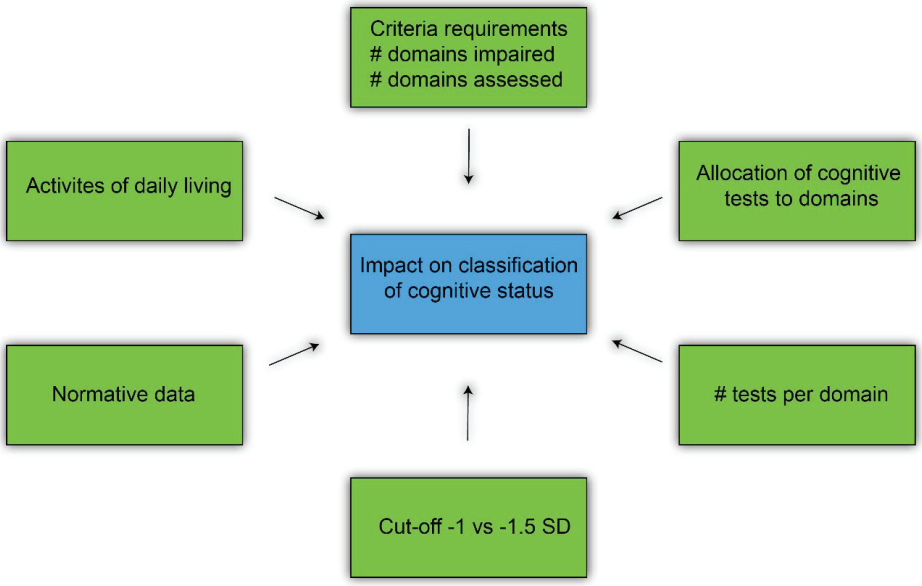


Figure 1. Aspects of importance for classification of poststroke cognitive impairment

= number of, vs =versus, SD = standard deviation

2.6.1 Diagnostic criteria for poststroke cognitive impairment

Over recent decades, the most commonly used criteria for defining PSCI have been the National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN), the fourth revision of the Diagnostic and Statistical Manual (DSM-IV) criteria, and the 10th revision of the ICD (ICD-10) criteria (3, 15, 19-25). The DSM-5 criteria, published in 2013; the VASCOG criteria, published in 2014; and the forthcoming 11th revision of the International

Classification of Diseases and Related Health Problems (ICD-11) criteria replace the older criteria, and their use is expected in future publications (8, 15, 16).

The recently published DSM-5 criteria, the VASCOG criteria, and the anticipated ICD-11 criteria define both mild and major NCD, while the older criteria lack a definition of mild NCD. For the diagnosis of major NCD, all the criteria require a cognitive decline severe enough to interfere with independence in daily functioning. The different criteria require different numbers of cognitive domains to be impaired to fulfill a diagnosis of NCD. In addition, they cite different cognitive domains for assessment when cognitive status is evaluated.

In the NINDS-AIREN, DSM-IV, and ICD-10 criteria, memory impairment is a mandatory requirement for a diagnosis of major NCD. The NINDS-AIREN criteria require memory impairment and impairment in two or more other cognitive domains, while the DSM-IV and ICD-10 criteria require memory impairment and impairment in one or more other cognitive domains. For the DSM-5, VASCOG, and ICD-11 criteria, the mandatory requirement of memory impairment has been eliminated because memory impairment is the prominent cognitive profile of Alzheimer's disease but not for other etiologies of major NCD. The DSM-5 and VASCOG criteria require impairment in one or more domains for both mild and major NCD, while the ICD-11 criteria require impairment in one or more domains for mild NCD and two or more domains for major NCD. For all the criteria, an impact on daily function is defined as impairment in ADL or instrumental ADL (I-ADL) for major NCD. Table 1 provides an overview of the cognitive requirements for the most commonly used and forthcoming criteria that define poststroke cognitive impairment.

Table 1. Cognitive proposals for the most commonly used diagnostic criteria defining poststroke cognitive impairment						
	NINDS-AIREN	**DSM-IV**	**ICD-10**	**DSM-5**	**VASCOG**	**ICD-11**
Classification of mild NCD				x	x	x
≥ 1 impaired domain				x	x	x
Classification of major NCD	x	x	x	x	x	x
Memory impairment and impairment in ≥ 1 other cognitive domains		x	x			
Memory impairment and impairment in ≥ 2 other cognitive domains	x					
≥ 1 impaired domain				x	x	
≥ 2 impaired domains						x
NINDS-AIREN = National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neurosciences DSM-IV = 4th revision of the Diagnostic and Statistical Manual ICD-10 = 10th revision of the International Classification of Diseases and Related Health Problems DSM-5 = 5th revision of the Diagnostic and Statistical Manual VASCOG = Vascular Cognitive and Behavioral Disorders ICD-11 = 11th revision of the International Classification of Diseases and Related Health Problems						

The proposed cognitive domains to be assessed for the different criteria are shown in Table 2.

Table 2. Proposed cognitive domains examined in the most commonly used diagnostic criteria for classification of poststroke neurocognitive disorders

Diagnostic criteria	Proposal of assessed cognitive domains
NINDS-AIREN	1. Memory 2. Orientation 3. Attention 4. Language 5. Visuospatial functions 6. Executive functions 7. Motor control 8. Praxis
DSM-IV	1. Memory 2. Language 3. Praxis 4. Gnosis 5. Executive function
ICD-10	1. Memory 2. Judgment and thinking, such as a. Executive function b. General processing of information
DSM-5	1. Complex attention 2. Executive function 3. Learning and memory 4. Language 5. Perceptual-motor function 6. Social cognition
VASCOG	1. Attention and processing speed 2. Frontal-executive function 3. Learning and memory 4. Language 5. Visuoconstructional-perceptual ability 6. Praxis-gnosis-body schema 7. Social cognition
ICD-11	1. Memory 2. Executive functions 3. Attention 4. Language 5. Social cognition and judgment 6. Psychomotor speed 7. Visuoperceptual or visuospatial abilities

NINDS-AIREN = National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neurosciences
DSM-IV = 4th revision of the Diagnostic and Statistical Manual
ICD-10 = 10th revision of the International Classification of Diseases and Related Health Problems
DSM-5 = 5th revision of the Diagnostic and Statistical Manual
VASCOG = Vascular Cognitive and Behavioral Disorders
ICD-11 = 11th revision of the International Classification of Diseases and Related Health Problems

For studies diagnosing major NCD according to NINDS-AIREN, DSM-IV, and ICD-10 criteria, mild NCD is diagnosed according to the core clinical criteria for MCI. These represent self-reported or informant-reported cognitive decline or objective evidence of cognitive decline that does not fulfill the criteria for major NCD. Commonly used definitions of mild NCD in recent decades include the following (26-30):

1) the Petersen criteria, also known as the Mayo criteria, requiring memory impairment and normal general cognitive function, where a cut-off of -1.5 SD has been widely used;

2) the Winblad criteria, a modification of the Petersen criteria that aimed to improve clinical applicability, requiring impairment within one or more cognitive domains, not necessarily memory, where the cut-off -1.5 SD in one or more cognitive tests per domain has widely been used; and

3) the Jak/Bondi criteria, requiring two tests showing impairment in one or more cognitive domains with a cut-off of -1 SD.

A variety of other definitions for mild NCD have also been used in research (3, 19). However, there is no clear consensus on which domains should be assessed (26-31). In the systematic review and meta-analysis by Sexton and colleagues on the prevalence of mild NCD after a stroke, the studies included based their diagnosis of mild NCD on various methods for defining mild NCD with different cut-offs and different requirements for the number of domains affected, as well as specific cut-offs on specified cognitive tests or assessment tools measuring cognitive function, such as the MMSE, MoCA, CAMCOG, or IQCODE (19). Taken together, this emphasizes the need for the harmonization of operational definitions of both mild and major NCD.

2.6.2 Allocation of cognitive tests to different cognitive domains

Cognitive tests often examine more than one cognitive domain, and there is a lack of consensus on the allocation of cognitive tests to specific domains (21, 32). None of the diagnostic criteria cites which cognitive tests or how many should be applied to specific domains. However, some international standardization has been achieved recently.

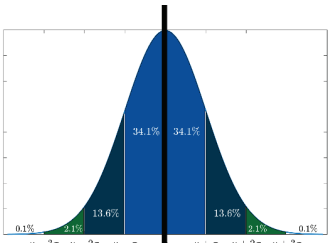
Aiming for greater consistency across studies on vascular cognitive impairment (33), the National Institute of Neurological Disorders-Canadian Stroke Network (NINDS-CSN) Vascular Cognitive Impairment Harmonization Standards made a few recommendations regarding the choice of cognitive tests. In a recent study, the STROKOG published an overview of the allocation of cognitive tests to cognitive domains used in the 25 studies included in their consortium (21). Examples from this overview include:

1. Trail Making Test A, Digit Span Forward, and Digit Symbol Coding – allocated to attention/processing speed;
2. Word Recall, Rey–Osterrieth Complex Figure Test: Recall and Logical Memory – allocated to memory;
3. Boston Naming Test, Verbal fluency category (animals, professions) and Token Test – allocated to language;
4. Rey–Osterrieth Complex Figure Test: Copy, and Clock-Drawing Test – allocated to construction (visuospatial); and
5. Trail Making Test B, Verbal fluency letter, Digit Span Backward and Stroop Test – allocated to executive function.

2.6.3 Cut-offs for neurocognitive disorders

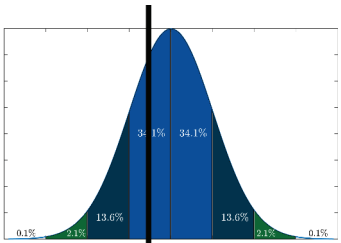
Traditionally, different cut-offs for mild NCD have been used in past decades (3, 19, 26-30). However, in recent research, z-scores have been commonly used and, thereby, the use of average z-scores for the cognitive tests allocated to a cognitive domain (4, 34). A z-score is a score normalized by mean and standard deviation. The z-score could be defined within the studied population, but it is more commonly used in cognitive research normalized by mean and standard deviation of the control group or normative data used. Figure 2 illustrates the interpretation of selected z-scores normalized by mean and standard deviation of the control group or normative data.

a



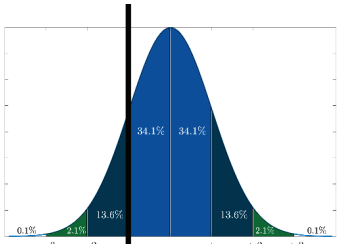
Z-score = 0
Larger portion = 50%

b



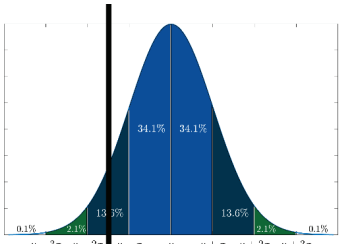
Z-score = -0.5
Larger portion = 69%

c



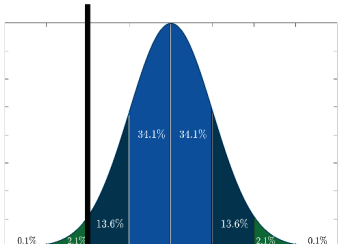
Z-score = -1.0
Larger portion = 84%

d



Z-score = -1.5
Larger portion = 93%

e



Z-score = -2.0
Larger portion = 98%

f

$$Z = \frac{X - \mu}{\sigma}$$

Figure 2. Interpretation of selected z-scores

The variable of interest in the control group or normative data is illustrated with the normal distribution in the panels a–e.
Panel a. A mean z-score of 0 in the studied population equals the mean of the control group or the normative data used.
Panel b. A mean z-score of -0.5 in the studied population represents a score where 69% of the control group or the normative data used have a better score.
Panel c. A mean z-score of -1.0 in the studied population represents a score where 83% of the control group or the normative data used have a better score.
Panel d. A mean z-score of -1.5 in the studied population represents a score where 93% of the control group or the normative data used have a better score.
Panel e. A mean z-score of -2.0 in the studied population represents a score where 98% of the control group or the normative data used have a better score.
Panel f. The definition of z for the normal distribution is shown.
X = the measured value of a patient
μ = mean of the control group or normative data
σ = standard deviation of the control group or normative data

For mild NCD, the updated DSM-5 and VASCOG criteria require a modest decline in one or more domains, typically in the range -1 to -2 SD. Although the cut-off of -1 SD is proposed, some room remains for interpretation of the cut-off, and this will have a significant impact on the prevalence of NCD. The implication of a -1 SD cut-off for mild NCD is that 13% of the normative data will have a cognitive performance within the range of mild NCD, while 4.4% of the normative data will have a cognitive performance within the range of mild NCD with a cut-off -1.5 SD (35) (Figure 3). Consequently, several studies that applied the DSM-5 and VASCOG criteria for mild and major NCD have used a cut-off -1.5 SD for NCD (25, 34, 36).

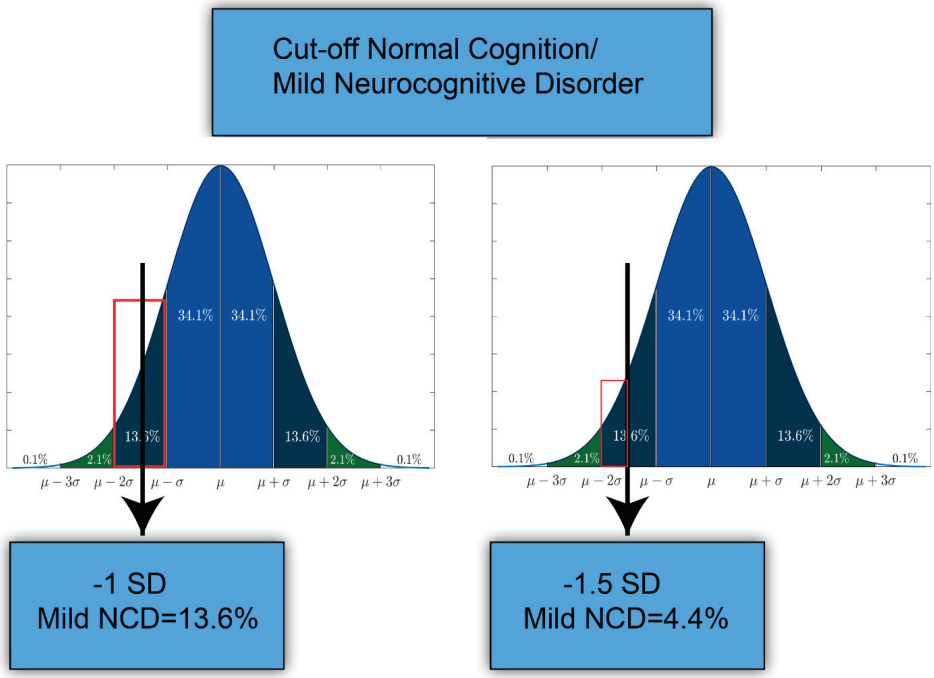


Figure 3. The implication of a cut-off of -1 instead of -1.5 standard deviation for mild neurocognitive disorder

2.6.4 Normative data

In the classification of NCD, a comparison of performance on cognitive tests with norms appropriate to the patient's age, education, and cultural background is part of the standard evaluation (15). In a clinical setting, published normative data are used for this comparison. In research, a control group representative of the normal population is most commonly used, but for studies without a control group, published normative data are applied.

However, as described by Petersen in 2004, there are several approaches to defining a normal population (26). One involves a population of persons with relatively low comorbidity. Another approach is a population that comprises a more typical aging cohort, often defined by no active neurological or psychiatric disease and no use of psychoactive medications, and where comorbidity could be present but does not interfere with cognitive function. Some have argued that a decline in cognitive function over time is abnormal and, therefore, the exclusion of persons with such declines over time is another approach. Moreover, several studies on normative data have excluded persons with major NCD, while others have also excluded those with mild NCD. These different approaches to the definition of a normal population produce different prevalence rates of NCD.

2.6.5 Activities of daily living (ADL)

ADL are divided into personal ADL (P-ADL) and instrumental ADL (I-ADL). P-ADL comprise self-maintenance skills such as bathing, getting dressed, and eating; I-ADL comprise complex instrumental activities such as managing finances and medications, and using public transport.

In all the diagnostic criteria for NCD, the ADL determine the severity of the disease; a cognitive decline severe enough to interfere with independence in daily functioning is classified as major NCD, while a cognitive decline not severe enough to interfere with independence in daily functioning is classified as mild NCD. Although this distinction is well-established for NCD, the WHO has raised the question of whether the degree of impairment produced by a disease should be used to diagnose the disease, and it has

recommended that the classification of functioning and disability be kept separate from the classification of diseases (16).

The descriptions of types and levels of severity of ADL impairment in major NCD vary across the different diagnostic criteria. The DSM-IV criteria propose a cognitive decline "severe enough to cause significant impairment in social or occupational functioning," and the NINDS-AIREN criteria propose a cognitive decline "that causes impaired functioning in daily living" (22, 23). The updated DSM-5 and VASCOG criteria are more specific, with requirements for I-ADL. The DSM-5 criteria for mild NCD specify that "The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required)," whereas, for major NCD, the cognitive deficits interfere with independence in everyday activities (15). The specification of ADL requirements in the VASCOG criteria is almost equivalent to that of the DSM-5 criteria (16). The forthcoming ICD-11 criteria do not specify the ADL requirements in as much detail as the DSM-5 and the VASCOG criteria. For mild NCD, the ICD-11 criteria require a cognitive decline "not sufficiently severe to significantly interfere with independence in the person's performance of activities of daily living", and for major NCD a cognitive decline that "significantly interferes with independence in the person's performance of activities of daily living" is required (8).

Although Winblad and colleagues proposed that P-ADL should be preserved and I-ADL be intact or minimally impaired for a diagnosis of mild NCD, any consensus regarding which ADL should be measured and which instruments and cut-offs should be used has been lacking (27, 37). In a review by Jekel et al. aiming to summarize the results of I-ADL performance in patients with normal cognition and mild and major NCD, 37 studies were included. They found that 31 different instruments were used to assess I-ADL, and impairments in I-ADL were identified in patients with mild NCD in 35 of the 37 studies (38). In stroke patients, it is challenging to differentiate whether impairments in ADL are related to cognitive impairment or stroke sequelae. Recent reviews and meta-analyses

on mild and major poststroke NCD have not addressed how different measures for ADL should be used to determine the severity of poststroke NCD (3, 18, 19).

Another challenge is how data should be retrieved. ADL is commonly assessed with rating scales administered to the patient or the patient's proxy, as objective assessment of ADL is both difficult and time-consuming (38). There is conflicting evidence regarding the reliability of self-reported ADL in patients with mild NCD because they might lack awareness of ADL impairment and overestimate their ADL performance. Moreover, the reliability of a proxy's evaluation of ADL is questionable since proxies have been found to have a tendency to over- or underestimate a patient's degree of ADL impairment.

To summarize, there still appears to be a need for the harmonization of operational definitions of ADL impairments in order to determine the severity of poststroke NCD.

2.6.6 The DSM-5 criteria

The DSM-5 criteria cite requirements for both cognitive and I-ADL performance (15). The cognitive requirement for mild NCD is evidence of a modest cognitive decline in one or more domains with a test score typically in the range of -1 SD to -2 SD; for major NCD, evidence of a significant cognitive decline in one or more domains with a test score typically ≤ -2 SD is required. The ADL requirement is independence in I-ADL for mild NCD and dependence in I-ADL for major NCD. Figure 4 illustrates the DSM-5 criteria requirements; they are not necessarily congruent with the requirements for ADL, leaving some room for interpretation even within the DSM-5 criteria.

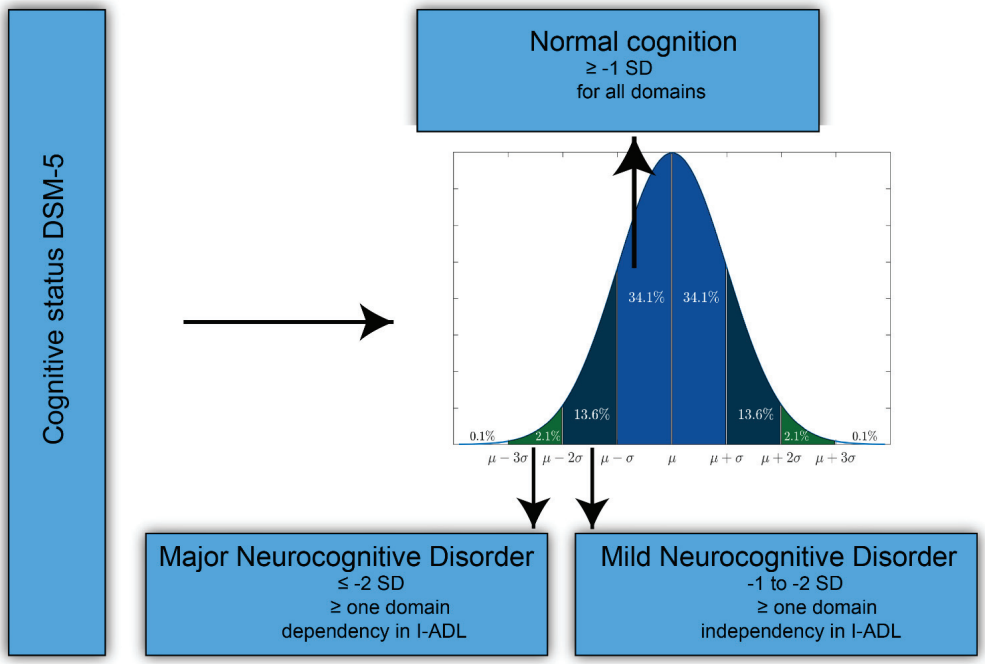


Figure 4. The requirements for cognitive and activities of daily living performance of the DSM-5 criteria

2.6.7 Different operational definitions applied within the same study population

In a cohort of 91 patients with stroke or TIA, Pendlebury and colleagues studied differences in operational definitions of criteria for mild NCD measured with short cognitive tests vs a cognitive test battery and Petersen (memory impairment required) vs Winblad criteria (requiring impairment in one of more cognitive domains) for the different cut-offs -1 SD, -1.5 SD, and -2 SD (39). They found that these operational differences resulted in a fourfold variation in the estimates for mild NCD, varying from 15% using the Petersen criteria and assessed with a single test with a cut-off of -2 SD to 67% for the Winblad criteria and using a single test with a cut-off -1 SD. Sachdev and colleagues validated the VASCOG criteria against older criteria for major NCD (i.e., i) NINDS-AIREN, ii) the Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC),

and iii) the DSM-IV criteria) in a stroke cohort of 165 patients. In the same study, they also validated the VASCOG criteria against other updated criteria for mild and major NCD (i.e., i) the DSM-5 and ii) the VICCCS criteria). They found very good agreement for mild and major NCD between the updated criteria (Cohen's kappa 0.83–1.0) but moderate to good agreement for major NCD between the older and the updated criteria (Cohen's kappa 0.47–0.63) (25). Except for these two studies, minimal research has examined the impact of different operational definitions in the same population.

2.6.8 Study population

For studies that aim to report reliable estimates of incidence and prevalence of mild and major poststroke NCD, the results are influenced by the study population, the setting, and the previously described operational decisions that influence the classification of NCD.

Age, education, sex, and comorbidity such as prestroke dementia and previous stroke are the most important predictors for PSCI (18). Therefore, the selection of the study population in regard to inclusion and exclusion criteria is important for the external validity of the results. Hospital-based studies are, to a larger degree than population-based studies, prone to exclude older patients, patients with impaired prestroke function, patients suffering severe strokes, and patients with comorbidity (40-42). However, case-finding is easier in a hospital than in a population-based setting, and comprehensive cognitive tests are often not feasible in stroke patients who were not initially managed in a hospital. These factors favor hospital-based studies for measuring poststroke NCD (3). In addition, some studies on PSCI have excluded patients with prestroke dementia while others have not (3, 18, 19).

Pendlebury and Rothwell made a generalization based on their results in the Oxford Vascular Study, a population-based cohort of 92,728 individuals, to estimate the incidence of major poststroke NCD in the United Kingdom. An estimated 97% of the true residential population was included, and pre- and postevent dementia after stroke and TIA was diagnosed on the basis of cognitive testing supplemented with data collected by hand-searching all records from hospital and primary care, conducted by Pendlebury

(41). Pendlebury and Rothwell found an incidence of postevent dementia at one year of 34% (95% CI 30–42) in patients with severe strokes, 8.2% (95% CI 6.2–10) in patients with minor strokes, and 5.2% (95% CI 3.4–7.0) in patients with TIA (41). They identified a stepwise association between the severity of the cerebrovascular event and postevent dementia that was modified by previous stroke and cognitive reserve. They also found that the 5-year incidence of dementia was strongly related to both age and severity of the event, indicating a low probability for poststroke major NCD in young patients with TIA and minor strokes in contrast to a high probability for poststroke major NCD in older patients with severe strokes. A strength of such a study is that it captures almost all cases of poststroke dementia. However, reproducibility is a limitation because the dementia diagnosis is based in part on data from hand-searching hospital and primary care records. Another limitation is that the diagnosis of major NCD based on the global scales of the MMSE and the MoCA is prone to an underestimation of major NCD due to the ceiling effect of the tests, whereas diagnosis based on a comprehensive test battery captures more impairments (39). In summary, this highlights a methodological problem with the comparison of the prevalence of poststroke NCD across studies to populations that have different clinical characteristics.

2.6.9 Selected studies illustrating methodological issues

As seen in the recent reviews and meta-analyses on mild and major NCD, different operational definitions for each have been applied (3, 18, 19). As the updated DSM-5 and VASCOG criteria were only recently published, none of the studies included in these reviews and meta-analyses used them. However, many publications using the updated criteria are expected. In Table 3, selected studies on the prevalence of mild and major NCD are presented to illustrate several factors that affect prevalence. These include (i) differences regarding the study population's age and prestroke comorbidity across studies, (ii) lower prevalence of NCD in a younger stroke population comprising first-ever stroke with prestroke dementia excluded and the use of diagnostic criteria demanding three impaired domains for a diagnosis of major NCD (43), (iii) low prevalence of mild NCD with the use of one global test with a ceiling effect (44), and (iv) relatively high prevalence of major NCD with use of cognitive tests only (45).

Table 3. Selected studies on prevalence of mild and major poststroke cognitive impairment

Study, Country	N	Population	Mean age, years (SD)	First-ever stroke	Prestroke dementia excluded	Number of cognitive tests	Cognitive domains assessed	Criteria and/or cut-off for mild NCD	Criteria and/or cut-off for major NCD	Follow-up, in months	Prevalence of mild poststroke NCD	Prevalence of major poststroke NCD
Censori et al. (43), Italy	110	IS	65.1 (9.5)	Yes	Yes	7	1. Attention 2. Memory 3. Language 4. Visuo-spatial	Own study definition (choice of cut-off not described)	NINDS-AIREN	3.5	5.4%	13.6%
Cumming et al. (45), Australia	60	IS, ICH	72.1 (13.9)	No	No	10	1. Attention 2. Executive function 3. Memory 4. Language 5. Visuo-spatial	≤-1 SD in ≥2 domains	≤-2 SD in ≥2 domains	3	23%	42%
Ihle-Hansen et al. (46), Norway	184	IS, ICH, TIA	72 (12.2)	Yes	Yes	7	1. Attention 2. Executive function 3. Memory 4. Language 5. Visuo-spatial	Winblad (cut-off not described)	ICD-10	12	37.5%	19.6%
Pendlebury et al. (41)*, England	2305	IS, ICH, TIA	74.4 (13.0)	No	No	2	Global tests only	NA	DSM-IV, MMSE<24	1, 6, 12, 60	NA	1-year incidence: 34.4% in severe strokes*, 8.2% in

Study, Country	N	Population	Mean age, years (SD)	First-ever stroke	Prestroke dementia excluded	Number of cognitive tests	Cognitive domains assessed	Criteria and/or cut-off for mild NCD	Criteria and/or cut-off for major NCD	Follow-up, in months	Prevalence of mild poststroke NCD	Prevalence of major poststroke NCD
												minor strokes, 5.2% in TIA
Rasquin et al. (47), The Netherlands	196	IS, ICH	68.4 (12.5)	Yes	Yes	6	1. Mental speed 2. Attention 3. Executive function 4. Memory 5. Language 6. Visuo-spatial 7. Orienta-tion 8. Praxis 9. Calcula-tion	Petersen (cut-off not described)	DSM-IV, NINDS-AIREN	1, 6, 12	71.1% (1 m), 61.3% (6 m), 51.5% (12 m)	10% (1 m), 7.7% (6 m), 7.7% (12 m)
Tang et al. (44), Hong Kong	179	IS, ICH	73.0 (7.5)	No	No	1	Global test only	MMSE education-based cut-offs	DSM-IV	3	21.8%	NA

IS = ischemic stroke, ICH = intracerebral hemorrhage, TIA = transient ischemic attack, m = months
*The method used for the study is further described in chapter 2.6.8 of this doctoral thesis.

2.7 Cognitive symptom profile

Due to the heterogeneity of stroke characteristics, the cognitive symptom profile in PSCI is complex (4). Several cognitive domains are affected, and of these, impairment in attention and executive function seem to be the most prevalent and severe in both the short and long term (34, 48-51). However, in their recently published review and meta-analysis of early PSCI, Lo and colleagues identified a high prevalence of impairment. Global impairment was found in 44% of the patients, and 30% to 35% of the patients exhibited impairments in the five most commonly assessed domains: attention, memory, language, perceptual-motor function, and executive function (4).

2.8 Course of poststroke cognitive impairment

Previous studies show conflicting results regarding the prognosis for patients suffering from PSCI. A vast majority of the studies indicate deterioration (41, 52, 53). In their prospective study of 515 patients with incident stroke and 23,057 stroke-free participants, Levine and colleagues found that incident stroke was associated with both acute decline in cognitive function and accelerated cognitive decline over the next 6 years (53). Pendlebury and Rothwell, in the Oxford Vascular study of 2305 patients with stroke or TIA, found an increase in cumulative incidence of poststroke dementia up to 5 years after stroke (41). Zheng and colleagues, in their population-based study of 9,278 participants without dementia and without previous stroke, of whom 471 had incidental stroke, identified accelerated prestroke and poststroke cognitive decline in patients with incidental stroke (52).

By contrast, in some studies, no progression has been reported. Douiri and colleagues, in their study of 4,212 stroke patients identified from the community-based South London Stroke Register, found that the overall prevalence of PSCI was relatively unchanged at approximately 22% over 14 years after suffering a stroke (54).

Moreover, even improvement in cognition over time has been reported (55, 56). In their study of 115 stroke patients, Ballard and colleagues found improvement in cognition 3–15 months poststroke in half the sample (56). Liman and colleagues, in their study of

630 stroke patients, found improvement in approximately one-third of the patients over three years (55).

In summary, more knowledge on the course of poststroke cognitive impairment is needed.

2.9 Impact of stroke subtype

Cognitive impairment has been shown to be less common early after stroke in SVD compared to other ischemic stroke subtypes, but SVD is associated with cognitive decline in long-term follow-up (4, 51, 54, 57, 58). However, in their review and meta-analyses, Makin et al. found similar proportions of PSCI in lacunar versus non-lacunar strokes (OR 0.75 [95% CI 0.47–1.20]) (59, 60).

ICH has been shown to be more strongly associated with dementia than ischemic stroke (41), and impairments in episodic memory, processing speed, and executive function are seen more frequently (9, 61).

2.10 Impact of vascular risk factors

Hypertension is a known risk factor for dementia; however, knowledge about its association with PSCI is limited (4, 62-64). Mid-life hypertension and smoking are associated with cognitive decline, while late-life hypertension alone might have a neutral or even a protective effect (62, 63, 65, 66).

In their review and meta-analysis from the STROKOG, Lo and colleagues found strong associations with PSCI for previous stroke and diabetes mellitus and less strong associations for hypertension, atrial fibrillation, and smoking (4). Levine and colleagues, in their recent study, showed an association between cognition and blood pressure levels early after a stroke; however, these findings were explained by sociodemographic and clinical factors (67).

Arba and colleagues found that diabetes was associated with PSCI one and three years poststroke in their study on the Virtual International Stroke Trials Archive (VISTA)(68).

Pendlebury and Rothwell, in their systematic review and meta-analysis of studies with both short- and long-term follow-ups after stroke, found that diabetes mellitus, atrial fibrillation, and previous stroke were shown to be predictors of poststroke dementia, but predictors related to the features of the stroke were the most important predictors (18). In the Oxford Vascular Study, the same researchers found that poststroke dementia was associated with previous stroke and diabetes mellitus in the long term after suffering a stroke (41).

2.11 Hypothesis of the thesis

To summarize, we still lack evidence about the impact of different operational definitions of PSCI, the course of PSCI, and the impact of stroke subtypes and vascular risk factors on PSCI.

For the work in this thesis, we hypothesized that:

I. Within a given patient population, models defining mild NCD would show greater variation in measured NCD rate and lower agreement than models defining major NCD.
II. We would find more-advanced cognitive impairment in the cortical infarcts LAD and CE compared to SVD. We also hypothesized that SVD would progress more rapidly than LAD and CE.
III. Prestroke vascular risk factors would be associated with PSCI both early and long term after a stroke and that the cognitive decline would be more advanced in patients with prestroke vascular risk factors compared to patients without such risk factors.

3 Aim of the thesis

The overall aim of the thesis was to study the impact of different operational definitions of PSCI, its course from early to late after a stroke, and the impact of stroke subtypes and vascular risk factors on PSCI.

More specifically, the aim was explored in three studies in three papers.

1. We aimed to assess the prevalence of all poststroke NCD and, separately, mild and major NCD in the Nor-COAST study population using DSM-5 and two other methods used for classification. Further, we aimed to explore agreement among these three methods.

2. We aimed to investigate whether time and etiological stroke subtype have an impact on the probability of PSCI and its severity and cognitive symptom profile 3 and 18 months poststroke.

3. We aimed to explore the association between prestroke vascular risk factors and cognitive impairment at 3 and 18 months poststroke within global cognitive measures and different cognitive domains. We also aimed to study the course of PSCI in patients with and without prestroke vascular risk factors.

4 Methods

4.1 Study design and study participants

The study was part of the Nor-COAST study, a multicenter, prospective cohort study where participants hospitalized with acute stroke in five Norwegian stroke units were recruited from May 2015 through March 2017 (69). The five stroke units were located at St. Olav's Hospital; Oslo University Hospital, Ullevål; Vestre Viken Hospital Trust, Bærum Hospital; Haukeland University Hospital; and Ålesund Hospital. Inclusion criteria were hospitalization with acute ischemic or hemorrhagic stroke within one week of symptom presentation, fluency in a Scandinavian language, and age over 18 years. The only exclusion criterion was expected survival less than three months. Follow-ups at 3 and 18 months were conducted at the outpatient clinics of the respective hospitals.

4.1.1 Study samples

In all, 2505 participants were diagnosed with stroke at the participating hospitals during the study period (42). Of these, 815 were included at baseline. Per study criteria, 559 were ineligible; 753 were not screened due to staff unavailability and 143 for other reasons. Of the 815 participants included in the Nor-COAST study, 700 were assessed at 3 months and 599 at the 18-month follow-up, 10 of whom were not assessed at 3 months (Figure 5).

Of the 700 participants assessed at 3 months, 101 were excluded from paper 1 due to missing data. Of the 710 participants assessed at either 3 or 18 months, 93 were excluded from paper 2 and 75 from paper 3 due to missing data. This resulted in a study sample of 617 participants in paper 2 and 635 participants in paper 3. Of the 617 participants included in paper 2 and the 635 included in paper 3, 21 were deceased at 18 months.

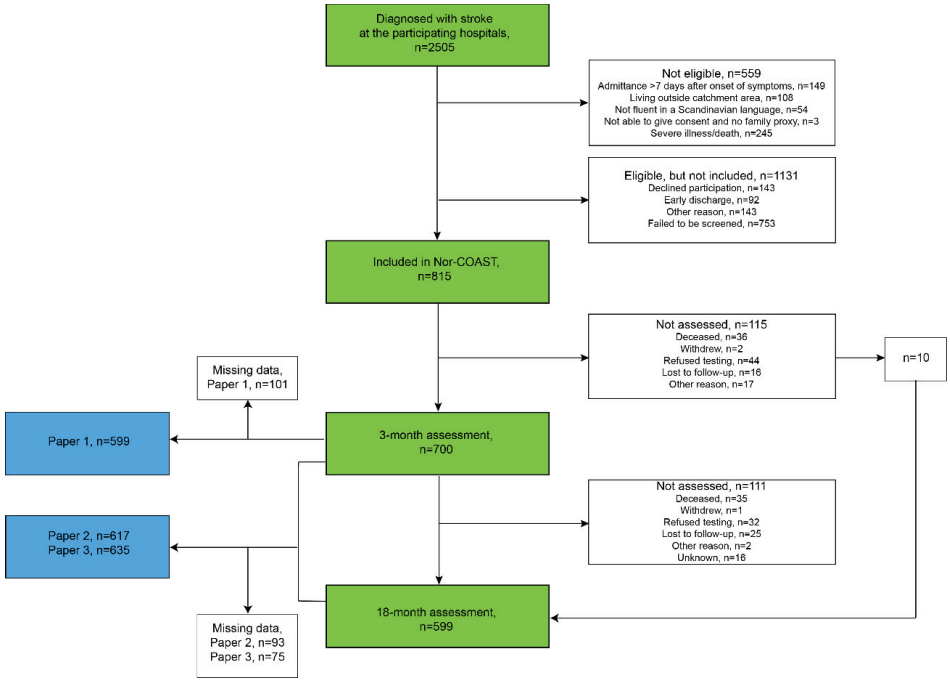


Figure 5. Flowchart of participants included in the papers

The baseline characteristics of the participants included in the three papers are shown in Table 4.

Table 4. Baseline characteristics of participants included in the three papers

Characteristics	Paper 1 N=599			Paper 2 N=617			Paper 3 N=635		
Demographics	N=599			N=617			N=635		
Mean age, years (SD)		71.6	(11.8)		71.6	(11.8)		71.6	(11.7)
Female sex, n (%)		257	(43)		257	(42)		266	(42)
Mean education, years (SD)		12.4	(3.8)		12.5	(3.8)		12.4	(3.8)
Vascular risk factors, n (%)									
Hypertension, n (%)	N=599	329	(55)	N=617	338	(55)	N=635	460	(72)
Hypercholesterolemia, n (%)	N=599	304	(51)	N=617	314	(51)	N=635	216	(34)
Current cigarette smoking, n (%)	N=597	112	(19)	N=615	119	(19)	N 631	121	(19)
Diabetes mellitus, n (%)	N=599	113	(19)	N=617	115	(19)	N=635	145	(18)
Mean BMI, kg/m^2 (SD)	N=567	26.1	(4.2)	N=583	26.1	(4.1)	N=600	26.1	(4.2)
Atrial fibrillation, n (%)	N=599	140	(23)	N=617	144	(23)	N=635	145	(23)
Coronary heart disease, n (%)	N=599	104	(17)	N=617	108	(18)	N=635	112	(18)
Previous stroke, n (%)	N=599	106	(18)	N=617	136	(22)	N=635	112	(18)

Characteristics	Paper 1		Paper 2		Paper 3	
Stroke subtype, n (%)	N=599		N=617		N=635	
Cerebral infarction	547	(92)	564	(91)	582	(92)
Cerebral hemorrhage	52	(8.7)	53	(8.6)	53	(8.3)
TOAST classification, n (%)	N=529		N=564	*	N=564	*
Large vessel disease	56	(11)	140	(25)	140	(25)
Cardioembolic disease	123	(23)	153	(27)	153	(27)
Small vessel disease	119	(23)	135	(24)	135	(24)
Other etiology	15	(2.8)	17	(3.0)	17	(3.0)
Undetermined etiology	216	(41)	119	(21)	119	(21)
Thrombolysis, n (%)	N=542	143 (26)	N=612	147 (24)	N=629	153 (24)
Thrombectomy, n (%)	N=547	11 (2.0)	N=617	12 (1.9)	N=635	12 (1.9)
Prestroke GDS (1–7), n (%)	N=594		N=611		N=629	
GDS = 1–2 (Normal cognition)	536	(90)	553	(91)	568	(90)
GDS = 3 (Mild NCD)	36	(6.1)	35	(5.7)	36	(5.7)
GDS = 4–7 (Major NCD)	22	(3.7)	23	(3.8)	25	(4.0)

Characteristics	Paper 1			Paper 2			Paper 3		
Assessments									
NIHSS (0–42) at admittance, mean (SD)	N=583	3.7	(4.7)	N=601	3.8	(4.8)	N=618	3.8	(4.8)
Prestroke mRS (0–6), mean (SD)	N=596	0.79	(1.0)	N=613	0.77	(1.0)	N=631	0.78	(1.0)
mRS (0–6) at discharge, † mean (SD)	N=597	2.1	(1.3)	N=615	2.1	(1.3)	N=633	2.1	(1.3)
Barthel Index (0–100) at discharge, † mean (SD)	N=597	89	(19)	N=615	89	(19)	N=633	89	(19)

SD = standard deviation, BMI = body mass index, TOAST = Trial of Org 10172 in Acute Stroke Treatment, GDS = Global Deterioration Scale, NIHSS = National Institutes of Health Stroke Scale, mRS = modified Rankin Scale, NCD=Neurocognitive Disorders

*TOAST modification; undetermined etiology of TOAST probable (12), first classified as TOAST possible, (12) then as TOAST likely (70) where participants with findings of carotid stenosis <50% were classified as large artery disease. Finally, TOAST modified was developed by merging TOAST probable, TOAST possible, and TOAST likely.

†at discharge or day 7 if length of stay extends beyond 7 days.

4.2 Data collection

4.2.1 Clinical assessments

Data on demographic characteristics, vascular risk factors, and medications were collected from participants' medical records during the hospital stay (Table 1). Smoking was defined as current smoking, coronary heart disease as a history of coronary heart disease according to medical records, and previous stroke as a history of previous stroke according to medical records. The presence of atrial fibrillation included a history of permanent, persistent, or paroxysmal atrial fibrillation or atrial flutter detected on electrocardiogram and described in medical records and/or detected in electrocardiogram and/or telemetry during hospital stay. Hypertension was defined as prestroke use of antihypertensive medication in Papers 1 and 2, and in Paper 3, in addition, and/or use of antihypertensive medication at discharge. Diabetes mellitus was defined as a history of diabetes mellitus from medical records and/or prestroke use of antidiabetic medication and/or HbA1c≥48 mmol/mol at admittance for stroke in Papers 1 and 2, and in Paper 3, in addition, and/or use of antidiabetic medication at discharge. Hypercholesterolemia was defined as prestroke use of lipid-lowering medication or total cholesterol ≥6.2 mmol/L and/or low-density lipoprotein ≥4.1 mmol/L at hospital admittance for stroke in Papers 1 and 2 (71, 72), and/or as prestroke use of lipid-lowering medication in Paper 3.

Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS) (73) at admittance. Ischemic stroke subtype was defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification as large artery disease (LAD), cardioembolism (CE), small vessel disease (SVD), stroke of other determined etiology, or stroke of undetermined etiology (UD) (12). The original TOAST classification was used in Paper 1. However, in keeping with the general idea of the modified TOAST classifications, we performed a TOAST modification as described in the following. Experienced stroke physicians first applied the original TOAST criteria and classified

these according to TOAST *probable* (12). This resulted in 232 of 564 (41%) ischemic strokes classified as UD. Based on collected data, including previous medical history, electrocardiograms, telemetry, transthoracic and transesophageal ultrasounds, and information from MRI and CT scans, we performed a stepwise classification of the UD group (12, 70), first as TOAST *possible,* as described by Adams et al. (12), resulting in 189 of 564 (34%) ischemic strokes still classified as UD. Next, these UD patients were classified as TOAST *likely* (70), where participants with carotid stenosis < 50% or plaques were classified as having LAD. In this last step, the UD group was reduced to 119 from 564 (21%). For the final TOAST classification in Paper 2, TOAST *modified* was developed by merging TOAST *probable*, TOAST *possible,* and TOAST *likely* (Figure 6). TOAST *modified* was also used in Paper 3.

	TOAST probable	TOAST possible	TOAST likely	TOAST modified
Large artery disease	**N=57 (10%)** Clinical symptoms of cortical or cerebellar dysfunction. Brain imaging findings of either significant (> 50%) stenosis or occlusion* Cortical or cerebellar lesion and brain stem or subcortical hemispheric infarcts > 1.5 cm in diameter on CT or MRI	**N=16** Occlusion or stenosis > 50% contra- or ipsilaterally to the stroke lesion	**N=67** Carotid stenosis < 50% or plaque	N=140 (25%)
Cardiac emboli	**N=130 (23%)** ≥ 1 Cardiac source for an embolus identified Potential large-artery atherosclerotic sources of thrombosis or embolism must have been eliminated	**N=23** Atrial fibrillation (AF) of any duration detected before or during stay or strong suspicion of AF based on clinical evaluation, or findings of patent foramen ovale**, or history of previous myocardial infarction as source of cardiac embolus	N=0	N=153 (27%)
Small vessel disease	**N=128 (23%)** Lacunar syndromes†. Evidence of cerebral cortical dysfunction should be absent. CT or MRI: Normal or brain stem/subcortical hemispheric lesion < 1.5 cm Findings of cortical dysfunction or large artery pathology should be absent.	**N=7** High suspicion of small vessel disease or small vessel disease detected on imaging before or during hospital stay	N=0	N=135 (24%)
Other determined etiology	**N=17 (3.0%)** Rare causes of stroke; dissection of cerebral or cervical arteries, hypercoaguable states, hematologic disorders or non-atherosclerotic vasculopathies	N=0	N=0	N=17 (3.0%)
Undetermined etiology	**N=232 (41%)** No etiology fulfilling the strict TOAST criteria is present despite extensive vascular, cardiac and biochemical evaluation, or no cause identified but the evaluation is incomplete, or two or more competing causes of stroke are identified	N=189 (34%)	**N=119 (21%)** Embolic stroke of undetermined source, multiple possible etiologies detected or incomplete investigation and no clear etiology detected	N=119 (21%)

Figure 6. TOAST classification. First classified as TOAST *probable* based on original classification (12), then undetermined etiology (UD) of TOAST *probable* was categorized as TOAST *possible,* also based on original classification (12); those still categorized as UD were then classified as TOAST *likely (70)*; finally, these were merged as TOAST *modified.*

*of a major cerebral artery or cortical branch of an artery

†most frequently being pure motor hemiparesis, pure sensory hemiparesis, ataxic hemiparesis, sensorimotor stroke, and dysarthria-clumsy hand syndrome

**on transesophageal ultrasound

4.2.2 Cognitive and functional assessments

The cognitive assessments were based on the recommended 30-minute neuropsychological test battery from the National Institute of Neurological Disorders-Canadian Stroke Network (NINDS-CSN) Harmonization Standards adapted to available validated tests in Norwegian (33). A short description of the cognitive and functional assessment scales used in the analyses of the thesis follows.

The **MoCA** is a screening tool assessing global cognitive function and was designed to screen for mild NCD (74). It is a 30-point assessment scale (range 0–30) comprising 10 items. Visuospatial function is assessed with figure copying and a clock-drawing test. Executive function is assessed with a task adapted from the Trail Making Test B, a letter fluency task, and a verbal abstraction task. Attention, concentration, and working memory are assessed with an attention task, serial subtraction, and digit span forward and backward. Language is assessed with a naming task with animals, repetition of sentences, and letter fluency. Orientation is evaluated by time and place (74, 75). Because education was found to affect performance, Nasreddine and colleagues added one point for patients with 12 or fewer years of education. In the original paper, a cut-off score of < 26 was recommended for the diagnosis of mild NCD. In a Cochrane review, Davis and colleagues found that thresholds lower than 26 are likely to be more useful for optimal diagnostic accuracy of the MoCA in major NCD, but they also called for more research to confirm this (76).

The **Trail Making Test A** (TMT-A) and **Trail Making Test B** (TMT-B) are assessment scales that evaluate attention, psychomotor speed, and mental flexibility (77). In TMT-A, the numbers 1 to 25 are scattered within circles, and the task is to draw lines connecting the numbers in numerical order as quickly as possible. In TMT-B, the numbers 1 to 13 and the letters A to L are scattered within circles, and the task is to draw lines connecting

the numbers and letters in alternating order as quickly as possible (78). We measured the amount of time the participant spent completing the tests.

The **CERAD Word List Memory and Recall Test** (79) is an assessment scale for memory comprising different memory tasks involving learning, delayed recall, and recognition. In the Nor-COAST study, we measured learning (range 0–30), where 10 unrelated words were presented visually in three trials and the order of the words was changed for each trial, and delayed recall (range 0–10) after nonverbal distracting tasks, where the participant was asked to recall as many of the 10 unrelated words as possible (78). Delayed recall was used in the analyses of the thesis.

The **Verbal Fluency Test Letter (FAS)** (80, 81) is an assessment scale measuring orally generated words beginning with the letters F, A, and S, with 60 seconds for each letter (78). The **CERAD Verbal Fluency Test Category (animals)** (82) is an assessment scale measuring orally generated words from the semantic category animal-naming within 60 seconds. The tests have commonly been seen as assessments for executive function and language, although other cognitive domains have been suggested to be involved (78).

The **Global Deterioration Scale (GDS)** (83) is a rating scale (range 1–7) originally designed to measure cognitive decline secondary to Alzheimer's disease, but it has also been shown to be valid for detecting vascular dementia (84, 85). As described by Petersen and colleagues, commonly used interpretations of the test's scores are 1–2 indicating normal cognition; 3 indicating mild NCD; and 4–7 indicating major NCD (26, 86).

The **Ascertain Dementia 8-item Informant Questionnaire (AD8)** (87) is an assessment scale comprising eight questions asking the informant to rate change in the areas of memory, temporal orientation, judgment, and function as "yes, a change"; "no, no change"; or "don't know" (87, 88).

The **National Institutes of Health Stroke Scale (NIHSS)** (73) is a measure of stroke severity with 15 items of cognitive function and neurological function (range 0–42); higher scores indicate poorer outcomes.

The **modified Rankin scale (mRS)** (89) is a measure of functional outcome (range 0–5); higher scores indicate poorer outcome. A sixth category is often added to indicate death. Lower scores indicate independence in ADL, and higher scores indicate dependence in ADL.

An overview of the assessment scales and time-points for follow-up assessments used in the thesis is shown in Table 5.

Baseline assessments were performed during the hospital stay. Follow-ups at 3 and 18 months were performed at the hospitals' outpatient clinics. For participants unable to attend follow-up assessments in person, telephone interviews with participants, their caregivers, or nursing home staff were performed using the Barthel Index (BI) (90), mRS (89), GDS (83), and, when possible, the Telephone-MoCA (T-MoCA) (91) for assessment.

Instrumental ADL (I-ADL) was defined according to DSM-5 (15) criteria as the ability to manage one's finances, based on the relevant item in the Ascertain Dementia 8-item Informant Questionnaire (AD8): "Trouble handling complicated financial affairs (e.g., internet banking, income taxes, paying bills)" and a study question asking participants about their ability to manage their medications.

Table 5. Assessments performed at hospital stay and at 3- and 18-month follow-ups

	T0: hospital stay	T1: 3 months	T2: 18 months
Demographic characteristics	x		
Vascular risk factors	x		
Medications	x		
Ability to manage medications		x	x
National Institutes of Health Stroke Scale (NIHSS) (73)	x		
Functional assessments			
Barthel Index (BI) (90)	x		
Modified Rankin Scale (mRS) (89)	x†		
Cognitive assessments			
Montreal Cognitive Assessment (MoCA) (74)*		x	x
Trail Making Test A (TMT-A) (77)		x	x
Trail Making Test B (TMT-B) (77)		x	x
CERAD Word List Memory and Recall Test (79)		x	x
Verbal Fluency Test Letter (FAS) (80, 81)		x	x
CERAD Verbal Fluency Test Category		x	x

	T0: hospital stay	T1: 3 months	T2: 18 months
(animals) (82)			
Global Deterioration Scale (GDS) (83)	x†	x	x
Ascertain Dementia 8-item Informant Questionnaire (AD8) (87)		x	x
CERAD = Consortium to Establish a Registry for Alzheimer's Disease *version 7.3 at 3-month follow-up; version 7.1 at 18-month follow-up †prestroke evaluation			

4.3 Normative data

We chose published normative data from high-income Western countries for the tests used in the cognitive test battery (Table 6).

Table 6. References for the normative data used for the cognitive test battery

Cognitive Test	Normative data
Montreal Cognitive Assessment (MoCA)	All participants: Borland et al. (75)
Trail Making Test A (TMT-A) and B (TMT-B)	Participants 18–59 years or > 80 years: Tombaugh (92) Participants 60–79 years: Luck et al. (93)
Word List Recall	Participants < 60 years: Welsh et al. (94) Participants 60–79 years: Luck et al. (93) Participants > 80 years: Luck et al. (95)
Verbal Fluency Test Letters (FAS)	All participants: Tombaugh et al. (96)
Verbal Fluency Test Category (animals)	Participants 18–59 years or > 80 years: Tombaugh et al. (96) Participants 60–79 years: Luck et al. (93)

An overview of country, sample size, and exclusion criteria regarding cognitive function according to the normative data is shown in Table 7.

Table 7. Country, sample size, and exclusion criteria regarding cognitive function according to the normative data

Normative data	Country	n	Exclusion criteria regarding cognitive function
Borland et al. (75)	Sweden	758	Participants who scored < 24 points on the MMSE, took > 90 seconds to complete A Quick Test of Cognitive Speed (AQT), or reported symptoms of cognitive impairment were summoned for a clinical investigation. Subjects diagnosed with any type of mild or major NCD according to the DSM-5 criteria were excluded.
Tombaugh (92)	Canada	911	Any person with a known history of neurological disease, psychiatric illness, head injury, or stroke was excluded.
Luck et al. (93)	Germany	1888	Any person who reported having been diagnosed with a serious medical, neurological, or psychiatric disorder/ condition that could have affected cognitive performance were excluded.
Welsh et al. (94)	US	413	Any person with serious neurological, medical, and/or psychiatric disorders that could affect cognition were excluded.
Luck et al. (95)	Germany	2891	Any person with serious medical, neurological, or psychiatric disorders /conditions that could have affected cognitive performance were excluded.
Tombaugh et al. (96)	Canada	1300	Any person with a known history of neurological disease, psychiatric illness, head injury, or stroke was excluded.

4.4 Outcome measures

4.4.1 Classifying cognitive status

We classified cognitive status according to the DSM-5 criteria for neurocognitive disorders (NCD) as normal cognition, mild NCD, and major NCD (15). The DSM-5 criteria require the

assessment of six cognitive domains: complex attention, executive function, memory, language, perceptual-motor function, and social cognition (15). Global cognition was measured by the MoCA (74). Aligned with the STROKOG and Vascular Impairment of Cognition Classification Consensus Study (VICCCS), we measured the cognitive domains for the DSM-5 criteria as follows: complex attention by TMT-A, executive function by TMT-B and FAS, memory by Word List Recall, language by Verbal Fluency Test Category, and perceptual-motor function by the visuospatial/executive part of the MoCA (15, 20, 21, 97). Social cognition was not measured.

Except for executive function, measured by two cognitive tests, we measured the cognitive domains using one cognitive test.

To assess the prevalence of all poststroke NCD and, separately, mild and major NCD using DSM-5 criteria and to compare the results with two other methods used for classification and explore agreement among these three methods, we defined three different models A, B, and C.

Model A

Model A was based strictly on the cognitive requirements of the DSM-5 criteria. Participants scoring < −1.5 SD in at least one of the five cognitive domains measured were defined as having poststroke NCD, with mild NCD scoring in the range −1.5 to −2 SD and major NCD scoring ≤ −2 SD.

Model B

Model B was based on the DSM-5 criteria comprising both cognitive and I-ADL requirements. Participants scoring < −1.5 SD in at least one cognitive domain were defined as having poststroke NCD. Major NCD was defined as poststroke NCD and dependency in I-ADL; mild NCD was defined as poststroke NCD without impairments in I-ADL.

Model C

Model C was based on the GDS, a global measure of cognitive function and the closest we could get to a clinical evaluation in the Nor-COAST study.

Stepwise algorithm

To minimize bias due to missing data, we developed a stepwise algorithm for the classification of cognitive status to meet the cognitive requirements of the DSM-5 criteria, used in models A and B.

Step 1: Neuropsychological performances were based on all completed neuropsychological tests except MoCA. Participants evaluated in this step included those with complete testing and those with incomplete testing who scored < −1.5 SD on at least one cognitive domain.

Step 2: Neuropsychological performance was based on MoCA scores for participants completing MoCA only and for those with incomplete neuropsychological testing but normal scores on completed tests.

A consensus group of experienced dementia researchers, namely Professor emeritus Knut Engedal, Professor Geir Selbæk, and Anne Rita Øksengård, PhD, approved this stepwise algorithm before data were analyzed.

4.5 Statistics

Z-scores normalized by mean and SD of the normative data were derived from the raw scores of the cognitive tests. The normative data used are presented in Table 6. The cognitive domains were measured by the z-score of the single completed cognitive test. Two tests were administered to measure executive function, and the average z-score was used. The z-scores were implemented with lower z-scores indicating poorer outcomes.

Paper 1: The proportions with normal cognition, mild NCD, and major NCD were calculated, with sensitivity analyses excluding prestroke major NCD, defined as a prestroke GDS score of 4–7 and previous stroke. Agreement between the models was

quantified using Cohen's kappa (κ), as well as positive and negative agreement for dichotomous categories (98). For ordinal categories with more than two categories, agreement between the models was quantified using Cohen's quadratic weighted kappa (κw) (99). The strength of agreement for Cohen's kappa was interpreted as suggested by Altman (35) as poor (< 0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80), or very good (> 0.80). For a 2x2 table, positive agreement is defined as $n_{22}/[n_{22}+(n_{12}+n_{21})/2]$, and negative agreement is defined as $n_{12}/[n_{12}+(n_{12}+n_{21})/2]$, as row 1 and column 1 in the data represent negative ratings, and row 2 and column 2 represent positive ratings (98). Positive and negative ratings are interpreted similar to sensitivity and specificity for a diagnostic test (98).

Paper 2: The symptom profile of PSCI was measured by the z-scores of the five cognitive domains attention, executive function, memory, language, and perceptual-motor function. The severity of PSCI was measured by z-scores of global z and MoCA; global z was defined as the average scores of the five cognitive domains assessed. Probability for PSCI and severity and symptom profile of PSCI were analyzed as appropriate with mixed-effects logistic or linear regression with PSCI according to DSM-5 criteria, MoCA, and global z and z-scores for the five cognitive domains of attention, executive function, memory, language, and perceptual-motor function as dependent variables one at a time. The independent variables were time (model 1); stroke subtype, time, and the interaction between stroke subtype and time (model 2); and stroke subtype (model 3). We adjusted for age, education, and sex. The estimated probability for PSCI according to DSM-5 criteria was calculated from the estimated odds in mixed-effects logistic regression as probability = odds (1+odds). Mixed-effects logistic and linear regression models were preferred since a mixed-effects linear regression model minimizes bias by handling missing data in an appropriate way under a missing-at-random assumption and also because mixed-effects logistic regression models with categorical time effects often produce fairly robust estimates in a mild departure from data missing completely at random (100). Hypothesis tests for the effects of time and stroke subtype in model 2

were conducted by likelihood ratio tests comparing model 1 and model 2, as well as comparing model 2 and model 3. The results were presented as estimates with mean and 95% confidence intervals (CI) and the test statistics with degrees of freedom and p-value.

Sensitivity analyses with the exclusion of participants deceased at 18 months (n=21), as well as the exclusion of prestroke dementia defined as prestroke GDS 4–7 (n=23), were performed to determine if these affected the outcome. We also performed unadjusted analyses; analyses adjusted for age, education, sex, prestroke mRS, and NIHSS combined; and analyses adjusted for age, education, sex, and location of symptoms in order to determine if these affected the outcome.

PSCI according to DSM-5 criteria, stroke subtype, time, and sex were analyzed as categorical variables, while global z, MoCA z-score, z-scores of the cognitive domains, age, education, mRS, and NIHSS were analyzed as continuous variables. Complete case analyses were used for stroke subtype, age, education, and sex, while available case analyses were used for PSCI according to DSM-5 criteria, global z, MoCA, z-scores for the cognitive domains, mRS, and NIHSS. Confounders were included as fixed effects, while subject and hospital were included as random effects.

Paper 3: PSCI was measured by global z, MoCA z-score, and z-scores of the four cognitive domains attention, executive function, memory, and language. Global z was defined as the average of the four cognitive domains. PSCI was analyzed with mixed-effects linear regression with global z, MoCA, and z-scores of four cognitive domains – attention, executive function, memory, and language – as dependent variables one at a time. The independent variables were vascular risk factors (hypertension, hypercholesterolemia, smoking, diabetes mellitus, atrial fibrillation, coronary heart disease, previous stroke) examined one at a time, follow-up time, and the interaction between the vascular risk factor and follow-up time (model 1). We adjusted for age, education, and sex. The results for model 1 were presented as the estimates with mean and 95% CIs. In order to

perform a hypothesis test for the effect of each vascular risk factor and follow-up time in model 1, the analyses were also performed with follow-up time (model 2), as well as with the vascular risk factor (model 3) as the independent variable. Hypothesis tests for the effects of vascular risk factors and follow-up times in model 1 were conducted by likelihood ratio tests comparing model 1 and model 2, as well as comparing model 1 and model 3. These results were presented as the test statistics with degrees of freedom and p-value.

Sensitivity analyses with the exclusion of participants deceased at 18 months, as well as with exclusion of prestroke dementia defined as prestroke GDS 4–7, were performed to explore whether this affected the outcome. We performed unadjusted analyses and analyses adjusted for age, education, sex, prestroke mRS, and NIHSS taken together to determine how this affected the outcome.

Vascular risk factors, follow-up time, and sex were analyzed as categorical variables, while global z, MoCA z-score, z-scores of the cognitive domains, age, education, mRS, and NIHSS were analyzed as continuous variables. Complete case analyses were used for vascular risk factors, age, education, and sex, while available case analyses were used for global z, MoCA, z-scores of the cognitive domains, prestroke mRS, and NIHSS. Confounders were included as fixed effects, while subject and hospital were included as random effects.

4.5.1 Missing data

To minimize bias due to excluded participants, imputation was performed as described in the following.

MoCA: Single items missing in the MoCA total scores were imputed by the mean of the available MoCA items for the same participant. This was done for:

Paper 1: n=1 at 3-month follow-up with one missing item;

Paper 2: n=1 at 3-month follow-up with one missing item; and

Paper 3: n=2 at 3-month follow-up and n=4 at 18-month follow-up with one missing item.

Telephone-MoCA: For participants assessed by T-MoCA, 8 of 30 points that could not be assessed by telephone were imputed by the mean of the available MoCA items for the same participant. This was done for:

Paper 1: n=21 participants, 3 of whom had one missing item in addition to the 8 points not assessed;

Paper 2: n=20 at 3-month follow-up, 3 of whom had missing items in addition to the 8 points not assessed; n=25 at 18-month follow-up, 5 of whom had missing items in addition to the 8 points not assessed; and

Paper 3: n=21 at 3-month follow-up, 3 of whom had a single item missing in addition to the 8 points not assessed; and n=25 at 18-month follow-up, 6 of whom had items missing in addition to the 8 points not assessed.

Trail Making Test A and B: For participants starting but not completing Trail Making Test A or B due to cognitive impairment, the test result was set to 300 seconds (101). This was done for:

Trail Making Test A:

Paper 1: n=13 at 3-month follow-up;

Paper 2: n=13 at 3-month follow-up and n=8 at 18-month follow-up;

Paper 3: n=14 at 3-month follow-up and n=8 at 18-month follow-up;

Trail Making Test B:

Paper 1: n=88 at 3-month follow-up;

Paper 2: n=87 at 3-month follow-up and n=53 at 18-month follow-up; and

Paper 3: n=91 at 3-month follow-up and n=57 at 18-month follow-up.

Global z:

Paper 2: We imputed missing values on the domains' z-scores using the mean z-scores from the other domains for the same participant at the same time point if z-scores were available for at least 3 of 5 domains. This was done for n=117 at the 3-month follow-up and n=126 at the 18-month follow-up.

Paper 3: We imputed missing values on the domains' z-scores using the mean z-scores from the other domains for the same participant at the same time point if z-scores were available for at least 2 of 4 domains. This was done for n=129 at the 3-month follow-up and n=127 at the 18-month follow-up.

Other missing data were not imputed but treated as missing.

4.5.2 Statistical software and statistically significant p-values

In Paper 1, data were analyzed using SPSS 25, with Extension Hub for analysis with κ_w. In Papers 2 and 3, data were analyzed using SPSS 25 and STATA 16.0. In Paper 1, a two-tailed $p<0.05$ was considered statistically significant. Due to multiple hypotheses, a two-tailed $p<0.01$ was considered statistically significant in Papers 2 and 3.

4.6 Ethical considerations

Participation in the Nor-COAST study was implemented according to the Declaration of Helsinki. The participants received oral and written information about the study and gave their informed written consent for participation. When a participant was unable to give consent, informed written consent was given by the next of kin. The study was approved by the Regional Committee for Medical and Health Research Ethics (REC Nord 2015/171).

5 Results

5.1 Paper 1

Title: Impact of different methods defining poststroke neurocognitive disorder: The Nor-COAST study

Results: Of the 815 participants included in the Nor-COAST study, 700 were assessed at 3 months poststroke. Of these, 101 had missing data; 93 had missing data on neuropsychological testing, almost exclusively due to severe illness, and 8 had missing data on I-ADL, resulting in a study sample of 599 participants (Figure 5 as well as Figure 3 in Paper 1). The mean age of the population was 71.6 (SD 11.8) years; 257 (43%) were female; mean education was 12.4 (SD 3.8) years; and mean NIHSS score was 3.7 (SD 4.7) (Table 4).

In models A and B, prevalence of all poststroke NCD was 332 (55%) compared to 196 (33%) in model C. The prevalence of mild NCD was highest in model B at 174 (29%) and lowest in model A at 83 (14%); the prevalence of major NCD was highest in model A at 249 (42%) and lowest in model C at 68 (11%) (Figure 7).

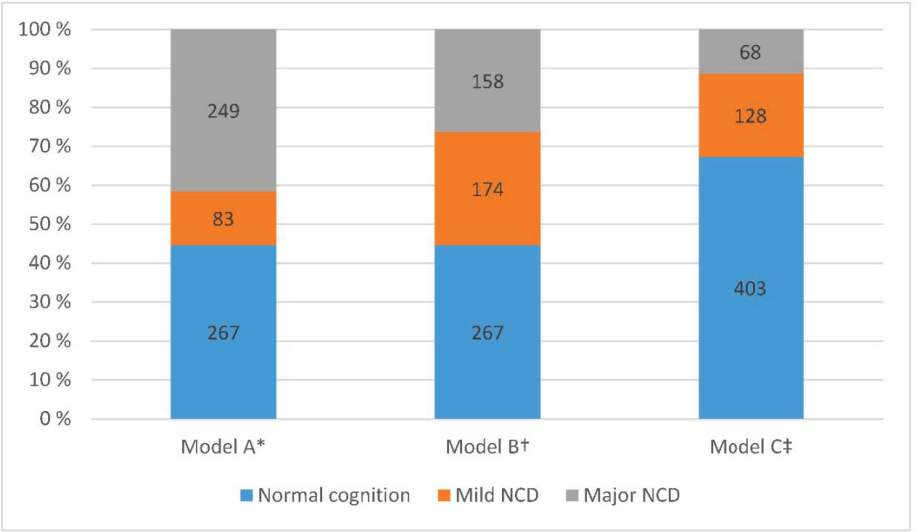


Figure 7. Proportion of participants with normal cognition, mild NCD, and major NCD three months poststroke, N=599.

NCD = neurocognitive disorder
*Model A: normal cognition defined as score ≥ -1.5 SD for all cognitive domains; mild NCD defined as score in the range of -1.5 to -2 SD for at least one cognitive domain; and major NCD defined as a score ≤ -2 SD for at least one cognitive domain.
†Model B: normal cognition defined as score ≥ -1.5 SD for all cognitive domains; NCD defined as score < -1.5 SD for at least one cognitive domain; major NCD defined as having poststroke NCD with dependency in instrumental activities of daily living (I-ADL), defined as the need for assistance managing one's finances and/or medications. Mild NCD was defined as poststroke NCD without impairments in I-ADL.
‡Model C: evaluation based on Global Deterioration Scale (GDS); normal cognition defined as a GDS score of 1–2; mild NCD defined as a GDS score of 3; and major NCD defined as a GDS score of 4–7.

Comparing the models regarding normal cognition versus all NCD, there was fair agreement between them (A/B and C; κ = 0.40 [95% CI 0.34–0.47]). As expected, very good agreement was found between models A and B (κw = 0.85 [95% CI 0.83–0.88]) because normal cognition was defined the same way. However, of 332 participants with

poststroke NCD in model A, 249 (75%) had major NCD compared to 158 (48%) in model B (Figure 7). There was fair agreement between models A and C (κw = 0.38 [95% CI 0.32–0.44]) and moderate agreement between models B and C (κw = 0.52 [95% CI 0.46–0.58]).

The poorest agreement between the models was seen in the classification of participants with mild NCD, as only 15% of the 128 classified with mild NCD in model C were classified with mild NCD in model A and 40% in model B. The greatest agreement was seen for the classification of participants with major NCD, as 85% of the 68 participants classified with major NCD in model C were classified with major NCD in model A and 93% in model B.

5.2 Paper 2

Title: Poststroke Cognitive Impairment—Impact of Follow-Up Time and Stroke Subtype on Severity and Cognitive Profile: The Nor-COAST Study

Results: Of the 815 participants included in the Nor-COAST study, 700 were assessed at the 3-month follow-up and 599 at the 18-month follow-up, 10 of whom were not assessed at 3 months. Of the 710 participants assessed at either 3 or 18 months, 93 were excluded due to missing data, resulting in a study sample of 617 participants (Figure 5). Of these 617 participants, 21 were deceased at 18 months. Their mean age was 72 years (SD 12); 42% were females; mean education was 12.5 years (SD 3.8); and mean NIHSS score at hospital admittance was 3.8 (SD 4.8). The participants' baseline characteristics are shown in Table 4. The 198 participants excluded were mean age 80 years (SD 9.1); 55% were females; mean years of education were 10.5 (SD 3.1); and mean NIHSS score at hospital admittance was 7.4 (8.2).

The probability (95% CI) for PSCI after 3 and 18 months was 0.59 (0.51–0.66) and 0.51 (0.52–0.60), respectively, and remained constant over time (LR = 2.17, p = 0.141) (Figure 8).

Global measures and most cognitive domains were assessed as impaired for the entire stroke population and for most stroke subtypes (Figures 2 and 3 in Paper 2).

Executive function and language improved for the entire stroke population (LR = 9.05, p = 0.003, and LR = 10.38, p = 0.001, respectively) (Figures 9 and 10).

After dividing the sample according to stroke subtypes, language was found to have improved for ICH patients (LR = 18.02, p = 0.003) (Figure 11). No significant differences were found in the severity of impairment between stroke subtypes except for attention,

which was impaired for LAD and CE in contrast to no impairment for SVD (LR = 56.58, p < 0.001) (Figure 12).

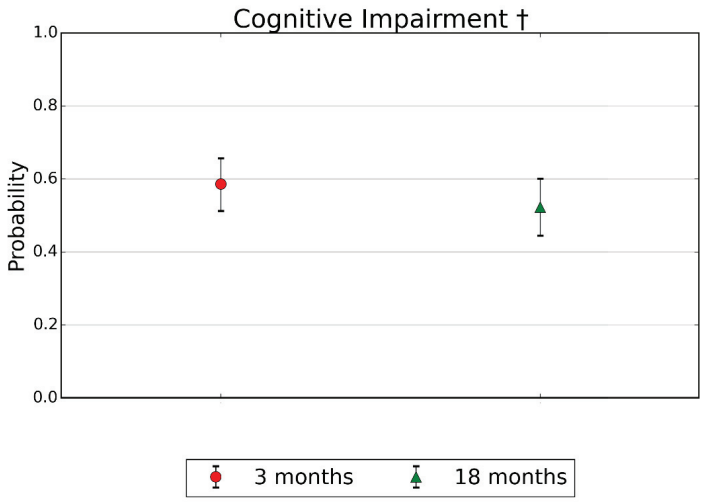


Figure 8. Probability for cognitive impairment according to DSM-5 criteria with 95% CI at 3 and 18 months poststroke in model 1
†adjusted for age, education, and sex

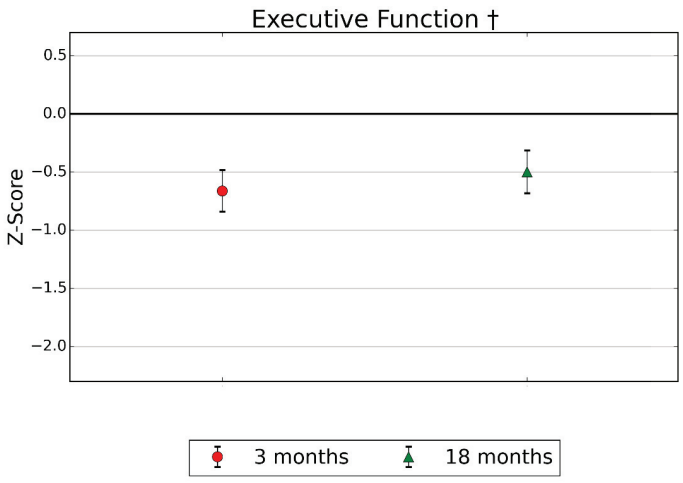


Figure 9. Mean z-score with 95% CI for executive function at 3 and 18 months poststroke in model 1

†adjusted for age, education, and sex

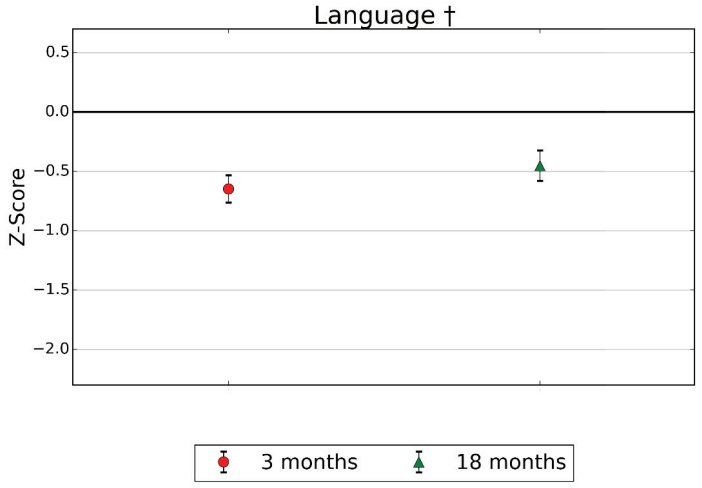


Figure 10. Mean z-score with 95% CI for language at 3 and 18 months poststroke in model 1

†adjusted for age, education, and sex

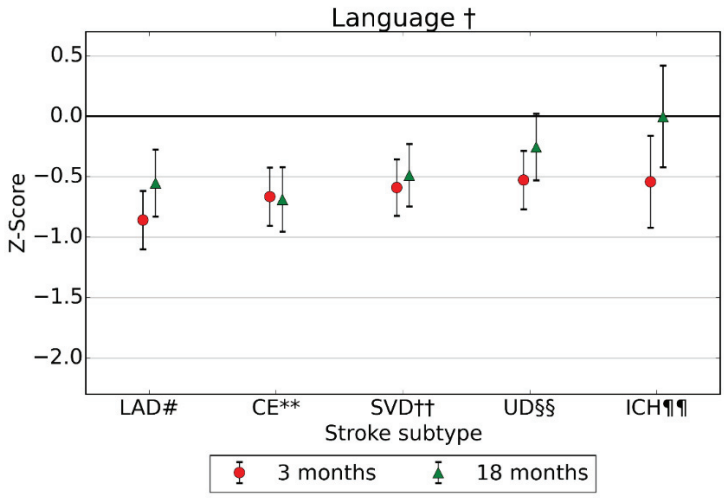


Figure 11. Mean z-score with 95% CI for language at 3 and 18 months poststroke in model 2

†adjusted for age, education, and sex; #LAD = large artery disease; **CE = cardiac emboli; ††SVD = small vessel disease; §§UD = undetermined and other determined strokes; ¶¶ICH = intracerebral hemorrhage.

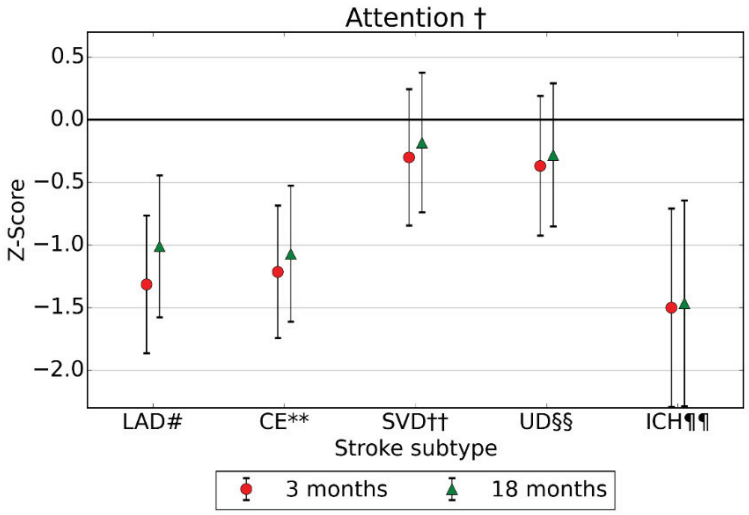


Figure 12. Mean z-score with 95% CI for attention at 3- and 18-months poststroke in model 2

†adjusted for age, education, and sex; #LAD = large artery disease; **CE = cardiac emboli; ††SVD = small vessel disease; §§UD = undetermined and other determined strokes; ¶¶ICH = intracerebral hemorrhage.

5.3 Paper 3

Title: The impact of vascular risk factors on poststroke cognitive impairment: The Nor-COAST study

Results: Of the 815 participants included in the Nor-COAST study, 700 were assessed at the 3-month follow-up and 599 at the 18-month follow-up. Of the 599 participants assessed at 18 months, 10 were not assessed at the 3-month follow-up. Of the 710 participants assessed at either 3 or 18 months, 75 were excluded due to missing cognitive data, resulting in a study sample of 635 participants (Figure 5). Of the 635 participants included in the study, 21 were deceased at 18 months.

The mean age of the participants was 71.6 years (SD 11.7); 42% were females; the mean for years of education was 12.4 years (SD 3.8); and mean NIHSS score at hospital admittance was 3.8 (SD 4.8). The participants' baseline characteristics are shown in Table 4. Excluded participants had a mean age of 80.2 years (SD 9.0); 55% were females; their mean education was 10.3 years (SD 3.0); and their mean NIHSS score at admittance was 7.7 (SD 8.5).

Coronary heart disease (CHD) was associated with poorer MoCA at 18 months (LR=8.32, p=0.004) (Figure 13).

Previous stroke was associated with poorer global z at both 3 and 18 months (LR=15.46, p<0.001) (Figure 14) and poorer attention at both 3 and 18 months (LR=16.20, p<0.001) (Figure 15).

Atrial fibrillation (AF) was associated with poorer language at 18 months (LR=12.80, p=0.002) (Figure 16).

In patients without AF, attention improved from 3 to 18 months (LR=10.42, p<0.001) (Figure 16). In patients without CHD, executive function improved from 3 to 18 months (LR=9.33, p=0.009) (Figure 17).

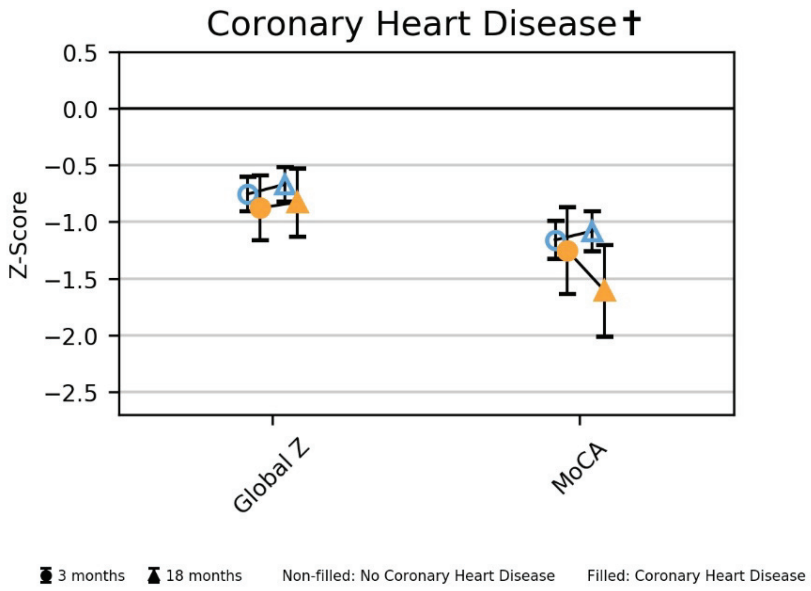


Figure 13. Mean z-score with 95% CI for the global cognitive measures for coronary heart disease at 3- and 18-months poststroke in model 1

†adjusted for age, education, and sex

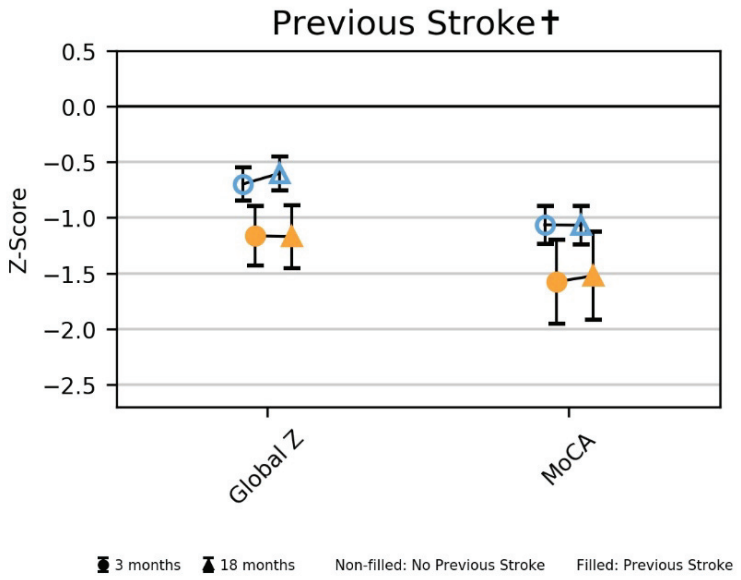


Figure 14. Mean z-score with 95% CI for the global cognitive measures for previous stroke at 3 and 18 months poststroke in model 1

†adjusted for age, education, and sex; MoCA = Montreal Cognitive Assessment

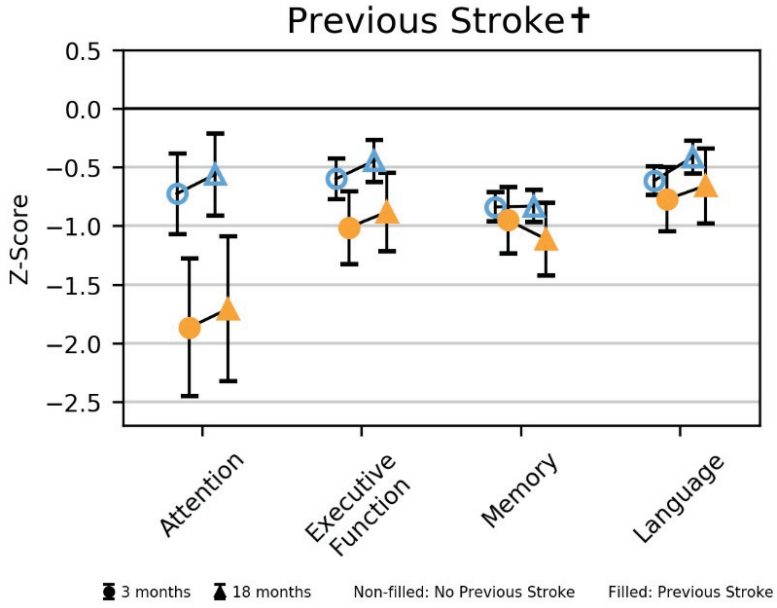


Figure 15. Mean z-score with 95% CI for the cognitive domains for previous stroke at 3 and 18 months poststroke in model 1

†adjusted for age, education, and sex

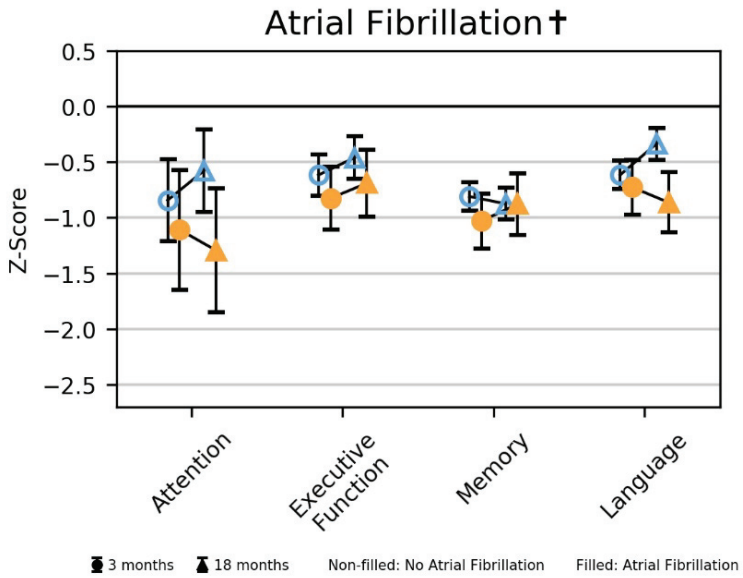


Figure 16. Mean z-score with 95% CI for the cognitive domains for atrial fibrillation at 3 and 18 months poststroke in model 1
†adjusted for age, education, and sex

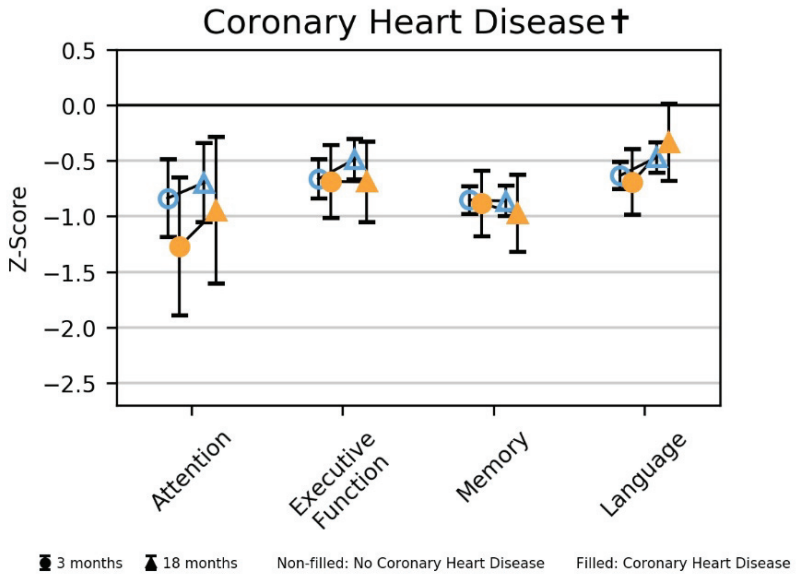


Figure 17. Mean z-score with 95% CI for the cognitive domains for coronary heart disease at 3 and 18 months poststroke in model 1
†adjusted for age, education, and sex

6 Discussion

6.1 Main findings

In the Nor-COAST descriptive cohort study, we assessed global cognition, memory, executive function, attention, and language at 3 and 18 months after patients suffered a stroke. The attempt to assess perceptual-motor function was methodologically flawed, and social cognition was not assessed. Our main findings were as follows:

- Prevalence of mild and major NCD varied depending on the diagnostic approach;
- Overall agreement was better between the different methods for identification of major NCD than for mild NCD;
- Prevalence of PSCI was high at both 3 and 18 months after stroke for the entire stroke population and for all stroke subtypes;
- The course over time was stable for global cognition, memory, and attention for the entire stroke population and for all stroke subtypes. Executive function and language improved for the entire stroke population, and language improved for patients with intracerebral hemorrhage;
- Impairment in global cognition, memory, attention, language, and executive function was common for all stroke subtypes, but attention was more impaired among patients with cortical stroke compared to those with small vessel disease;
- PSCI was common both 3 and 18 months after stroke regardless of patients' exposure to prestroke vascular risk factors;
- Established vascular disorders such as previous stroke, coronary heart disease, and atrial fibrillation were associated with poorer global impairment or more severely impaired cognitive domains at 3 and/or 18 months after stroke; and
- Absence of atrial fibrillation or coronary heart disease was associated with improvement from 3 to 18 months in attention and executive function, respectively.

6.2 Methodological considerations

Methodological considerations of the reliability of the measurements used in the thesis and the validity of the results of the thesis are discussed in the following sections.

6.2.1 Study design

The Nor-COAST study is a prospective observational cohort study that included stroke patients hospitalized in the acute phase of stroke. Strengths of the study include its large sample size and multicenter design. As a descriptive study, there was no control group; thus, only associations could be studied, and no causal inferences could be made. However, its design is appropriate for studying prognoses for different categories of patient characteristics. Lacking a stroke-free control group, we were unable to evaluate whether the associations found in the Nor-COAST study were stronger for those who had suffered a stroke than for the background population. However, with the use of z-scores for the cognitive tests, we were able to study the cognitive performance of the stroke population compared to the normative data used.

6.2.2 Selection bias

The inclusion criteria for the Nor-COAST study were broad, aiming to include a study population representative of the general Norwegian stroke population. It is well-known in stroke research that selection bias is quite common as older patients, patients with impaired prestroke function, patients suffering severe strokes, and patients with comorbidity are likely to be excluded, and this affects the outcome (40, 42). A strength of the Nor-COAST study was the minimization of missing data by conducting telephone interviews with patients, their caregivers, or nursing home staff for participants unable to attend follow-up assessments in person.

Kuvås and colleagues studied the selection bias in the Nor-COAST study by comparing baseline data from those participating in the Nor-COAST study to those not participating but registered in the Norwegian Stroke Registry (42). They found that the participants in the Nor-COAST study tended to be slightly healthier before the stroke and to have milder strokes. However, the annual report from the Norwegian Stroke Registry should be regarded as a standard of reference for the general stroke population (102). The

participants included in the Nor-COAST study were more similar to the general stroke population than those not participating in regard to stroke severity and prestroke function. Kuvås and colleagues concluded that the selection bias in the Nor-COAST study resulted in participants who were representative of the majority of the stroke population, which is known to suffer mild strokes.

As shown in Figure 5, of the 815 participants included in the Nor-COAST study, 115 were not assessed at the 3-month follow-up for various reasons. In addition, 101 were excluded in Paper 1, 93 in Paper 2, and 75 in Paper 3 due to missing data. The excluded participants were older and suffered more-severe strokes than those included in the analyses. In summary, the results of Kuvås and colleagues' paper and the dropouts in this thesis show that there is a selection bias in the thesis regarding participants suffering minor strokes. However, in Papers 1 and 2, the selection bias was reduced by developing a stepwise algorithm for the evaluation of cognitive performance.

To study the true prevalence of PSCI in a general Norwegian study population would require a method in line with that of Pendlebury and Rothwell in the Oxford Vascular study, where diagnoses of poststroke major NCD were based on cognitive testing supplemented with data from hand-searching all medical records from hospital and primary care with the aim of capturing almost all events (41). Thus, the population was not suited to studying a true prevalence of PSCI, resulting in underestimation.

6.2.3 Different operational definitions

Considerations regarding classification of poststroke NCD are discussed in the following sections.

Criteria

The work of classifying cognitive status in the study began after the publication of DSM-5 and VASCOG criteria for mild and major NCD but before the release of the draft for the ICD-11 criteria. We considered the DSM-5 and VASCOG criteria superior to the older criteria for major NCD: the DSM-IV, NINDS-AIREN, and ICD-10 criteria.

In addition to the syndromal diagnosis of mild and major NCD, the VASCOG criteria comprise detailed proposals for neuroimaging features for establishing a predominantly vascular etiology for NCD. Due to the DSM-5 criteria's clarity of a stepwise diagnostic process with a syndromal diagnosis in step one and an etiological diagnosis in step two, we chose to perform classification according to the syndromal diagnosis of the DSM-5 criteria as valid MRI data and cerebrospinal fluid (CSF) were not available when the workup with classification of cognitive status was conducted.

The DSM-5 and VASCOG criteria on the syndromal step differ only in regard to the visuospatial domain. Thus, we believe that choosing the VASCOG criteria instead would not have inserted a significant impact on the prevalence of NCD in the study. This is also supported by Sachdev and colleagues' validation of the VASCOG criteria, finding them comparable to the DSM-5 criteria (25).

However, if the DSM-5 criteria were replaced by the forthcoming ICD-11 criteria in Paper 1, the result would probably be a lower prevalence of major NCD in models A and B. This would be due to the ICD-11 criteria's requirement of both impairment in at least two cognitive domains and dependency in I-ADL for major NCD. Future studies comparing the ICD-11 with the DSM-5 and VASCOG criteria will probably find lower agreement between the ICD-11 criteria and the DSM-5 and VASCOG criteria, respectively, than between the DSM-5 and VASCOG criteria.

A mandatory requirement of diagnostic criteria for NCD is whether there is evidence of cognitive decline from a previous (habitual) level of performance. A limitation in the Nor-COAST study is the lack of reliable measures to answer this question. AD8 was originally planned as a measure for this; however, we did not find a reliable way of including this information in the algorithm. We could have used a cut-off score for AD8 for evaluating a decline in cognitive function, but considering this measurement's reliability, discussed in the next section, we chose not to include AD8 as a measure of cognitive decline in the algorithm. Hence, alteration in cognition is not included in Paper 1. This has potentially resulted in misclassification bias of cognitive function, where some participants with poor performance on cognitive tests but without evidence of decline were categorized

as cognitively impaired. By the same token, some participants with cognitive decline but good performance on cognitive tests who could have been classified with cognitive impairment in a clinical setting were probably categorized with normal cognition. However, this misclassification bias is probably difficult to remove from studies, and in a study with a large sample size, the estimates for the different categories are likely to be adequate on a group but not on an individual level. In an effort to reduce this misclassification bias, the Nor-COAST study could have been planned with study questions inquiring about changes in cognition that aimed to fulfill this mandatory requirement of the diagnostic criteria. Another possibility may have been to measure change in cognition with the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), for instance, dichotomizing change in cognition based on the widely used cut-off of 3.44 (103, 104).

Cognitive test battery and cognitive domains

We used the 30-minute test battery proposed by Hachinski for stroke populations (33), adapted to validated tests translated into Norwegian. Although we have not measured the time spent on the test battery, the assessors' impression was that most participants spent more than 30 minutes on the cognitive test battery, often up to 60 minutes, and they were fatigued when they finished. The Nor-COAST study also comprises time-consuming tests for physical activity, and altogether, this limited the possibilities for extending the cognitive test battery. However, the use of a more comprehensive cognitive test battery would also probably result in a selection bias of less cognitively impaired participants as well as in more missing data due to partial or non-completion of cognitive tests. A strength of the data collection was the standardized order of the cognitive test battery to minimize missing data on global tests. Additionally, the cognitive tests were performed before the physical tests to optimize participants' cognitive test condition. One test in most cognitive domains may have overestimated impairment, resulting in poorer agreement between models A and B. However, overall, the results point toward equally severe levels of impairments across cognitive domains. This might indicate that an extended cognitive test battery would have a small impact

on the severity of impairments of the cognitive domains and, thereby, counter the previous argument of overestimation.

An alternative allocation of cognitive tests to cognitive domains in our study would be the allocation of the verbal fluency test letter (FAS) to language instead of executive function. The participants' performance status on this test was better than for executive function, while their performance status on verbal fluency test letter (FAS) and verbal fluency test category (animal) were more similar. This alternative allocation of the verbal fluency test FAS would result in more impairments in executive function and might have resulted in a larger proportion of participants being identified with NCD. It would also result in a broader 95% CI for executive function, possibly resulting in less statistically significant findings for differences across subgroups of patients and across time points in Papers 2 and 3. If we had scored the clock-drawing test in MoCA according to a 5-point scale, we might have avoided the ceiling effect we observed with the use of the visuospatial section of the MoCA. Hence, this might have resulted in more impairments in perceptual-motor function and thereby, again, in a larger proportion with NCD. It is difficult to predict how this would affect the comparisons of models A and B as the presence of I-ADL impairment would be the determinant for the agreement. However, it would result in poorer agreement between model C and models A and B, respectively. An alternative approach for measuring the cognitive domain perceptual-motor function was the 9-hole peg test. However, we did not include this test as it was not part of Hachinski and colleagues' widely used test battery, possibly making our results less comparable with those of other studies (33).

Assessments of participants in the Nor-COAST study were performed by healthcare personnel. To improve the reliability of the data, all assessors underwent a training program to improve standardization. The reliability of all the cognitive measures used in the test battery, i.e., the MoCA, TMT-A and -B, word list memory and recall, verbal fluency test letter and category, and GDS, is reported to be high (74, 82, 88, 96, 105-108). The results of the cognitive measures used in the 3 papers are, thus, not likely to be threatened by a lack of inter-rater reliability caused by different assessors conducting

the tests. Regarding the cognitive tests, there is little room for different interpretations of the test information provided by the assessors or the evaluation of patients' performances.

In the Nor-COAST study, a cognitive decline was hypothesized, and the GDS was chosen to assess change over time in our prospective cohort study (69). An alternative measure would be the Clinical Dementia Rating Scale (CDR), but CDR is prone to capture memory impairments and, thus, may not be feasible for assessing PSCI (109). Both the GDS and CDR are designed to measure severity of cognitive and functional impairment and not the classification of cognitive status (26). This threatens both the reliability and validity of using the GDS in this study as a surrogate measure for clinical assessment. However, the GDS was the closest we could get to a clinical assessment in our study. The reliability of the GDS depends on the assessor's clinical impression. Although high reliability has been shown, in our study, GDS reliability could be threatened by inter-rater reliability due to different assessors conducting data collection and having a variety of clinical experience diagnosing NCD. The GDS results would probably be different if they were conducted by healthcare personnel working in a memory clinic and accustomed to evaluating cognitive function. Healthcare personnel experienced in evaluating cognitive function would probably identify more cognitive impairments than personnel with less training. Therefore, cognitive impairment identified by the GDS in the study might be underestimated.

Regarding the GDS, although the reliability of the AD8 is shown to be high (88), in this study, it might have been threatened by inter-rater reliability. AD8 was conducted by healthcare personnel not necessarily experienced in the clinical evaluation of cognitive status. This might have resulted in an underestimation of subtle cognitive impairment. Additionally, we used the relevant question on ability to manage finances from the AD8 as a measure for I-ADL impairment, but the reliability of single questions from the AD8 is unknown. The methods used for data collection in the study might have resulted in an underestimation of the ability to manage finances.

In accordance with the MoCA website's recommendations, we used different versions due to the short amount of time between assessments at baseline and at 3-month follow-up. MoCA version 7.1 was used at baseline and 18-month follow-up, and version 7.3 was used at 3-month follow-up. The different versions are based on variations of all the different tasks, except for the trail making part and the orientation questions. We found no normative data for the MoCA version 7.3 and, therefore, used normative data for version 7.1. This could threaten the reliability of the MoCA at the 3-month follow-up and the reliability of change in MoCA scores over time, i.e., the test-retest reliability. Version 7.1 involves a cube and version 7.3 a cylinder, and we would point out that copying a cylinder is most likely easier than copying a cube.

Contrary to other studies, we found no impairment in perceptual-motor function (4, 49). We used the executive/visuospatial part of the MoCA as a measure for perceptual-motor function. We chose this approach to reflect the clinical approach, where the clinician includes all relevant information in the diagnostic setting. We found no normative data for the figure-copying and clock-drawing tests in the MoCA, only Borland and colleagues' normative data on the trail making, figure copying, and clock-drawing tests all together (75). We asked for these data, but unfortunately, they were unavailable. Additionally, the MoCA subdomains have been found to be insufficient for drawing conclusions about performance in cognitive domains as measured by a cognitive test battery (110-112). Hence, the executive/visuospatial part of the MoCA as a measure for perceptual-motor function in our study threatens the validity of this variable as well as the reliability of change in the variable over time (test-retest reliability). Summarized, our finding of normal perceptual-motor function is most likely explained by our limited measurement of this cognitive domain with difficulties identifying impairment in the visuospatial/executive part of the MoCA. The decline in perceptual-motor function is most likely explained by the different MoCA versions, e.g., version 7.3 comprising cylinder copying versus version 7.1 comprising cube copying. This bias could have been reduced by using version 7.3 at baseline and version 7.1 at 3-

month and 18-month follow-ups. The use of version 7.1 at all assessments would likewise reduce this bias.

For verbal fluency test letter FAS, we used fluency in the MoCA as a measure of the first letter, F, to minimize the practice effect. However, there is a trade-off between the practice effect and threatening the reliability of the test as validated with assessments of the three letters consecutively. However, we would point out that verbal fluency letter FAS at 3-month follow-up should have been assessed with F in addition to A and S, as letter B was assessed in MoCA version 7.3.

Social cognition was not measured. However, Hachinski's et al.'s proposed test battery for stroke populations does not include cognitive tests for social cognition, and social cognition is not yet commonly measured in studies on PSCI (3, 19, 33, 113).

We believe that the cognitive test battery used in our study was appropriate for our study population. Using a more comprehensive cognitive test battery would probably result in a selection bias of less cognitively impaired patients as well as in more missing data due to partial or non-completion of cognitive tests. However, the cognitive domain perceptual-motor function was not measured appropriately. This could have been resolved by evaluating the clock-drawing test in the MoCA according to a 5-point scale. In addition to the clock-drawing test, measuring the domain by, for instance, the Rey–Osterrieth Complex Figure Test Copy could have been an option. However, this would have involved a trade-off between the patients' ability to complete the test and missing data due to partial or non-completion of this test.

Cut-off -1 vs -1.5

Although the DSM-5 criteria suggest using -1 SD as a cut-off between normal cognition and mild NCD, several studies still used -1.5 SD when they applied the DSM-5 criteria (25, 34, 36). Traditionally, the -1.5 SD cut-off is more commonly used than -1 SD. In addition, the statistical implication of the -1 SD cut-off, defining 13.6% of the normal population with a performance in the range of mild NCD, is much more concerning than the choice of -1.5 SD, which defines 4.4% of the normal population with a performance

in the range of mild NCD. Therefore, we chose -1.5 SD as the cut-off between normal cognition and NCD. If we had chosen -1 SD, the proportion with NCD would increase considerably in the study and would likely result in an overestimate of the prevalence of NCD in the cohort. The presence of I-ADL impairments in the group with scores between -1 and -1.5 SD would probably differ from the group with test scores in the range -1.5 SD to -2 SD and, hence, also affect the agreement between the models.

Normative data

Due to costs and feasibility, a control group was not included in the Nor-COAST study. Lacking Norwegian normative data, we used published normative data from high-income Western countries for the tests used in the cognitive test battery to ensure a comparable normal population. This lack threatens the reliability of the results, and the inclusion of a control group representative of a normal population would have been helpful. For all the normative data we used, participants with serious medical, neurological, or psychiatric disorders that could have affected cognitive performance were excluded (Table 7). However, for the normative data for the MoCA from Borland and colleagues, the evaluation of cognitive function seemed to be more thorough, with the exclusion of participants diagnosed with mild or major NCD. This might have resulted in a supernormal population.

Measures for instrumental activities of daily living

The I-ADL measures that are traditionally considered related to cognitive function are typically the measures of the 4-IADL scale, including ability to use a telephone, mode of transportation, responsibility for one's own medications, and the ability to manage one's finances (114). In the DSM-5 criteria, the exemplified I-ADL measures used to determine severity of NCD are paying bills and managing medications (15). The specification of I-ADL in the VASCOG criteria is almost the same as in the DSM-5 criteria (16). However, in stroke patients, it is challenging to differentiate between impairment in I-ADL due to cognitive function and stroke sequelae. This could be resolved in the manner that Barbay and colleagues used in the GRECog-VASC study; they added a study

question on the mechanism responsible for the impairment of the different domains of the 4-IADL scale: stroke sequelae, cognitive impairment, or psychiatric disorder (34).

The available validated measures for ADL in Nor-COAST were the Barthel Index and Nottingham EADL. The Barthel Index comprises P-ADL and lacks information on I-ADL, and I-ADL is proposed to determine the severity of NCD in the DSM-5 criteria. The Nottingham EADL includes more questions related to mobility than cognitive function and is not generally used for evaluating I-ADL deficits due to cognitive impairment in stroke populations. Its use would, therefore, threaten the external validity of the results. Thus, we used the two measures for I-ADL exemplified in the DSM-5 criteria: paying bills and managing medications. Information on paying bills was taken from the relevant question on ability to manage finances from the AD8. Information on medication was collected from a study question asking participants about their ability to manage their own medications. These limited measures of I-ADL may have led to an underestimation of I-ADL impairments. We lacked information on whether the I-ADL impairment was due to stroke sequelae or cognitive impairment, possibly leading to an overestimation of the I-ADL impairments. While the two biases point in opposite directions, we think that underestimation due to limited I-ADL measures was more important as the participants included in the study had experienced mostly minor strokes. There is also a ceiling effect in most I-ADL scales due to difficulties capturing subtle I-ADL impairments (38). This probably also affected our study, resulting in an underestimation of I-ADL impairments. The traditionally used I-ADL scales do not capture difficulties using a PC, which affect younger people's ability to work and can be captured in a clinical setting.

If we sum up the I-ADL biases, we think that the I-ADL measures in the study probably underestimated I-ADL impairments. This underestimation results in poorer agreement between models A and B.

6.2.4 Definition of poststroke cognitive impairment in Papers 2 and 3

In Paper 1, we found that the prevalence of mild and major NCD varied depending on the diagnostic approach. As all diagnostic criteria for NCD comprise both cognitive and ADL requirements, model B would be the most relevant model to use in further analyses.

However, we were concerned about the construct validity of the I-ADL measures in our study and whether they measured a true function of I-ADL. To minimize misclassification bias from the diagnostic approach to the classification of cognitive function, we chose to focus on measures for cognition as continuous variables in Papers 2 and 3. Using continuous measures for cognitive function is meaningful as the severity of impairments of PSCI is on a continuum (4). Additionally, it is preferable to keep variables as continuous measures when possible to avoid a loss of statistical power when categorizing them. However, the course of poststroke cognitive impairment according to DSM-5 criteria had to be addressed. To avoid the low construct validity of the I-ADL measures, cognitive function dichotomized as normal cognition and NCD according to DSM-5 criteria (instead of a three-category variable for NCD) was included in Paper 2 in addition to the continuous measures for PSCI.

6.2.5 Classification of stroke subtype in Paper 2

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (12), widely used to classify etiological stroke subtypes, generates a large group in the category undetermined etiology (UD) and may underestimate clinically relevant risk factors for ischemic stroke (13, 115-119). Several modified TOAST classifications have updated the criteria to comprise a more clinically relevant approach. However, these modified classifications have resulted in complex algorithms that are less feasible for clinical use than the original TOAST classification, including the SSS-TOAST and the Causative Classification System (CCS), the Spanish Classification system (GEECV/SEN), and the SPARKLE classification (13). To achieve an etiology as clinically relevant as possible for ischemic stroke, we aimed to identify the most likely stroke etiology, even in the TOAST classification group labeled UD in Paper 2. We did not have variables available for classification according to the abovementioned modified TOAST criteria (13). However, in keeping with the general idea of these modified classifications, we performed a TOAST modification as described in methods section 4.2.1. on clinical assessments called TOAST *modified*. We believe that this clinically relevant TOAST modification reduced the misclassification bias of stroke subtype and provided results valid for a clinical setting,

whereas the use of strict TOAST probable, as described by Adams and colleagues (12), would probably not be valid from a clinician's perspective.

6.2.6 Classification of vascular risk factors in Paper 3

To study the impact of vascular risk factors, we aimed to measure prestroke vascular risk factors as the Nor-COAST study comprises participants with acute stroke and the whole cohort suffers from established vascular disease when admitted with stroke. Measuring prestroke vascular risk factors is challenging when data are available only from the hospital stay with admittance for acute stroke, and this increases the risk of misclassification bias. However, retrieving accurate measures for prestroke vascular risk factors in a study of stroke patients is not feasible.

Hypertension: The inclusion of participants in the acute phase of stroke, when most patients have temporarily elevated blood pressure, limited the definition of hypertension to "use of antihypertensive medication," and this might introduce a misclassification bias. To minimize bias from the participants with undetected prestroke hypertension, we defined hypertension as prestroke use of antihypertensive medication and/or use of antihypertensive medication at discharge. Hypertension defined as "use of antihypertensive medications" will also include users of antihypertensive medications for other reasons than hypertension, comprising mainly participants with coronary heart disease or heart failure, and thus, resulting in an overestimation of hypertension and potentially weakening an association with PSCI.

Hypercholesterolemia: As shown in a systematic review and meta-analysis by Yang and colleagues, a variety of poorly described definitions of hypercholesterolemia have been used in studies of vascular risk factors and cognitive impairment (120). Anstey and colleagues, in a systematic review and meta-analysis, found that high total cholesterol in midlife was associated with Alzheimer's disease, but total cholesterol, HDL cholesterol, or triglycerides in late life were not associated with NCD for any etiologic subtypes (121). Older studies focused on total cholesterol and HDL, while more-recent studies have focused on LDL cholesterol. The effect of statins beyond lowering lipids has been discussed in research. To most effectively address all these challenges, we chose

to define hypercholesterolemia as the use of lipid-lowering medications prestroke. This is also probably closer to a measure of midlife hypercholesterolemia than if the variable comprised cholesterol level at admission as well.

Smoking, diabetes mellitus, coronary heart disease, and previous stroke are probably less affected by misclassification bias. By defining smoking exposure as current smoking only, we missed participants with a substantial lifetime smoking history who had recently stopped smoking. We had the available data on ever-smoking, but approximately 70% of the population were classified as ever-smokers. Due to this large percentage, this variable probably included a large proportion of participants with a period of smoking without substantial lifetime smoking history. We considered the validity of this variable to be low. An alternative measure for smoking could be pack-years, but data for this was not available.

6.2.7 Statistical considerations

As the Nor-COAST study did not include a control group, the assumptions for studying confounding were violated (122). However, to assess the robustness of the results, we performed several analyses with and without adjustment for clinically relevant variables as well as several sensitivity analyses to see how this affected the outcome.

In Paper 1, we performed sensitivity analyses with the exclusion of prestroke dementia and previous stroke.

In Papers 2 and 3, the main analyses were adjusted for age, education, and sex as these were considered clinically relevant. We also performed analyses without adjustment and analyses with adjustment for the clinically relevant variables age, education, sex, and prestroke mRS as a measure of prestroke function and the NIHSS as a measure for the severity of the stroke combined to see how this affected the outcome. We performed sensitivity analyses with the exclusion of prestroke dementia and participants deceased at 18 months. In Paper 2, we also performed analyses adjusted for age, education, sex, and location of symptoms combined.

The estimates remained substantially the same for the analyses with and without adjustment for covariates and for the sensitivity analyses. Additionally, for most of the analyses, the p-values remained at the same level of statistical significance. Altogether, we believe that these analyses show robustness in the models and the results.

In Papers 2 and 3, we considered separate analyses for different categories of age, sex, education, prestroke mRS, and NIHSS, but we decided not to perform them due to expected lack of power.

Available case analyses are unbiased under the assumption missing completely at random. In our study, those excluded were older and had more-severe strokes (Figure 3 in Paper 1, Figure 1 in Papers 2 and 3), and therefore, data were not missing completely at random. Partial test completion or non-completion can plausibly relate to cognitive status. Missing data are likely to relate to the outcome of interest as patients with incident dementia are more likely to drop out (123). Excluding patients with partial test completion probably results in biased estimates. To minimize bias from missing data, we performed some imputation of the missing cognitive data. There was a small amount of missing data in the MoCA, and therefore, its imputation affected few participants. For those participants who were able to start but not complete Trail Making Tests A and B due to cognitive impairment, we believe that setting the tests' results equal to the time at the interruption of the tests was a better strategy for managing bias from missing data's impact on the estimates for cognition than exclusion of those participants. Additionally, for global z, we believe that imputing missing values on the domain z-scores using the mean z-scores from the other domains for the same participants at the same time point, if z-scores were available for at least three of five domains in Paper 2 and two of four domains in Paper 3, was a better way of managing bias from missing data's impact on the estimates for cognition than exclusion.

As described by Veierød and colleagues, missing-data mechanisms refer to the extent to which the missing data are dependent on observed and/or unobserved values of the data. Missing data can be categorized as i) missing completely at random (MCAR), where the probability that values are missing does not depend on the observed or unobserved

data; ii) missing at random (MAR), where the probability that values are missing might depend on the observed but not the unobserved data; and iii) missing not at random (MNAR), where the probability that values are missing might depend on the unobserved data. There is no way to determine from a data set whether data are MAR or MNAR, so we can seldom be sure which they are (124). Although data from clinical studies are often, to some degree, MNAR, incorrectly assuming MAR generally has a lower impact on the results than incorrectly assuming MCAR. If data are MNAR, no standard methods are valid (124). But even if they are MNAR, using a method valid under MAR results in less bias than using a method valid under MCAR. Therefore, mixed-effects logistic and mixed-effects linear regression models were preferred since a mixed-effects linear regression model minimizes bias by handling missing data in an appropriate way under a MAR assumption and also because mixed-effects logistic regression models with categorical time effects often produce fairly robust estimates in a mild departure from data missing completely at random (100).

The TMT-A and -B and the MoCA are prone to differ from the normal distribution. Z-scores normalized by mean and standard deviation of the normative data are applicable for normally distributed normative data, and skewness and kurtosis can be used to determine whether the data differ from the normal distribution (35). In our stroke population, we expected the outcome variables to have heavy tails as stroke is known to be associated with PSCI, but normal distribution of the normative data is an assumption for the application of z-scores normalized by mean and standard deviation of the normative data. The appropriate transformation of variables can be applied to achieve normal distribution of the transformed variable (35) where, for instance, logarithmic transformation of TMT-A and -B are commonly used (125, 126). As our study lacked a control group, we considered applying for the complete data sets of the normative data we used. However, it is unlikely that we would get access to all data sets for all the normative data we used. Due to the time constraints of a PhD study, we decided not to apply. For all the normative data we used, the sample size for all groups exceeded 30. In addition, mean and standard deviation were available from the

publications, and for the TMT-A and -B, skewness and kurtosis were available. For the normal distribution, the skewness is 0 and kurtosis is 3 (127). By inspecting the normative data for TMT-A and -B, we found that the skewness did not differ considerably from 0, and the kurtosis did not differ considerably from 3. We concluded that z-scores normalized by mean and standard deviation of the normative data could be justified. Interruption of TMT-A was performed at 300 seconds. However, a more reasonable interruption is probably 180 seconds (101). Our choice for interruption likely resulted in considerably wider CIs than interruption at 180 seconds. With an interruption of TMT-A at 180 seconds, we might have found more statistically significant results for the analysis on the cognitive domain attention.

Due to multiple hypotheses in Papers 2 and 3, we considered two-tailed p-values <0.01 statistically significant in these papers. We could also have considered two-tailed p-values < 0.05 as statistically significant as the dependent variables are probably highly associated, thus reducing the need to adjust for multiple hypotheses. This could have produced more statistically significant associations in Papers 2 and 3.

Unfortunately, power calculations were not performed for the analyses of this thesis. Post-hoc power calculations are flawed although sometimes requested, but we have reported uncertainty in the results in terms of confidence intervals and p-values, as recommended in (128) and references therein. The Nor-COAST study aimed for approximately 900 participants in order to include at least 100 for each stroke subtype. This number was not achieved for ICH or for all the analyses of the other stroke subtypes due to non-completion of all the cognitive tests. For some of the analyses, we probably have a lack of power, thereby increasing the possibility of type II errors and thus failing to reject the null hypothesis that is actually false in the study population.

In Papers 2 and 3, we considered alternative statistical models for the analyses. We could have performed multivariate analyses with several dependent variables considered simultaneously (129, 130), where, for instance, the outcome measure cognitive domain could have been measured as a 5-dimensional variable in Paper 2 and a 4-dimensional variable in Paper 3. This might have been possible to perform in

statistical packages but with uncertainty related to whether the analyses would converge or not. Moreover, interpreting the results would be highly complex and non-comparable to other studies. A multivariate analysis with cognitive domain and analyses with the cognitive domains one by one answer different questions. Analyses with cognitive domain as a multidimensional outcome would answer a question of overall cognitive function, while analyses with the cognitive domains one by one would answer questions for each different domain. After considering the pros and cons of all of these, we chose to perform analyses using the latter approach.

We included subject and hospital as random effects to allow different intercepts for different participants and hospitals. Alternatively, hospitals could have been included as fixed effects. The independent variables and the variables adjusted for were included only as fixed effects as we did not find the random effects of these variables clinically relevant. In addition, such random effects would have implied adding random slopes to the statistical model, making the model substantially more complex and estimation more unstable or not converging.

In Papers 2 and 3, we reported the number of participants scoring < -1.5 SD from the raw data (Supplementary Table 2 in Papers 2 and 3). It would be informative to present the number of participants scoring < -1.5 SD for the estimates for the statistical models. However, the SD is not well-defined for these estimates and, therefore, presenting the number of participants scoring < -1.5 SD for the estimates is not possible. The estimates from the statistical models were presented as z-scores with mean and 95% confidence intervals (CI).

In Paper 3, we considered performing multivariable analyses with the vascular risk factors analyzed combined to determine the effect of coexistence of these factors. We would then have to consider multicollinearity to avoid inclusion of highly correlated vascular risk factors in the analyses since this can result in misleading interpretations of the results (131). Multicollinearity could be considered by studying the correlation coefficients between the vascular risk factors and the variance inflation factors (VIF) for the mixed-effects regression models. Due to several vascular risk factors and interaction

between time and vascular risk factors, we were uncertain whether these analyses would converge or not. Additionally, interpreting the result is rather complex, producing estimates for the outcome for a participant with or without the presence of the actual vascular risk factor and with the same value for all the other risk factors. Considering these pros and cons, we did not perform multivariable analyses with the vascular risk factors analyzed combined. An alternative way of measuring the burden of vascular risk factors would be to assess the association between the number of these factors and PSCI. However, these analyses were not performed due to the already large number of analyses included in the paper.

6.2.8 External validity

The results from the Nor-COAST study are likely to be valid for patients admitted to the five participating hospitals included in the study. However, the multicenter design with hospitals representing three of every four healthcare organizations in Norway and comprising both large university hospitals and smaller hospitals increases the probability of results being valid for patients admitted with a diagnosis of acute stroke in a Norwegian stroke unit. The Norwegian stroke units follow national guidelines for stroke treatment. The selection bias in the Nor-COAST study (42) and in the thesis of participants suffering minor strokes may make the results valid among patients with minor strokes admitted for a diagnosis of acute stroke in a Norwegian stroke unit. Although the vast majority of the Norwegian general stroke population has milder strokes, the results should be interpreted with caution in a general stroke population and especially among patients suffering severe strokes. The older age of the excluded participants might be due to higher prevalence of severe strokes in older patients, but age alone could also be an independent factor for the generalizability of the results. Thus, the results are probably valid for patients slightly younger than the Norwegian general stroke population. The results are probably valid for patients suffering minor strokes admitted to stroke units in high-income Western countries following stroke guidelines similar to the Norwegian guidelines. The results being valid for minor strokes

results in an underestimation of the true prevalence of PSCI in a general stroke population.

6.3 Discussion of the results

In the following sections, the results of the thesis are discussed in a wider context than the discussion of the results presented in Papers 1, 2, and 3. However, Paper 1 is a methodological paper and was, therefore, discussed mainly in section 6.2 on methodological considerations.

6.3.1 Clinical consensus methods versus diagnostic algorithm methods

For classification of NCD in research, application of either clinical consensus methods or diagnostic algorithm methods have been used for several decades (132). The strength of a clinical consensus method is that it encompasses the clinical practice, making the clinically relevant diagnoses we search for in research. The strength of the diagnostic algorithm method is the standardization resulting in a very high reliability. Clinical consensus methods have lower inter- and intra-rater reliability than diagnostic algorithm methods. However, they are limited by a tendency to drifting over time due to shifts in diagnostic approach (132). For studies with large sample sizes, the clinical consensus method is not as feasible due to cost and its recourse-demanding process. In summary, it remains questionable whether clinical or research diagnoses should be looked upon as the gold standard in research. We chose the diagnostic algorithm method in our study due to its high reliability and resource use and applied this method to models A and B. The GDS used in model C was the closest we could get to a clinical assessment and a clinical consensus method in our study. Our findings clearly demonstrate the differences in the prevalence of mild and major NCD depending on diagnostic approach. This emphasizes the need for further studies assessing the reliability of different diagnostic approaches and validating the diagnostic algorithm method for poststroke NCD vs. the clinical consensus method. The use of more-complex algorithms in the future will probably provide an opportunity to unify the methods by integrating clinical approaches in the diagnostic algorithm methods. The integration of

such classification algorithms in applications for smartphones can be a valuable decision-making support in clinical settings.

6.3.2 Global impairment and impairments in cognitive domains

In our study population of stroke patients mainly suffering a minor stroke, we confirmed our hypothesis of PSCI being common. We identified severe global cognitive impairment, and overall, we found cognitive impairment to be relatively equally distributed across the cognitive domains.

Overall, we found the MoCA to show more severe impairment than global z. As the MoCA measures a broader spectrum of domains than the cognitive test battery used to assess global z, this might be an expression of global cognitive deficits seen following stroke. However, another explanation for severe impairment according to the MoCA results could be the normative material used, which might represent a supernormal population (75).

In the Nor-COAST study, Munthe-Kaas and colleagues showed that the MoCA has reasonable accuracy for poststroke NCD diagnosed according to the DSM-5 criteria early after a stroke (for the standard MoCA cut-off < 26: area under the receiver operating characteristic curve (AUC) was 0.80, sensitivity was 0.71, and specificity was 0.60) (133). Bearing in mind the common and severe impairment we identified in both global cognition and cognitive domains, these findings have an important clinical implication. It seems reasonable to screen stroke patients for cognitive impairment early after a stroke, and in the Norwegian national guidelines for treatment of stroke, screening for PSCI is recommended as routine at the 3-month follow-up (134). The MoCA is, therefore, an important assessment tool in clinical work for identifying patients in need of more-comprehensive cognitive testing.

We did not measure the cognitive domain social cognition. In a small study of 43 stroke patients with a mean age of 67 years, Sensenbrenner and colleagues assessed patients three years after suffering a stroke and identified a high frequency of impairment in social cognition. In their population, 47% and 34% showed impairment in the two

assessment scales the researchers used for social cognition (113). There is a lack of knowledge and a need for more research on impairments in social cognition after stroke.

Looking at the results more closely, we found memory impairment to be the most severe impairment in the entire stroke population. This is in contrast to the findings of Lo and colleagues and Barbay and colleagues (4, 34) and was significant even when participants with prestroke dementia were excluded. One explanation for this could be the older ages of our study population, as Alzheimer's disease pathology is prevalent among older people and is more strongly associated with memory impairment than cerebrovascular disease (14). However, long-lasting memory impairment may also be related to a stroke or other cerebrovascular disease. This is supported by the findings of Schellhorn and colleagues in the Nor-COAST study showing that prestroke cognitive impairment was mainly related to cerebrovascular disease and not neurodegeneration (135). However, they also found that PSCI in the early phase after a stroke was associated with characteristics of the stroke and with neurodegenerative brain pathology, indicating a contribution from both (136). This aligns with the findings of a systematic review and meta-analysis by Wang and colleagues comprising studies both in the early phase and long term after suffering a stroke; medial temporal lobe atrophy (MTLA) and white matter hyperintensities (WMH) were associated with increased risk of PSCI (137). Awareness of memory impairment in stroke populations might be significant when tailoring rehabilitation for individual stroke patients since relearning to understand and commit to the rehabilitation programs is known to be important (138).

6.3.3 Course of cognition

Studying the course of PSCI could offer new insights into the underlying pathophysiological mechanisms. Knowledge about the prognosis of PSCI is important for the patient, his or her relatives, and the healthcare system. Due to the current lack of knowledge on the course of PSCI in the literature, this is one of the main contributions of this thesis to the existing evidence. We have studied both global cognition and different cognitive domains early and long term after a stroke for the entire stroke population, different stroke subtypes, and vascular risk factors.

Contrary to several studies but in agreement with others, a main finding of this thesis is stability in cognitive function from the early period after a stroke to long term (41, 52-56). Exceptions were improvement in certain cognitive domains over time, for example, language in the entire stroke cohort and in ICH, attention in patients without atrial fibrillation, and executive function in patients without coronary heart disease. No data are available regarding the rehabilitation of participants in the Nor-COAST study. We are unable to conclude whether the improvements in attention, executive function, and language were due to the natural course of brain regeneration or to the effects of medical treatment and/or rehabilitation. Most Norwegian stroke patients receive high-quality rehabilitation, and there is also a focus on secondary prevention (139). Additionally, most patients in Norway with aphasia after suffering a stroke receive speech rehabilitation from a qualified therapist according to Norwegian guidelines for stroke treatment (134). In summary, this may emphasize the need for further research on the effects of medical treatment and rehabilitation in the future.

Our findings of PSCI being very common in a Norwegian stroke cohort comprising mainly minor strokes is discouraging. However, our findings of stability and even some improvement in cognitive function from the early period to long term after a stroke is more encouraging. Improvement in cognitive domains is highly valuable for patients' general functioning and well-being as well as for healthcare systems. Attention deficit can affect one's ability to engage in rehabilitation. Working memory and attention are important for executive function, and executive dysfunction can reduce the ability to regain independence in activities of daily living (140, 141). Language skills are also important for communication in rehabilitation. Cochrane reviews have identified a lack of knowledge on the effects of cognitive rehabilitation on attention and executive function in stroke populations and call for more research to clarify the impact of cognitive rehabilitation on PSCI (140, 141). Our findings of improvements in these cognitive domains in the entire stroke population or a subgroup of the population support the need for such research.

SVD is considered the most important contributor to delayed-onset PSCI (17). Follow-up at 18 months might be too short to capture development; a longer follow-up period in our studies would add more information. Moreover, repeated follow-ups between 3 and 18 months could have clarified whether there was an initial improvement followed by a decline in cognition, or whether the participants at 18 months poststroke were actually on track for improvement or decline. However, data on 3-year follow-ups were not available when the analyses for this thesis were performed. Still, we think an advantage of not including three years of data is the increasing uncertainty of the estimates due to loss to follow-up between 18 months and 3 years.

6.3.4 Differences across stroke subtypes

Increased evidence on stroke subtypes could provide new insights into underlying pathophysiological mechanisms of stroke. Clinically relevant research on characteristics widely available in clinic and research settings, with, for instance, TOAST criteria, is low-hanging fruit, but knowledge in the field could generate hypotheses for more-complex research questions to be addressed by future studies.

For attention, we could confirm our hypothesis of more-severe impairments for cortical infarcts (LAD and CE) compared to SVD but not for global cognitive function or the other cognitive domains. We could not confirm our hypothesis of a steeper cognitive decline for SVD than cortical infarcts (LAD and CE). As the research question involved studying prognoses in patients with cortical infarcts (LAD and CE) compared to SVD, the use of MRI data with WMH is favored. While MRI data were not available for this thesis, a subsequent study in the Nor-COAST project has found that pathological WMH score was associated with all NCD and major NCD (136). The association between WMH and cognitive domains and the course of PSCI from early to late after stroke would be interesting to explore in the Nor-COAST study.

6.3.5 Differences between patients with and without vascular risk factors

We confirmed our hypothesis of vascular risk factors being associated with PSCI both early and long term after a stroke. In contrast to Lo and colleagues in the STROKOG, this did not apply to all the vascular risk factors or to all measures of cognitive function (4).

Contrary to most other studies, we found no association between PSCI and diabetes mellitus (4, 18, 41, 68). One explanation for this could be a lack of power.

Midlife hypertension and smoking are associated with cognitive decline, while late-life hypertension alone might not be associated (62, 63, 65, 66). We were not able to measure the burden of vascular exposition in terms of exposure time, severity over time, or duration of medical treatment but were only able to measure prestroke vascular risk factors at admission for stroke. We included a slightly older study population than that of Lo and colleagues in the STROKOG consortium (4). The hypertensive group in an older study population probably comprises a larger proportion of patients with late-life hypertension and, thereby, a lower proportion of patients with midlife hypertension. In addition, defining prestroke hypertension as the use of antihypertensive medication at admittance or discharge for acute stroke instead of antihypertensive medication use at admittance only might lead to an increase in the proportion of patients with late-life hypertension. In a younger study population, vascular risk factors measured at the incidental stroke might come closer to capturing midlife exposure than in our older study population. This might explain our lack of findings for hypertension. The same argument would apply to the lack of findings for smoking.

The severe impairment we found regardless of vascular risk factors emphasizes the importance of primary prevention of first-ever stroke and WMH, which are strongly associated with hypertension, and the poorer prognoses of patients with previous stroke emphasize the importance of secondary prevention of recurrent stroke (142). The poorer prognoses of PSCI in patients with vascular risk factors emphasize the need for further research focusing on the effectiveness of a complex intervention targeting all risk factors to prevent PSCI, preferably with a randomized controlled design. Based on our findings of severe global impairment, we might hypothesize that a focal stroke lesion may initiate pathophysiological processes leading to global cognitive impairment, which is an interesting question for future research.

7 Conclusion

Paper 1: In this study, the prevalence of mild and major NCD varied depending on the diagnostic approach. Overall agreement was better between the different methods for identification of major NCD than for mild NCD. The DSM-5 criteria were not specific enough regarding which cut-off values for impairments in cognitive tests should be applied and for determining the severity of NCD. Furthermore, I-ADL measures associated with cognitive impairment in a stroke population need to be better defined.

Paper 2: In this study, we confirmed that PSCI is common short term as well as long term after a stroke. This was consistent in the entire stroke population and for all stroke subtypes. We identified improvement over time for executive function and language for the entire stroke population, and for language among ICH patients. In regard to attention, we found better outcomes among SVD patients than among patients with cortical strokes. Increased evidence in regard to the cognitive symptom profile might be important for personalizing rehabilitation, while stroke subtypes could provide new insights into underlying mechanisms. Further research is needed on pathophysiological mechanisms, prevention, and treatment, as well as on relevance for rehabilitation.

Paper 3: In this study, we confirmed that PSCI is common short term as well as long term after a stroke in patients with and without prestroke vascular risk factors. We found poorer prognoses for patients with vascular risk factors than for patients without these. Our findings of severely impaired global cognitive function indicate that a focal stroke lesion may initiate pathophysiological processes leading to global cognitive impairment.

8 Future perspectives

To improve the quality of knowledge about PSCI, further harmonization of classification methods is needed as this is important for comparing findings across different studies. The use of more-advanced algorithms for classifying mild and major NCD in research will potentially contribute to increasing the reliability of the classification. Integrating such classification algorithms into applications for smartphones can be a valuable decision-making support in clinical settings.

There is a greater focus on patients' and next of kin's perspectives on outcomes in a clinical setting than in research. As cognitive impairment affects patients' understanding, the use of patient-reported outcome measures (PROMs) in PSCI is complicated. However, a wider integration in research of PROMs from the next of kin's perspective as well as the patients' would probably be valuable for moving the research toward more clinically relevant topics.

Future research is needed on the effect of optimization of medical treatment and of physical and cognitive rehabilitation on PSCI. Improved knowledge about cognitive profiles can be valuable for identifying different effects of rehabilitation across patients with different cognitive profiles. Randomized controlled trials designed to study whether the effects of medical treatment and rehabilitation play a preventive role in cognitive decline or improve cognitive function will be valuable. A multidomain intervention might have a larger probability of success.

Additionally, future research on stroke subtypes can improve the knowledge about the underlying mechanisms for PSCI; this is important for tailoring prevention and treatment of PSCI in a heterogeneous stroke population. Knowledge from clinical studies on clinical data can generate more-complex hypotheses regarding underlying pathophysiological mechanisms aimed to be studied with biomarkers.

The effectiveness of vascular risk factor interventions to prevent PSCI should also be studied in future research, preferably with a randomized controlled design.

Future research on PSCI will benefit from greater use of register data, including register studies with randomized controlled design (rRCT) as these are likely to be increasingly available in coming years. This emphasizes the importance of including data related to cognitive function in stroke registries. Strengths of register studies include large sample sizes and clinically relevant variables. In addition, retrieving research data from medical records will be facilitated by improved technological advances, and this is especially significant for improving knowledge about the course of PSCI.

The increasing use of computerized cognitive tests will likely add knowledge to this field. With low costs, computerized tests are feasible for distribution in large populations and for large population-based studies. Data from population-based studies combined with data on PSCI could contribute knowledge on prestroke cognitive function, which is a major limitation of many PSCI studies today.

Additionally, the use of artificial intelligence (AI) in research on PSCI will most likely increase knowledge. AI will probably contribute to knowledge about the associations with and predictors for PSCI that we seek to establish in current research. It is useful for identifying patterns in data sets with large numbers of variables, especially when graphics such as MRI data and drawings such as those used in the Trail Making Tests and parts of the MoCA are available. AI is also likely to be a valuable addition to traditional research as it may narrow research gaps regarding the complexity of the brain, which is not captured by more-conventional statistical methods such as those applied in the present thesis.

9 References

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Paper 1

Received: 12 November 2019 | Revised: 23 January 2020 | Accepted: 29 January 2020

DOI: 10.1002/trc2.12000

Alzheimer's & Dementia
Translational Research & Clinical Interventions

RESEARCH ARTICLE

Impact of different methods defining post-stroke neurocognitive disorder: The Nor-COAST study

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Clinical Trial Registration: ClinicalTrials.gov Identifier: NCT02650531.

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Abstract

Introduction: Post-stroke neurocognitive disorder (NCD) is common; prevalence varies between studies, partially related to lack of consensus on how to identify cases. The aim was to compare the prevalence of post-stroke NCD using only cognitive assessment (model A), DSM-5 criteria (model B), and the Global Deterioration Scale (model C) and to determine agreement among the three models.

Methods: In the Norwegian Cognitive Impairment After Stroke study, 599 patients were assessed 3 months after suffering a stroke.

Results: The prevalence of mild NCD varied from 174 (29%) in model B to 83 (14%) in model C; prevalence of major NCD varied from 249 (42%) in model A to 68 (11%) in model C. Cohen's kappa and Cohen's quadratic weighted kappa showed fair to very good agreement among models; the poorest agreement was found for identification of mild NCD.

Discussion: The findings indicate a need for international harmonization to classify post-stroke NCD.

KEYWORDS
classification, cognition, cognitive impairment, dementia, stroke

SUBJECT TERMS:
cerebrovascular disease/stroke, cognitive impairment

1 | INTRODUCTION

Stroke increases the risk of cognitive impairment. However, no consensus exists on how best to measure cognitive function post-stroke, and the estimated prevalence of mild and major neurocognitive disorder (NCD) varies according to the threshold for defined abnormalities, the diagnostic criteria chosen, and how they are applied.[1–6]

The National Institute of Neurological Disorders-Canadian Stroke Networks (NINDS-CSN) Harmonization Standards[7] made a number of recommendations regarding the choice of cognitive tests, aiming for greater consistency across studies on vascular cognitive impairment (VCI). The more-recent Stroke and Cognition consortium (STROKOG)[2] highlighted the importance of standardizing measures and methods to improve research quality. Widely accepted definitions of major NCD, such as the 10th version of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)[8] and the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV),[9] include memory impairment as an absolute feature, which is appropriate for Alzheimer's disease (AD) but not necessarily for VCI.[5,10,11] In contrast, in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), any cognitive impairment—not necessarily memory—is sufficient to meet NCD diagnostic criteria,[12] an approach that may be more appropriate for impairment caused by cerebrovascular disease.[5]

In a systematic review of major NCD after stroke, rates ranged from 7.4% (95% confidence interval [CI] 4.8 to 10.0) in population-based studies of first-ever stroke excluding pre-stroke major NCD, to 53.4% (95% CI 46.9 to 59.8) in hospital-based studies of recurrent stroke including participants with pre-stroke major NCD.[4,13–15] However, heterogeneity in the case mix explained most of this variance rather than method of dementia diagnosis. The incidence of major NCD in the first year after severe major stroke is 45 times higher than the background major NCD rate, compared to only three times higher after minor stroke.[14] In contrast, different methods of diagnosing mild NCD post-stroke result in widely varying rates of cognitive impairment, even within a given set of diagnostic criteria in the same set of patients.[1,6]

Therefore, we hypothesized that, within a given patient population, models defining mild NCD would show greater variation in measured NCD rate and lower agreement than models defining major NCD. Diagnosing post-stroke NCD based on cognitive tests alone is used in research.[6] The recommended DSM-5 criteria[11] combines a requirement for neuropsychological performance with a requirement for instrumental activities of daily living (I-ADL) function as part of the diagnosis, but these requirements are not necessarily congruent.[16] The global deterioration scale (GDS)[17] is a tool assessing cognitive function as well as the ability to perform daily life activities. In research settings, it can be considered to be close to a clinical assessment. Thus, this study's primary aim was to assess the prevalence of all post-stroke NCD and, separately, mild and major NCD in the Norwegian Cognitive Impairment After Stroke (Nor-COAST) study population using DSM-5 and to compare that with two other methods used for classification. Further, we aimed to explore agreement among these three methods.

2 | METHODS

Nor-COAST, a multicenter prospective cohort study, recruited consecutive participants in five Norwegian stroke units (May 2015 to March 2017). Inclusion criteria were hospitalization with acute ischemic or hemorrhagic stroke within 1 week after symptom onset, fluency in a Scandinavian language, and age >18 years. The only exclusion criterion was an expected survival of less than 3 months. Participants unable to complete all tests due to, for example, dysphasia, poor vision or hearing, or inability to use their dominant arm were not excluded. Participants gave informed written consent; if unable to give consent, informed written consent was given by a family proxy. The study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REK) North (REC number 2015/171). The protocol for Nor-COAST has been published previously.[18]

2.1 | Baseline characteristics and neuropsychological assessment

Demographic characteristics and vascular risk factors were collected from medical records at the first assessment; stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS),[19] and ischemic stroke subtype was defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[20]

Cognitive function was assessed by trained study nurses with a 30-minute neuropsychological test battery based on NINDS-CSN Harmonization Standards[7] using broadly similar neuropsychological tests available and validated in Norwegian. The test battery comprised the Word List Memory and Recall Test and Verbal Fluency Test Category

(animals) from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery[21,22]; Verbal Fluency Test Letter (FAS)[23,24]; Trail Making Tests A (TMT-A) and B (TMT-B)[25]; and the Montreal Cognitive Assessment (MoCA),[26] version 7.3. In addition, cognitive function was assessed with GDS[17] and the Ascertain Dementia 8-item Informant Questionnaire (AD8).[27] Activities of daily living (ADL) were assessed with the Barthel Index (BI)[28] and functional outcome with the Modified Rankin Scale (mRS).[29] I-ADL was defined as the ability to manage finances (from the relevant question in AD8) and a study question to participants regarding their ability to manage their medications.

Baseline assessments were performed during hospital stays. Three-month follow-ups were performed at the hospitals' outpatient clinics. For participants unable to attend, assessments were performed through telephone interviews with the participants, their caregivers, or nursing home staff with assessment of AD8, mRS, GDS, BI, information on drugs, and whether study participants were able to administer their own medications. For telephone assessments, the Telephone MoCA (T-MoCA)[30] was used.

2.2 | Classifying cognitive status

Five of six cognitive domains cited in DSM-5 criteria were assessed; social cognition was not measured. Complex attention was measured by TMT-A, executive function by TMT-B and FAS, memory by Word List Recall, language by Verbal Fluency Test Category (animals), and perceptual-motor function by the visuospatial/executive part of MoCA (Figure 1).[2,31]

To classify cognitive status, we created three different models (Figure 2).

Model A was based strictly on neuropsychological test scores[6] meeting the cognitive requirements of the DSM-5 criteria requiring modest cognitive decline for mild NCD and a score in the range of −1 standard deviation (SD) to −2 SD.[12] Following other studies,[11,32,33] we chose −1.5 SD as the cut-off between normal cognition and mild NCD. Participants scoring < −1.5 SD in at least one of the five cognitive domains were defined as having post-stroke NCD, with mild NCD scoring in the range −1.5 to −2 SD and major NCD scoring ≤ −2 SD. Model A is illustrated in Figure S1 in supporting information. Published international normative data from high-income Western countries comparable to Norway were used (Table S1 in supporting information).

Model B was based on the DSM-5 criteria, which base diagnostic workups on both neuropsychological test scores and I-ADL function.[12] As in model A, participants scoring < −1.5 SD in at least one cognitive domain were defined as having post-stroke NCD (Table S1). Major NCD was defined as post-stroke NCD and dependency in I-ADL; mild NCD was defined as post-stroke NCD without impairments in I-ADL.[34]

Model C was based on GDS, a global measure of cognitive function. The assessors were authorized nurses carefully instructed in the use of the scale; they used all available information from cognitive and functional tests and self-/proxy reporting, making this assessment the closest we could get to a clinical evaluation in our study. GDS was originally designed to measure cognitive decline secondary to AD[17] but has also been shown to be valid for detecting vascular dementia.[35,36] Scores 1–2 indicated normal cognition; 3, mild NCD; and 4–7, major NCD.[32,37]

To include participants who did not complete the entire test battery and to minimize bias from missing data, a stepwise algorithm meeting the cognitive requirements of DSM-5 criteria was developed for use in models A and B when analyzing data (Figure 1).

Step 1 (n = 505): neuropsychological performances were based on all completed neuropsychological tests except MoCA. Participants included those with complete testing and those with incomplete testing scoring <−1.5 SD on at least one cognitive domain.

Step 2 (n = 94): neuropsychological performance was based on MoCA scores for participants completing MoCA only and for those with incomplete neuropsychological testing but normal scores on completed tests.

HIGHLIGHTS

- No consensus exists on how to best measure post-stroke neurocognitive disorder.
- In this study we compared three different methods for defining the prevalence of post-stroke neurocognitive disorder.
- The prevalence of post-stroke neurocognitive disorder varies according to the method used to define cases.
- The poorest agreement was found among models defining mild neurocognitive disorder

RESEARCH IN CONTEXT

1. Systematic review: The authors searched the literature using standard databases (eg, PubMed) for articles on how to measure post-stroke neurocognitive disorder (PSNCD). The estimated prevalence of mild and major neurocognitive disorder (NCD) seemed to vary according to the threshold for defined abnormalities, the diagnostic criteria chosen, and how they were applied. We recognized that there were higher discrepancy and lower agreement for defining mild than major NCD.
2. Interpretation: By using three different methods for classifying NCD 3 months post stroke, we demonstrated that the prevalence of mild and major NCD varied depending on diagnostic approach. Overall agreement was better among the methods for identification of major than for mild NCD.
3. Future directions: Before a final consensus on the definition of PSNCD can be made, more studies assessing the reliability of different diagnostic approach are needed. There is also a need for studies validating the research criteria for PSNCD against clinical diagnosis.

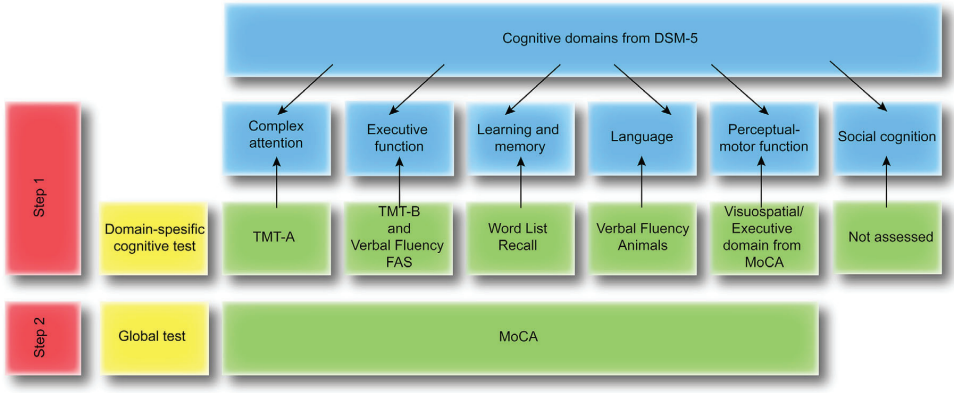

FIGURE 1 Stepwise algorithm for evaluation of participants' performance on the neuropsychological test battery used in models A and B. DSM-5, Diagnostic and Statistical Manual of Mental Disorders; MoCA, Montreal Cognitive Assessment; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B. The tests shown in Step 1 were used to evaluate performance on the neuropsychological test battery for participants with complete testing and those with incomplete testing scoring <−1.5 SD on at least one cognitive domain. Step 2, MoCA total score, was used to evaluate neuropsychological performance of the participants completing MoCA only and for those with incomplete neuropsychological testing but normal scores on completed tests

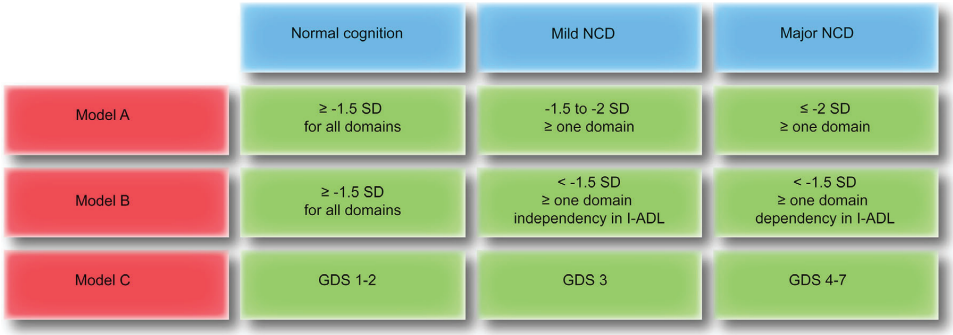

FIGURE 2 The three different analytic models for classifying neurocognitive disorder: Model A, based on neuropsychology alone; Model B, based on DSM-5 and including I-ADL impairment; and Model C, based on the GDS. GDS, Global Deterioration Scale; I-ADL, Instrumental activities of daily living; NCD, neurocognitive disorder; SD, standard deviation

A consensus group of experienced dementia researchers (KE, GS, and ARØ) approved this stepwise algorithm before data were analyzed.

2.3 | Statistics

Z-scores normalized by mean and SD of the normative data (Table S1) were derived from the raw scores of the neuropsychological tests as shown in Figure 1. Lower *z*-scores indicate poorer outcomes. The executive-function domain comprised two tests. If *z*-scores from both tests were available, the average was taken; otherwise, the single completed test score was used.

Single items missing in MoCA and T-MoCA were imputed as described in the supporting information. For participants starting but not completing Trail Making Test A or B, the test result was set to 300 seconds.[38] Other missing data were not imputed but treated as missing.

The proportions with normal cognition, mild, and major NCD were calculated, with sensitivity analyses excluding pre-stroke major NCD, defined as a pre-stroke GDS score of 4–7 and previous stroke. Agreement between the models was quantified using Cohen's kappa (κ), as well as positive and negative agreement for dichotomous categories.[39] For ordinal categories with more than two categories, agreement between the models was quantified using Cohen's quadratic weighted kappa (κ_w).[40] (See details in supporting information.) Data were analyzed using SPSS 25, with Extension Hub for analysis with κ_w.

3 | RESULTS

Of the 815 participants included in the Nor-COAST study, 700 were assessed at 3 months post-stroke. Of these, 101 had missing data; 93 had missing data on neuropsychological testing, due almost exclusively

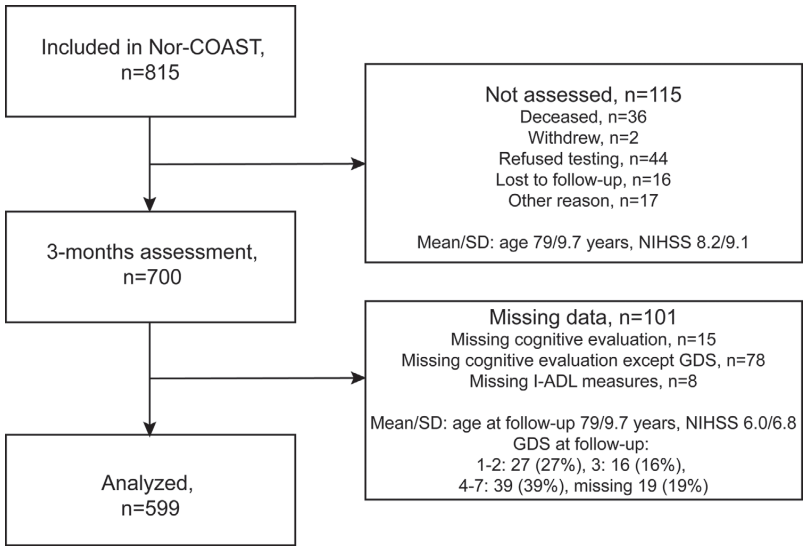

FIGURE 3 Flowchart for inclusion of participants. GDS, Global Deterioration Scale; I-ADL, Instrumental Activities of Daily Living; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation

to severe illness; and 8 had missing data on I-ADL, resulting in a study sample of 599 participants (mean/SD age = 72/12 years, 257 (43%) female, mean/SD education = 12/3.8 years, mean/SD NIHSS = 3.7/4.7) assessed at a mean/SD 3.8/0.9 months from the index stroke event (Figure 3, Table 1).

The percentage of participants defined as having normal cognition was highest in model C at 403 (67%) and lowest in models A and B at 267 (45%; Figure 4). The prevalence of mild NCD was highest in model B at 174 (29%) and lowest in model A at 83 (14%); the prevalence of major NCD was highest in model A at 249 (42%) and lowest in model C at 68 (11%).

Comparing the models regarding normal cognition versus all NCD, there was fair agreement among them (A/B and C; $\kappa = 0.40$ [95% CI 0.34 to 0.47]; Table 2). As expected, very good agreement was found between models A and B ($\kappa_w = 0.85$ [95% CI 0.83 to 0.88]) because normal cognition was equally defined. However, of 332 participants with post-stroke NCD in model A, 249 (75%) had major NCD compared to 158 (48%) in model B (Figure 4). There was fair agreement between models A and C ($\kappa_w = 0.38$ [95% CI 0.32 to 0.44]) and moderate agreement between models B and C ($\kappa_w = 0.52$ [95% CI 0.46 to 0.58]; Table 2). The details underlying the counts in Table 2 are provided in Table S2 in supporting information.

Model C was more restrictive in defining cognitive impairment than model B, which was, in turn, more restrictive than model A (Figure 4). Of 403 participants classified with normal cognition in model C, 60% were also classified with normal cognition in models A and B (Table S2). The poorest agreement among models was seen in the classification of participants with mild NCD, as only 15% of the 128 classified with mild NCD in model C were classified with mild NCD in model A and 40% in model B. The greatest agreement was seen for the classification of participants with major NCD, as 85% of the 68 participants classified with major NCD in model C were classified with major NCD in model A and 93% in model B.

The exclusion of participants with pre-stroke major NCD and previous strokes resulted in a slightly higher proportion of participants having normal cognition and a lower prevalence of major NCD, while the prevalence of mild NCD was stable (Figure S2 and Figure S3 in supporting information).

4 | DISCUSSION

In this descriptive study, we aimed to assess the prevalence of all post-stroke NCD and subtypes mild and major NCD using three different models. We showed that prevalence varied considerably among these models. Overall agreement was greater among the different methods for identification of major NCD than for mild NCD, supporting the pre-hoc hypothesis.

To our knowledge, this is one of the few studies using DSM-5 criteria (model B) to classify post-stroke NCD and comparing prevalence with other methods used for classifying post-stroke NCD. The prevalence of all post-stroke NCD based on neuropsychological testing (models A and B) at 55% is slightly higher than that of other recent studies of post-stroke NCD.[4,15] In these models, we found a higher proportion of major NCD and a lower proportion of mild NCD compared to the most recent review and meta-analysis,[6,15] probably due to the stepwise algorithm developed to avoid bias from missing data, including participants unable to complete the entire neuropsychological test battery. However, the rate of major NCD in model B at 26% aligns with findings for hospital-based studies on first or recurrent

TABLE 1 Baseline characteristics

Demographics	N = 599		
Mean age, years (SD)		72	(12)
Female sex, n (%)		257	(43)
Mean education, years (SD)		12	(3.8)
Vascular risk factors, n (%)			
Hypertension, n (%)	N = 599	329	(55)
Hypercholesterolemia, n (%)	N = 599	304	(51)
Current cigarette smoking, n (%)	N = 597	112	(19)
Diabetes mellitus, n (%)	N = 599	113	(19)
Mean BMI, kg/m^2 (SD)	N = 567	26.1	(4.2)
Vascular disease, n (%)	N = 599		
Coronary heart disease, n (%)		104	(17)
Atrial fibrillation, n (%)		140	(23)
Previous stroke, n (%)		106	(18)
Previous TIA, n (%)		27	(4.5)
Stroke subtype, n (%)	N = 599		
Cerebral infarction		547	(91)
Cerebral hemorrhage		52	(8.7)
TOAST classification, n (%)	N = 529		
Large-vessel disease		56	(11)
Cardioembolic disease		123	(23)
Small-vessel disease		119	(23)
Other aetiology		15	(2.8)
Undetermined etiology		216	(41)
Thrombolysis, n (%)	N = 542	143	(26)
Thrombectomy, n (%)	N = 547	11	(2.0)
Pre-stroke GDS (1-7), n (%)	N = 594		
GDS = 1-2		536	(90)
GDS = 3		36	(6.1)
GDS = 4-7		22	(3.7)
Assessments			
NIHSS (0-42) at admittance, mean (SD)	N = 583	3.7	(4.7)
mRS (0-6) at discharge,[a] mean (SD)	N = 597	2.1	(1.3)
Barthel Index (0-100) at discharge,[a] mean (SD)	N = 597	89	(19)

Abbreviations: BMI, body mass index; GDS, Global Deterioration Scale; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

[a]At discharge or day 7 if length of stay extends beyond 7 days.

stroke including pre-stroke dementia in another recent review and meta-analysis.[13]

In a recent paper comparing the prevalence of NCD classified by different criteria, Sachdev et al. showed very good agreement among DSM-5, The International Society of Vascular Behavioural and Cognitive Disorders (VAS-COG), and The Vascular Impairment of Cognition Classification Consensus Study (VICCCS) criteria, which all require impairment in at least one cognitive domain, and lower agreement between these criteria and DSM-IV criteria,[9] requiring impairment in memory in addition to one other cognitive domain.[11] Use of the updated DSM-5[12] and VAS-COG[41] criteria could, therefore, lead to a higher prevalence of all post-stroke NCD compared to studies using DSM-IV[9] or ICD-10[8] criteria, but for criteria demanding impairment in the same number of cognitive domains, the prevalence of all post-stroke NCD is probably more similar.[11]

Furthermore, the prevalence of mild and all post-stroke NCD will obviously differ considerably based on the choice of cut-offs.[1] The DSM-5 criteria define modest cognitive decline as test performance typically in the 1–2 SD range below normative mean, leaving room for interpretation; this will significantly affect prevalence. Therefore, even within DSM-5 criteria, the prevalence of mild and all post-stroke NCD will vary with the use of different cut-offs.[33,34,42] As we mostly used one test per cognitive domain in the present study, we chose −1.5 SD as the cut-off,[42] which also aligns with some other studies using DSM-5 criteria.[11,33]

The GDS, with similarities to clinical evaluation, was performed by experienced nurses after explicit instruction, and it showed the lowest prevalence of all post-stroke NCD. The prevalence of major NCD based on the GDS (model C) aligns with two other recent studies[4,15]; however, the prevalence of mild NCD is lower, possibly indicating the need for more-comprehensive testing for classifying mild NCD.[43]

The three models agreed fairly well regarding those with major NCD but showed less agreement regarding those with mild NCD. This supports the hypothesis that, within a given patient population, there will be greater variation between methods used to define mild NCD than in those defining major NCD, in line with the findings of systematic reviews on post-stroke NCD[14,15] and studies of mild NCD methodology.[1,6,44] Most participants classified with major NCD by the GDS were also classified with major NCD in models A and B, indicating a high specificity of this method. The discrepancy for mild and major NCD between models A and B highlights a problem with applying the DSM-5 criteria, as the criteria have requirements for both neuropsychological performance and for I-ADL to decide on the severity of NCD. This could be interpreted differently across different studies and affect prevalence and agreement.

The advantage of classifying NCD using neuropsychological tests alone (model A) is the avoidance of the ceiling effect of commonly used I-ADL scales that could possibly underestimate the prevalence of major NCD, as subtle changes are difficult to detect.[45] In contrast, using neuropsychological tests alone may also result in overestimating the prevalence of major NCD.[16] In model B, in line with the DSM-5 criteria, I-ADL impairment was mandatory for major NCD, which resulted in a shift from major to mild NCD compared to model A and moved the prevalence of mild and major NCD closer to the findings of other studies.[13,15] The I-ADL measures we used were defined only by ability to manage one's medications and finances; more extensive I-ADL measures may have given different results as I-ADL impairment was probably underestimated. In contrast, I-ADL impairments may also be caused by physical rather than cognitive impairment; therefore, I-ADL measures constructed and validated for stroke survivors should be used.[31] However, most participants in the present study had

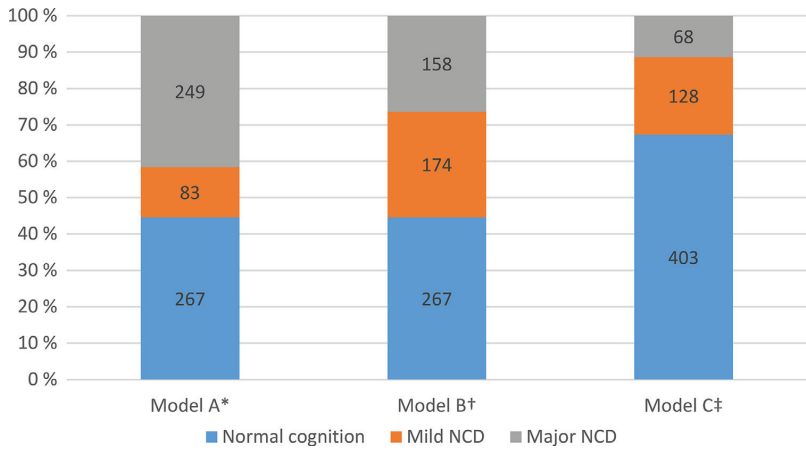

FIGURE 4 Proportion of participants with normal cognition, mild, and major NCD three months post-stroke, N = 599. NCD = Neurocognitive disorder. *Model A: normal cognition defined as score ≥ −1.5 SD for all cognitive domains; mild NCD defined as score in the range of −1.5 to −2 SD for at least one cognitive domain; and major NCD defined as a score ≤ −2 SD for at least one cognitive domain. †Model B: normal cognition defined as score ≥−1.5 SD for all cognitive domains; NCD defined as score <−1.5 SD for at least one cognitive domain; major NCD defined as having post-stroke NCD with dependency in instrumental activities of daily living (I-ADL), defined as the need for assistance in managing one's finances and/or medications. Mild NCD was post-stroke NCD without impairments in I-ADL. ‡Model C: evaluation based on Global Deterioration Scale (GDS); normal cognition defined as a GDS score of 1–2; mild NCD defined as a GDS score of 3; and major NCD defined as a GDS score of 4–7

experienced milder strokes, so this may have been less important. Based on prevalence of all post-stroke NCD, mild, and major NCD in other studies, our findings support the classification of post-stroke NCD based on both neuropsychological tests and I-ADL measures.

Major strengths of the present study were its multicenter design, providing a fairly representative stroke population, and the use of recommended robust tests for stroke patients.[7] Another strength is the stepwise algorithm developed to avoid bias from missing data, allowing inclusion of participants unable to complete the entire test battery.

The study also has several limitations. The lack of a stroke-free control group made it difficult to evaluate the extent to which the measured post-stroke NCD was greater than expected in the background population.[14] Additionally, cognitive domains were assessed using a limited number of neuropsychological tests; only one test in most domains that may have overestimated the impairments,[34] but lengthy batteries are often poorly tolerated by frail older patients and may result in selection bias underestimating the impairments.[46] In line with DSM-5 criteria, we included measures of I-ADL, but this was defined only by ability to manage one's medications and finances, probably underestimating the I-ADL impairments.

5 | CONCLUSION

In this study, the prevalence of mild and major NCD varied depending on diagnostic approach. Overall agreement was better between the different methods for identification of major NCD than for mild NCD, supporting our hypothesis. The present study shows that there is need for more research with focus on validating research diagnosis against clinical diagnosis of post-stroke NCD. Data collected for research are more limited than the information used in clinical diagnostic work-up on patients' cognitive status, on the other hand making clinical diagnosis in large research studies not feasible. Issues remain in the interpretation and application of methods for classifying post-stroke NCD. The DSM-5 criteria are not specific enough regarding which cut-off values for impairments in cognitive tests should be applied and to decide on the severity of NCD. Furthermore, I-ADL measures associated with cognitive impairment in a stroke population need to be better defined.

We recommend using the combination of neuropsychological tests and a valid measure of I-ADLs when classifying post-stroke NCD.

ACKNOWLEDGMENTS

We thank all study participants for their contributions to the study and the dedicated study staff at the Clinical Trial Unit in all the participating hospitals.

Thank you to Professor emeritus Knut Engedal (KE); Professor Geir Selbæk (GS); and Anne Rita Øksengård, MD, PhD (ARØ), for helpful advice as part of the expert panel for Nor-COAST.

CONFLICT OF INTEREST

The authors declare they have no 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.

AUTHOR CONTRIBUTIONS

IS manages the Nor-COAST study. IS and HIH had the idea for the design of the present study. SA, RMK, HIH, and IS were responsible

TABLE 2 Comparison of the models A, B, and C

Comparison of Model A/B and C			
	Model A/B		
Model C	Normal cognition, n	Mild and major NCD, n	Total, n (%)
Normal cognition, n	242	161	403 (67)
Mild and major NCD, n	25	171	196 (33)
Total, n (%)	267 (45)	332 (55)	599
κ = 0.40 (95% CI 0.34 to 0.47) Positive agreement 0.65. Negative agreement 0.72.			
Comparison of Models A and B			
	Model A		
Model B	Normal cognition, n	Mild NCD, n	Major NCD, n	Total, n (%)
Normal cognition, n	267	0	0	267 (45)
Mild NCD, n	0	60	114	174 (29)
Major NCD, n	0	23	135	158 (26)
Total, n (%)	267 (45)	83 (14)	249 (42)	599
κ_w = 0.85 (95% CI 0.83 to 0.88)				
Comparison of Models A and C			
	Model A		
Model C	Normal cognition, n	Mild NCD, n	Major NCD, n	Total, n (%)
Normal cognition, n	242	57	104	403 (67)
Mild NCD, n	22	19	87	128 (21)
Major NCD, n	3	7	58	68 (11)
Total, n (%)	267 (45)	83 (14)	249 (42)	599
κ_w = 0.38 (95% CI 0.32 to 0.44).				
Comparison of Models B and C			
	Model B		
Model C	Normal cognition, n	Mild NCD, n	Major NCD, n	Total, n (%)
Normal cognition, n	242	121	40	403 (67)
Mild NCD, n	22	51	55	128 (21)
Major NCD, n	3	2	63	68 (11)
Total, n (%)	267 (45)	174 (29)	158 (26)	599
κ_w = 0.52 (95% CI 0.46 to 0.58).				

NCD, neurocognitive disorder; κ, Cohen's kappa; κ_w, Cohen's quadratic weighted kappa.

for writing the present report with additional critical input from STP. SA developed the work-up for the diagnostic algorithm; SA and SL performed the statistical analysis. RMK, HIH, YS, HE, and HN were responsible for collecting data at their respective hospitals and PT for managing the data. All authors interpreted the data and read and approved the final manuscript.

SOURCES OF FUNDING

The Nor-COAST study is funded by the Norwegian Health Association, and additional funding was provided by the Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Science, NTNU-Norwegian University of Science and Technology. The authors are funded elsewhere: RMK by the Vestre Viken Hospital Trust and SA by the Liaison Committee for Education, Research and Innovation in Central Norway. STP is supported by the NIHR Oxford Biomedical Research Centre, UK.

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SUPPORTING INFORMATION

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

How to cite this article: Munthe-Kaas R, Aam S, Ihle-Hansen H, et al. Impact of different methods defining post-stroke neurocognitive disorder: The Nor-COAST study. *Alzheimer's Dement*. 2020;6:e12000. https://doi.org/10.1002/trc2.12000

Paper 2

frontiers in Neurology

ORIGINAL RESEARCH
published: 17 July 2020
doi: 10.3389/fneur.2020.00699

Post-stroke Cognitive Impairment—Impact of Follow-Up Time and Stroke Subtype on Severity and Cognitive Profile: The Nor-COAST Study

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OPEN ACCESS

Edited by:
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Aarhus University Hospital, Denmark

Reviewed by:
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University of Glasgow,
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Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: 16 April 2020
Accepted: 09 June 2020
Published: 17 July 2020

Citation:
Aam S, Einstad MS, Munthe-Kaas R, Lydersen S, Ihle-Hansen H, Knapskog A-B, Ellekjær H, Seljeseth Y and Saltvedt I (2020) Post-stroke Cognitive Impairment—Impact of Follow-Up Time and Stroke Subtype on Severity and Cognitive Profile: The Nor-COAST Study. Front. Neurol. 11:699. doi: 10.3389/fneur.2020.00699

Background: Post-stroke cognitive impairment (PSCI) is common, but evidence of cognitive symptom profiles, course over time, and pathogenesis is scarce. We investigated the significance of time and etiologic stroke subtype for the probability of PSCI, severity, and cognitive profile.

Methods: Stroke survivors ($n = 617$) underwent cognitive assessments of attention, executive function, memory, language, perceptual-motor function, and the Montreal Cognitive Assessment (MoCA) after 3 and/or 18 months. PSCI was classified according to DSM-5 criteria. Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS). Stroke subtype was categorized as intracerebral hemorrhage (ICH), large artery disease (LAD), cardioembolic stroke (CE), small vessel disease (SVD), or un-/other determined strokes (UD). Mixed-effects logistic or linear regression was applied with PSCI, MoCA, and z-scores of the cognitive domains as dependent variables. Independent variables were time as well as stroke subtype, time, and interaction between these. The analyses were adjusted for age, education, and sex. The effects of time and stroke subtype were analyzed by likelihood ratio tests (LR).

Results: Mean age was 72 years (SD 12), 42% were females, and mean NIHSS score at admittance was 3.8 (SD 4.8). Probability (95% CI) for PSCI after 3 and 18 months was 0.59 (0.51–0.66) and 0.51 (0.52–0.60), respectively and remained constant over time. Global measures and most cognitive domains were assessed as impaired for the entire stroke population and for most stroke subtypes. Executive function and language improved for the entire stroke population (LR) = 9.05, $p = 0.003$, and LR = 10.38, $p = 0.001$, respectively). After dividing the sample according to stroke subtypes, language

improved for ICH patients (LR = 18.02, $p = 0.003$). No significant differences were found in the severity of impairment between stroke subtypes except for attention, which was impaired for LAD and CE in contrast to no impairment for SVD (LR = 56.58, $p < 0.001$).

Conclusions: In this study including mainly minor strokes, PSCI is common for all subtypes, both early and long-term after stroke, while executive function and language improve over time. The findings might contribute to personalizing follow-up and offer new insights into underlying mechanisms. Further research is needed on underlying mechanisms, PSCI prevention and treatment, and relevance for rehabilitation.

Keywords: post-stroke cognitive impairment, vascular dementia, stroke, stroke subtype, cognitive domains, cerebrovascular disease, intracerebral hemorrhag, prognosis

INTRODUCTION

Stroke is one of two leading causes of disability-adjusted life-years worldwide (1), and post-stroke cognitive impairment (PSCI) has been shown to be common among stroke survivors. Recent reviews and meta-analyses identified a pooled prevalence of PSCI of 53.4% and mild and major PSCI of 36.4–38 and 16% respectively, measured within 1.5 years post-stroke (2, 3).

Previous studies have reported conflicting results regarding the prognosis for patients suffering PSCI; these have indicated deterioration, no progression, and even improvement in cognition over time for subgroups (4–11). Several cognitive domains are affected in PSCI; of these, impairment in attention and executive function seem to be the most prevalent and severe shortly after and a long time after suffering a stroke (12–16). A recent study on PSCI a short time after a stroke showed a high prevalence of impairment in global cognition and in the five most commonly assessed domains: attention, memory, language, perceptual-motor function, and executive function (17).

The underlying pathological mechanisms for suffering a stroke are heterogeneous, and severity and localization of the stroke are important for PSCI (6, 17, 18). About 10–20% of strokes are hemorrhagic; the rest are ischemic and typically related to large artery disease (LAD), cardioembolic stroke (CE), or small vessel disease (SVD), often labeled lacunar infarction, with about 25% in each category (19–21). LAD and CE strokes are often cortical strokes of large volume, while SVD strokes are subcortical and of small volume (22). Cognitive impairment has been shown to be less common in the early post-stroke period in SVD compared to other stroke subtypes, but SVD is associated with cognitive decline long after a stroke (16, 17, 23, 24). However, in their review and meta-analyses, Makin et al. found similar proportions to have PSCI in lacunar vs. non-lacunar stroke [OR 0.75 (95% CI 0.47–1.20)] (25, 26). ICH has been reported to be more strongly associated with dementia than ischemic stroke (6), and impairments in processing speed, executive function, episodic memory, language, and visuo-spatial abilities have been found to be most prevalent (19, 21, 27).

There remains a need for additional knowledge about the course of PSCI and the impact of stroke subtypes on PSCI. Therefore, the aim of this study was to investigate whether time and etiological stroke subtype impact the probability for PSCI and its severity and cognitive symptom profile three and 18 months post-stroke.

METHODS

The present study is part of the Norwegian Cognitive Impairment After Stroke (Nor-COAST) study, a multicenter prospective cohort study that recruited participants hospitalized with acute stroke in five Norwegian stroke units from May 2015 through March 2017 (28). Inclusion criteria were hospitalization with acute ischemic or hemorrhagic stroke within one week after symptom appearance, fluency in a Scandinavian language, and age over 18 years. The only exclusion criterion was expected survival <3 months. Participation in the study was voluntary, and the participants gave informed written consent. When a person was unable to give consent, informed written consent for participation was given by a proxy family member. The study was approved by the Regional Committee for Medical and Health Research Ethics (REC Nord 2015/171) and registered in ClinicalTrials.gov (NCT02650531). Further details are described in the protocol for the Nor-COAST study (28).

Clinical Assessments

Data on demographic characteristics and vascular risk factors were collected from medical records. Vascular risk factors were defined as described in previous work in the Nor-COAST study (29) and in the **Supplementary Material**. Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS) (30). Ischemic strokes were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (22) by experienced stroke physicians. Further stepwise classification into TOAST modified was done as described in the **Supplementary Material** and **Supplementary Figure S1**. Stroke subtype was defined by ICH and modified TOAST classification into large artery disease (LAD), cardioembolic stroke (CE), small vessel disease (SVD), other etiology, and undetermined strokes; as the subtype other etiology comprised a small number, it was grouped with undetermined etiology (UD). Localization of symptoms in the acute phase was collected at admission and categorized as right, left, bilateral, or unable to locate by side.

Cognitive and Functional Assessments

Cognitive function was assessed by trained study staff with a cognitive test battery recommended by the National Institute of Neurological Disorders–Canadian Stroke Network (NINDS–CSN) Harmonization Standards (31) adjusted to available and validated cognitive tests in Norwegian. The test battery comprised the Word List Memory and Recall Test and Verbal Fluency Test Category (animals) from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery (32, 33); Verbal Fluency Test Letter (FAS) (34, 35); Trail Making Tests A (TMT-A) and B (TMT-B) (36); and the Montreal Cognitive Assessment (MoCA) (37), version 7.3 at the 3-months follow-up and version 7.1 at the 18-months follow-up. Cognitive function was also assessed with the Global Deterioration Scale (GDS), a global measure of cognitive function originally designed to measure cognitive decline in Alzheimer's disease but shown to be valid also in measuring vascular dementia (29, 38–40). Activities of daily living (ADL) were assessed with the Barthel Index (BI) (41) and functional outcome with the Modified Rankin Scale (mRS) (42). Baseline assessments were performed during hospital stays. Follow-ups at 3 and 18 months were performed at the hospitals' outpatient clinics. For participants unable to attend, assessments were performed through telephone interviews with the participants, their caregivers, or nursing home staff with the mRS, BI, GDS, and if possible, the Telephone MoCA (T-MoCA) (43).

Outcomes

Cognitive outcome assessments included complex attention measured by TMT-A, executive function by TMT-B and Verbal Fluency Test Letters (FAS), memory by Word List Recall, language by Verbal Fluency Test Category (animals), and perceptual-motor function by the visuospatial/executive part of MoCA. Cognitive status was dichotomized into normal cognition and cognitive impairment; cognitive impairment comprised both mild and major neurocognitive disorders (NCD), and the cut-off for cognitive impairment was defined according to the cut-off for mild NCD in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for mild and major neurocognitive disorders (44). Details are described in previous work in the Nor-COAST study (29) and summarized in the **Supplementary Material**.

Statistics

Z-scores normalized by mean and SD of the normative data were derived from the raw scores of the cognitive tests. The normative data used are presented in previous work (29) as well as in **Supplementary Table S1**. The symptom profile of PSCI was measured by the z-scores of the five cognitive domains. The cognitive domains were measured by the z-score of the single completed cognitive test. Two tests were administered to measure executive function, and the average z-score was used. The z-scores were implemented with lower z-scores indicating poorer outcomes. The severity of PSCI was measured by z-scores of global z and MoCA; global z was defined as the average scores of the five cognitive domains assessed.

To minimize bias from excluded participants, imputation was performed as described in previous work (29) and as described in the **Supplementary Material**.

Probability for PSCI and severity and symptom profile of PSCI were analyzed as appropriate with mixed-effects logistic or linear regression with PSCI according to DSM-5 criteria, MoCA, and global z and z-scores for the five cognitive domains of attention, executive function, memory, language, and perceptual-motor function as dependent variables one at a time. The independent variables were time (model 1), stroke subtype, time and the interaction between stroke subtype and time (model 2), and stroke subtype (model 3). We adjusted for age, education, and sex. The estimated probability for PSCI according to DSM-5 criteria was calculated from the estimated odds in mixed-effects logistic regression, as probability = odds (1+odds). Mixed-effects logistic and linear regression models were preferred since a mixed-effects linear regression model minimizes bias by handling missing data in an appropriate way under a missing at random assumption, and also because mixed-effects logistic regression models with categorical time effects often produce fairly robust estimates in a mild departure from data missing completely at random (45). Illustrations of the statistical models for the logistic and linear regressions are provided in **Supplementary Figures S2, S3**. Hypothesis tests for the effects of time and stroke subtype in model 2 were conducted by likelihood ratio tests comparing model 1 and model 2, as well as comparing model 2 and model 3. The results were presented as estimates with mean and 95% confidence intervals (CI) and the test statistics with degrees of freedom and p-value.

Sensitivity analyses with the exclusion of participants deceased at 18 months ($n = 21$), as well as with the exclusion of pre-stroke dementia defined as pre-stroke GDS 4–7 ($n = 23$), were performed to determine if these affected the outcome. We also performed sensitivity analyses for unadjusted analyses; analyses adjusted for age, education, sex, pre-stroke mRS, and NIHSS combined; and analyses adjusted for age, education, sex, and location of symptoms combined.

PSCI according to DSM-5 criteria, stroke subtype, time, and sex were analyzed as categorical variables, while global z, MoCA z-score, z-scores of the cognitive domains, age, education, mRS, and NIHSS were analyzed as continuous variables. Complete case analyses were used for stroke subtype, age, education, and sex, while available case analyses were used for PSCI according to DSM-5 criteria, global z, MoCA, z-scores for the cognitive domains, mRS, and NIHSS. Confounders were included as fixed effects, while subject and hospital were included as random effects.

Due to multiple hypotheses, we considered two-tailed $p < 0.01$ as statistically significant. Data were analyzed using SPSS 25 and STATA 16.0.

RESULTS

Baseline Characteristics

Of the 815 participants included in the Nor-COAST study, 700 were assessed at 3 months and 599 at the 18-months follow-up, 10 of whom were not assessed at 3 months. Of the 710 participants

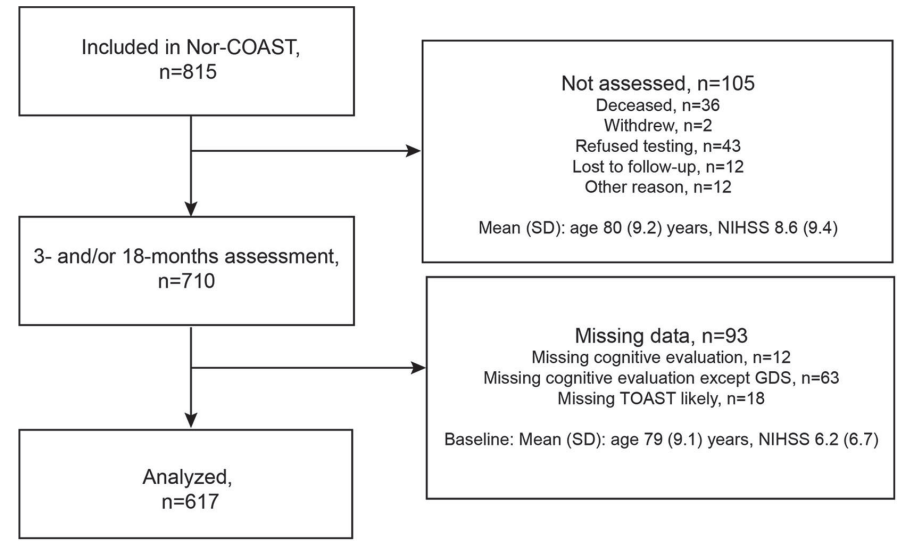

FIGURE 1 | Flowchart of participants included in the study.

assessed at either 3 or 18 months, 93 were excluded due to missing data, resulting in a study sample of 617 participants (**Figure 1**). Of these 617 participants, 21 were deceased at 18 months.

The mean age was 72 years (SD 12), 42% were females, the mean education was 12.5 years (SD 3.8), and the mean NIHSS score at admittance was 3.8 (SD 4.8). The baseline characteristics of the participants are shown in **Table 1**. The 198 participants excluded were age 80 years (SD 9.1); 55% were females; mean years of education were 10.5 years (SD 3.1); and mean NIHSS score at admittance was 7.4 (8.2). Among 192 of those excluded, 36 (19%) had a pre-stroke GDS of 1 (mild NCD) and 38 (20%) had a pre-stroke GDS of 4–7 (major NCD).

The numbers of participants completing cognitive tests for the cognitive domains, with mean z-scores of the tests and proportions with z-scores <-1.5, are shown in **Supplementary Table S2**.

Probability for PSCI and Impairments in the Cognitive Domains at 3 and 18 Months

For the entire study population, the probability for PSCI according to DSM-5 criteria was 0.59 (95% CI 0.51–0.65) after 3 months and 0.51 (95% CI 0.52–0.60) after 18 months (**Figure 2**). For the different stroke subtypes, the probability for PSCI at 3 months ranged from 0.50 (95% CI 0.35–0.65) for SVD to 0.66 (95% CI 0.41–0.84) for ICH, while the corresponding results at 18 months ranged from 0.35 (95% CI 0.22–0.51) for SVD and 0.61 (95% CI 0.44–0.75) for LAD (**Figure 3**). The differences between subtypes or between time points were not statistically significant.

There were impairments in terms of z-score < 0 for the global measures MoCA and global z for the entire study population. MoCA z-scores were −1.18 (95% CI −1.33 to −1.02) and −1.15 (95% CI −1.31 to −0.99) at 3 and 18 months, respectively (**Figure 3**). The global scores were found to be impaired in terms of z-score < 0 for all stroke subtypes at 3 and 18 months (**Figure 3**). All cognitive domains except perceptual-motor function were found to be impaired in terms of z-score < 0 for the entire study population, and memory was found to be most severely impaired with a z-score of −0.85 (95% CI −0.97 to −0.73) and −0.85 (95% CI −0.97 to −0.72) at 3 and 18 months, respectively. For almost all stroke subtypes, all the cognitive domains except for perceptual-motor function were found to be impaired in terms of z-score < 0 at both time points (**Figure 3**).

Course of Cognition and Differences Between Stroke Subtypes

Executive function and language were found to be impaired in terms of z-score < 0 in the entire stroke population at 3 months but had improved from 3 to 18 months (**Figures 2C,E**). Perceptual-motor function was normal in the entire stroke population at 3 months but declined from 3 to 18 months (**Figure 2F**). Among ICH patients, language was impaired in terms of z-score < 0 at 3 months and normalized at 18 months (**Figure 3E**), and for LAD patients, perceptual-motor function was normal at 3 months but declined from 3 to 18 months (**Figure 3F**). Differences between stroke subtypes were found for attention, with impairment in terms of z-score < 0 for LAD and CE but not for SVD and UD (**Figure 3B**).

The results were substantially the same for sensitivity analyses for unadjusted analyses; analyses excluding participants deceased at 18 months ($n = 21$) adjusted for age, education and sex; analyses excluding participants with pre-stroke dementia

TABLE 1 | Baseline characteristics.

Demographics	***N* = 617**		
Mean age, years (SD)		72	(12)
Male sex, *n* (%)		360	(58)
Mean education, years (SD)		12.5	(3.8)
Vascular risk factors, *n* (%)			
Hypertension, *n* (%)	*N* = 617	338	(55)
Hypercholesterolemia, *n* (%)	*N* = 617	314	(46)
Current cigarette smoking, *n* (%)	*N* = 615	119	(19)
Diabetes mellitus, *n* (%)	*N* = 617	115	(19)
Mean BMI, kg/m^2 (SD)	*N* = 583	26.1	(4.1)
Vascular disease, *n* (%)	*N* = 617		
Coronary heart disease, *n* (%)		108	(18)
Atrial fibrillation, *n* (%)		144	(23)
Previous stroke or TIA, *n* (%)		136	(22)
Stroke subtype, *n* (%)	*N* = 618		
Cerebral infarction		564	(91)
Cerebral hemorrhage		53	(8.6)
TOAST classification*, *n* (%)	*N* = 564		
Large vessel disease		140	(25)
Cardioembolic disease		153	(27)
Small vessel disease		135	(24)
Other etiology		17	(3.0)
Undetermined etiology		119	(21)
Symptom locations, *n* (%)	*N* = 599		
Right		243	(41)
Left		272	(45)
Bilateral		18	(3.0)
Not able to locate by side		66	(11)
Thrombolysis, *n* (%)	*N* = 612	147	(24)
Thrombectomy, *n* (%)	*N* = 617	12	(1.9)
Pre-stroke GDS (1-7), *n* (%)	*N* = 611		
GDS = 1–2 (Normal cognition)		553	(91)
GDS = 3 (Mild Neurocognitive Disorder)		35	(5.7)
GDS = 4–7 (Major Neurocognitive Disorder)		23	(3.8)
Assessments			
NIHSS (0–42) at admittance, mean (SD)	*N* = 601	3.8	(4.8)
Pre-stroke mRS (0–6), mean (SD)	*N* = 613	0.77	(1.0)
mRS (0–6) at discharge, † mean (SD)	*N* = 615	2.1	(1.3)
Barthel Index (0–100) at discharge, † mean (SD)	N = 615	89	(19)
MoCA total score (0–30) during hospital stay, mean (SD)	*N* = 575	24	(4.8)

SD, Standard Deviation; BMI, Body Mass Index; TIA, Transient Ischemic Attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment; GDS, Global Deterioration Scale; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

**TOAST modification; Undetermined etiology of TOAST probable, based on original classification (22); first classified as TOAST possible, also based on original classification (22); then as TOAST likely (47) where participants with findings of carotid stenosis <50% were classified as large artery disease. Finally, TOAST modified was developed by merging TOAST probable, TOAST possible, and TOAST likely.*

†*at discharge or day 7 if length of stay extends beyond 7 days.*

defined as pre-stroke GDS of 4–7 (n = 23) adjusted for age, education and sex; analyses adjusted for age, education, sex, pre-stroke mRS, and NIHSS combined; and analyses adjusted for age, education, sex and location of symptoms for those categorized with right or left symptom location, combined (**Supplementary Figures S4–S13**). The exceptions were that no statistically significant differences were found between stroke subtypes regarding attention in the analyses with the exclusion of pre-stroke dementia and for the analyses adjusted for age, education, sex, pre-stroke mRS, and NIHSS combined. In addition, for executive function for the entire stroke population, the improvement did not reach statistical significance for the analyses adjusted for age, education, sex, pre-stroke mRS, and NIHSS combined and for the analyses adjusted for age, education, sex and location of symptoms combined. Also, the improvement in language for the entire stroke population and in patients with ICH did not reach statistical significance for the analyses adjusted age, education, sex and location of symptoms combined. The numbers of participants for the different stroke subtypes included in the analyses are shown in **Supplementary Table S3**.

DISCUSSION

In this descriptive study of stroke survivors accessible for cognitive assessment, we demonstrated a high probability for PSCI at 3- and 18-months post-stroke. Impairments in global cognitive measures and several cognitive domains were identified for the entire stroke population and for almost all stroke subtypes after 3 and 18 months. Executive function and language improved for the entire stroke population, and, after categorizing the sample according to stroke subtypes, language normalized a long time after a stroke in ICH patients. No significant differences were identified between stroke subtypes in regard to severity of impairment, except for attention, which was impaired for cortical strokes but not impaired in SVD.

Our results showed a high probability for PSCI according to DSM-5 criteria in the entire stroke population at 3 and 18 months, which aligns with the findings of other recent studies (2, 3). Lo et al. reported global impairment among 35–50% of stroke victims across the different stroke subtypes early after stroke, which is in accordance with our findings (17). On a group level, we found severe impairment in almost every cognitive domain. This corresponds with findings of other recent studies; however, contrary to those studies, we found memory to be the most severely impaired of the cognitive domains (12, 17). This finding continued to be significant when patients with pre-stroke dementia were excluded. One possible explanation for this could be the older ages of our study population, as Alzheimer's disease pathology is prevalent among older people and is more strongly associated with memory impairment than with cerebrovascular disease (18). Although PSCI is a prognostic factor for disability and is demanding for patients and their caregivers, it is commonly underdiagnosed. Little is known about impairment in global cognition or in specific cognitive domains and rehabilitation outcomes in these patients (48). For example,

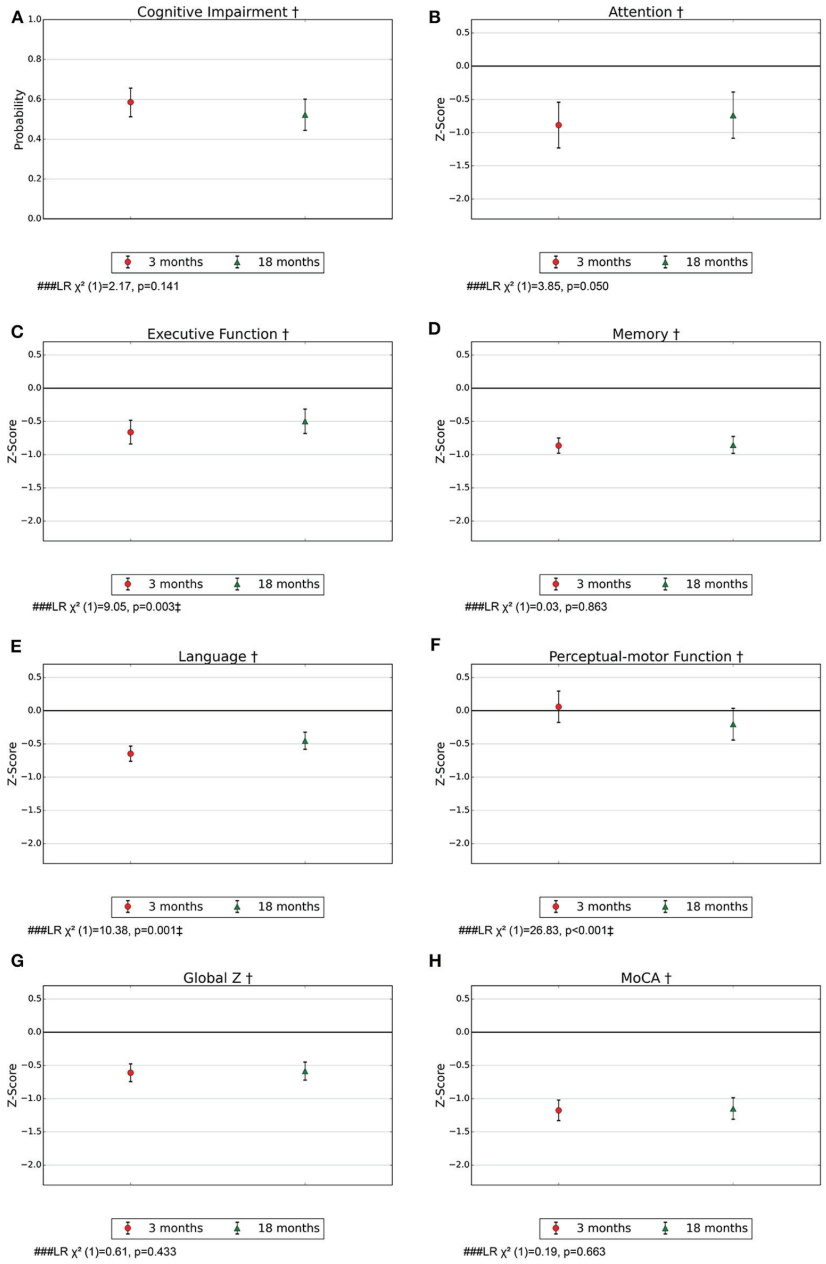

FIGURE 2 | (A–H) Probability for cognitive impairment according to DSM-5 criteria with 95% CI and mean z-score with 95% CI for the cognitive domains at 3 and 18 months post-stroke in model 1. MoCA, Montreal Cognitive Assessment. †Adjusted for age, education, and sex. ### LR $\chi^2(1)$, Likelihood Ratio test model 1 vs a model with only age, education, and sex as confounders, with one degree of freedom; hypothesis test of whether there is an effect of time. ‡$p < 0.01$.

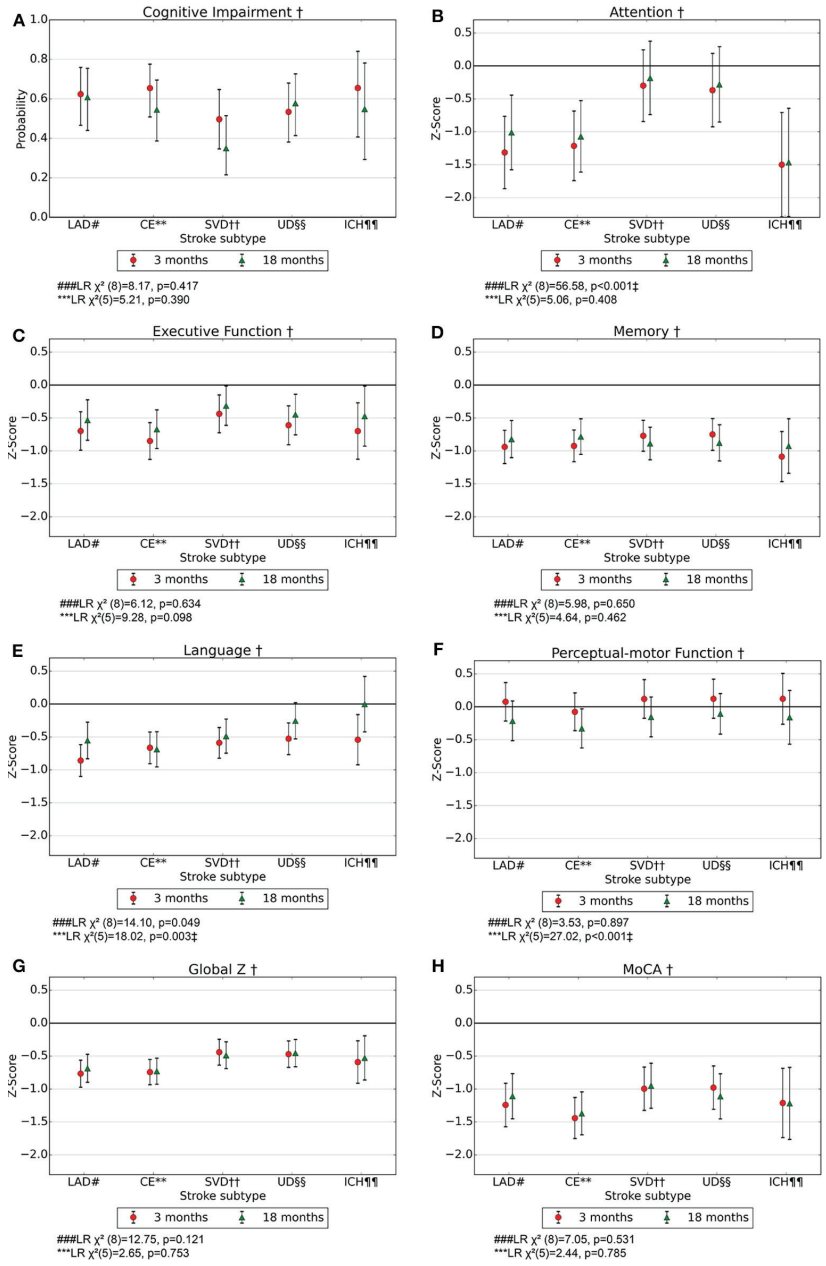

FIGURE 3 | (A–H) Probability for cognitive impairment according to DSM-5 criteria with 95% CI and mean z-score with 95% CI for the cognitive domains at 3- and 18-months post-stroke in model 2. MoCA, Montreal Cognitive Assessment. † Adjusted for age, education, and sex. $^{\#}$LAD, Large artery disease. **CE, Cardiac emboli. ††SVD, Small vessel disease. §§UD, Undetermined and other determined strokes. ¶¶ICH, Intracerebral hemorrhage. $^{\#\#\#}$LR $\chi^2(8)$, Likelihood Ratio test model 1 vs. model 2 with 8 degrees of freedom; hypothesis test of whether there is an effect of stroke subtype. ***LR $\chi^2(5)$, Likelihood Ratio test model 2 vs. model 3 with 5 degrees of freedom; hypothesis test of whether there is an effect of time for at least one stroke subtype. $^{\ddagger}p < 0.01$.

patients with memory impairment may experience challenges in regard to learning and commitment to rehabilitation programs. Moreover, working memory and attention are, among other factors, important for executive function and, thus, for the ability to regain independence in activities of daily living (49–52). As specific cognitive rehabilitation has received little attention, there is a need for randomized clinical trials focusing on rehabilitation for patients with PSCI.

The prognosis over time for global cognition and the cognitive domains is very important for patients, for caregivers, and for the healthcare system in order to personalize rehabilitation and plan for follow-up after stroke. While most studies have found deterioration of cognition over time (4–7), we found improvement between 3 and 18 months for executive function and language for the entire population and for language among ICH patients. One explanation for this could be that the sickest patients were either excluded, lost to follow-up, or unable to complete the entire test battery. Therefore, the study population comprised people who had suffered mild strokes, and the results are valid for patients with mild strokes. Furthermore, additional assessment between 3 and 18 months could have clarified whether we had missed a curve of initial improvement followed by a longer-term cognitive decline (18). Most Norwegian stroke patients receive high-quality rehabilitation, and there is also a focus on secondary prevention of new strokes (46); thus, we are unable to conclude whether the improvements in executive function and language are due to the natural course of brain regeneration or to the effect of medical treatment and/or rehabilitation. The improvement could be explained partially by hemisphere; a greater proportion of impairment in relation to left than right hemisphere strokes, as improvement in executive function and language did not reach statistical significance when controlling for location of symptoms. However, due to a certain amount of missing data for the location of symptoms, we are unable to conclude whether the loss of statistical significance is caused by the variable or by a different population.

Research on the impacts of different etiologic stroke subtypes on the prevalence and severity of PSCI could provide new insights into the underlying mechanisms for the development and course of PSCI and, thereby, on its prevention and treatment. In agreement with several studies but in contrast to others, we found better outcomes among SVD patients than among the other stroke subtypes, as attention was most impaired in relation to cortical infarcts (CE and LAD) (17, 23). We used the TOAST classification (22) to assess the etiologic subtype of ischemic stroke, which, to a small extent, reflects the severity and localization of the stroke and is known to be important for cognitive function (6, 17, 18, 22). When controlling for premorbid function and severity of the stroke, the differences between stroke subtypes diminished, indicating that our findings are partially explained by these. There was a non-significant improvement among SVD patients from 3 to 18 months, which is in contrast to findings by Mok et al., who found that severe SVD contributed to post-stroke dementia after three years (24). Our findings could be a result of too short a follow-up time. Classifying SVD by TOAST is challenging as many patients with other subtypes also have SVD, characterized by white matter hyperintensities (WMHs) seen on MRI. Using MRI provides better visualization of SVD than CT scan, and thus, routine imaging in acute stroke patients will have an impact on the TOAST classification of SVD. In addition, the risk of misclassification bias is greater when measuring SVD by TOAST instead of by WMHs as the intensity of clinical evaluation affects the misclassification bias in TOAST. However, MRI data are less available in large research studies.

The strengths of this study are its large sample size, its multicenter design, and its highly representative group of stroke patients who were assessed both early and later after suffering a stroke. However, participants with the most severe strokes were lost to follow-up or unable to complete the entire test battery and, thereby, less likely to contribute to the analyses. Therefore, the results of our study will be more valid for patients who have experienced mild strokes. Other strengths of the study are the standardization with z-scores and the use of mixed-effects logistic and linear regression models, which minimize selection bias to some extent. The study's major limitation is its lack of its own control group and normative data for Norwegian populations. Second, all domains except one are measured with only one test per domain. Third, in the analyses of stroke subtypes, there is a lack of power, especially for the smallest group, ICH. Fourth, we encountered problems evaluating the results for perceptual-motor function based on copying different figures in the two different versions of MoCA; 7.1 was used at 18 months and 7.3 at 3 months. There was probably also a ceiling effect as most patients had normal scores (14, 17).

CONCLUSION

PSCI is common for all stroke subtypes, with impairment in several cognitive domains a short time as well as a long time after a stroke. We identified improvement over time for executive function and language for the entire stroke population, and language was found to be normalized a long time after a stroke among ICH patients. In regard to attention, we found better outcomes among SVD patients than among patients with cortical strokes. Increased evidence in regard to cognitive symptom profile might be important for personalizing rehabilitation, while stroke subtypes could provide new insights into underlying mechanisms. Further research is needed on pathophysiological mechanisms, prevention, and treatment as well as on relevance for rehabilitation.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of Norwegian regulations and conditions for informed consent. Requests to access the datasets should be directed to IS, ingvild.saltvedt@ntnu.no.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Committee for Medical and Health Research Ethics (REC Nord), UiT Norges arktiske universitet,

Postboks 6050 Langnes, 9037 Tromsø. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IS manages the Nor-COAST study and conceived the idea for the design of the present study. SA and IS were responsible for writing the present report. SA and SL planned the statistical analyses and SA performed them. ME was responsible for the work-up with the categorization according to TOAST modified. RM-K, HI-H, HE, and YS were responsible for collecting data at their respective hospitals and for performing the TOAST classification. All authors interpreted the results and read and approved the final manuscript.

FUNDING

The Nor-COAST study was funded by the Norwegian Health Association, and additional funding is provided by the Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Science, NTNU-Norwegian University of Science and Technology. The authors are funded elsewhere: SA by the Liaison Committee for Education, Research and Innovation in Central Norway.

ACKNOWLEDGMENTS

We thank all the participants for their valuable contributions, as well as the Nor-COAST research group and dedicated study staff at St. Olavs Hospital, Haukeland University Hospital, Ålesund Hospital, Vestre Viken Hospital Trust, Bærum Hospital and Oslo University Hospital, Ullevål. We would also like to acknowledge Prof. Trygve Kristiansen and Associate Professor David Kristiansen, both at the Department of Marine Technology, Faculty of Engineering, NTNU-Norwegian University of Science and Technology, for their valuable contributions of graphing in Python(x,y).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00699/full#supplementary-material

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Conflict of Interest: IS and A-BK have been investigators in the drug trial Boehringer-Ingelheim 1346.0023, and A-BK has also been an investigator for Roche BN29553.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Paper 3

The impact of vascular risk factors on post-stroke cognitive impairment: The Nor-COAST study

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Clinical Trial Registration: ClinicalTrials.gov Identifier: NCT02650531

Keywords: post-stroke cognitive impairment, vascular dementia, stroke, vascular risk factors, cognition

Abstract

Introduction: Post-stroke cognitive impairment (PSCI) is common, but evidence on the impact of vascular risk factors is lacking. We explored the association between pre-stroke vascular risk factors and PSCI and studied the course of PSCI.

Materials and methods: Vascular risk factors were collected at baseline in stroke survivors (n=635). Cognitive assessments of attention, executive function, memory, language, and the Montreal Cognitive Assessment (MoCA) were performed at three and/or 18 months post-stroke. Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS). PSCI was measured with global z; MoCA z-score; and z-score of the four assessed cognitive domains. Mixed-effects linear regression was applied with global z, MoCA z-score, and z-scores of the cognitive domains as dependent variables. Independent variables were the vascular risk factors, time, and the interaction between these. The analyses were adjusted for age, education, and sex.

Results: Mean age was 71.6 years (SD 11.7), 42 % were females and mean NIHSS score at admittance was 3.8 (SD 4.8). Regardless of vascular risk factors, global z, MoCA and all the assessed cognitive domains were impaired at three and 18 months, with MoCA being the most severely impaired. Atrial fibrillation (AF) was associated with poorer language at 18 months and coronary heart disease (CHD) with poorer MoCA at 18 months (LR=12.80,

p=0.002, and LR=8.32, p=0.004, respectively). Previous stroke was associated with poorer global z and attention at three and 18 months (LR=15.46, p<0.001, and LR=16.20, p<0.001). In patients without AF, attention improved from three to 18 months, and in patients without CHD, executive function improved from three to 18 months (LR=10.42, p<0.001, and LR=9.33, p=0.009, respectively).

Discussion: Our findings indicate that a focal stroke lesion may initiate pathophysiological processes leading to global cognitive impairment. The poorer prognosis of PSCI in patients with vascular risk factors emphasizes the need for further research on complex vascular risk factor interventions to prevent PSCI.

Introduction

Post-stroke cognitive impairment (PSCI) is prevalent and reported to be 53.4% in a recent review and meta-analysis of hospital-based studies (1). Recently published results from the STROKOG consortium showed global impairment in 44% of patients a short time after a stroke, with 30% to 35% of impairments in the following individual domains: attention and processing speed, memory, language, perceptual-motor function, and frontal executive function (2).

Knowledge about vascular risk factors as predictors of PSCI and its trajectories in patients with vascular risk factors is important because of the opportunity for both primary and secondary prevention strategies to be applied to intervene in these factors, and studies have shown contradicting results (3). Hypertension is a known risk factor for dementia; however, the knowledge about its association with PSCI is scarce (2-5). Mid-life hypertension and smoking are associated with cognitive decline, while late-life hypertension alone might not be associated and may even be protective against dementia (3, 4, 6, 7). The STROKOG consortium found associations between cognition and diabetes mellitus, previous stroke,

hypertension, atrial fibrillation, and smoking, early after a stroke (2). Another recent study showed an association between cognition and blood pressure levels early after a stroke; however, these findings were explained by sociodemographic and clinical factors (8).

In a systematic review and meta-analysis of studies with both short- and long-term follow-ups after stroke, diabetes mellitus, atrial fibrillation, and previous stroke were shown to be predictors of post-stroke dementia (9). In the Oxford Vascular Study, post-stroke dementia was associated with previous stroke and diabetes mellitus in the long term following a stroke (10).

The aim of this study was to explore the association between pre-stroke vascular risk factors and cognitive impairment at 3 and 18 months post-stroke within both global cognitive measures and different cognitive domains. We also aimed to study the course of PSCI in patients with and without pre-stroke vascular risk factors.

Methods

The study is part of the Norwegian Cognitive Impairment After Stroke (Nor-COAST) study, a multicenter prospective cohort study that recruited patients in five Norwegian stroke units from May 2015 through March 2017 (11-13). Inclusion criteria were hospitalization with acute ischemic or hemorrhagic stroke within one week after symptom presentation, fluency in a Scandinavian language, and age > 18 years. The exclusion criterion was an expected survival of < three months. The patients gave informed written consent for participation, and when a person was unable to do so, informed written consent was provided by his or her next of kin. The study was approved by the Regional Committee for Medical and Health Research Ethics (REC Nord 2015/171) and registered in ClinicalTrials.gov (NCT02650531). Further details are described in the previously published protocol article for the Nor-COAST study (11).

Clinical assessments

Demographic characteristics and vascular risk factors were collected from the patients' medical records. Hypertension was defined as pre-stroke use of antihypertensive medication or use of antihypertensive medication at discharge, hypercholesterolemia as pre-stroke use of lipid-lowering medication, smoking as current smoking, and diabetes mellitus as a history of diabetes mellitus noted in the medical records and/or pre-stroke use of antidiabetic medication and/or HbA1c≥48mmol/mol at admittance for stroke and/or use of antidiabetic medication at discharge. Atrial fibrillation included a history of permanent or paroxysmal atrial fibrillation or atrial flutter detected by electrocardiogram and described in the medical records and/or detected by electrocardiogram and/or telemetry during the hospital stay. Coronary heart disease was defined as a history of coronary heart disease according to the medical records, and previous stroke was defined as a history of previous stroke based on the medical records (12, 13). Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS) at admission (14). Etiology of ischemic strokes was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (15). TOAST modification was performed where the undetermined etiology of TOAST probable (15); first was classified as TOAST possible (15), then as TOAST likely (16) where patients with findings of carotid stenosis <50% were classified as having large artery disease (13).

Cognitive and functional assessments

Cognitive function at 3- and 18-month follow-ups was assessed by a trained study staff using a cognitive test battery based on the National Institute of Neurological Disorders and Stroke–Canadian Stroke Network (NINDS–CSN) Harmonization Standards (17) adapted to validated cognitive tests in Norwegian (12, 13). The test battery comprised the Trail Making Tests Part A (TMT-A) and Part B (TMT-B) (time to completion) (18), Word List Memory and Recall Test and Verbal Fluency Test Category (animals) from the Consortium to Establish a Registry for

Alzheimer's Disease (CERAD) battery (19, 20), the Verbal Fluency Test Letter (FAS) (21, 22), and the Montreal Cognitive Assessment (MoCA) (23), version 7.3 at 3-month follow-up and version 7.1 at 18-month follow-up. To minimize practice effect, the letter F in Verbal Fluency Test Letter (FAS) was retrieved from the MoCA. In addition, cognitive function was assessed with the Global Deterioration Scale (GDS) (24). Activities of daily living (ADL) were assessed with the Barthel Index (BI) (25) and global functional outcome with the Modified Rankin Scale (mRS) (26). GDS, ADL and BI were performed at baseline and at 3- and 18 months follow-ups. Baseline assessments were performed during the hospital stay; 3- and 18-month follow-ups were performed at the hospitals' outpatient clinics. For patients unable to attend follow-up assessments, telephone interviews with the patients, their caregivers, or nursing home staff were conducted for assessment using the mRS, BI, GDS, and the Telephone MoCA (T-MoCA) (27).

Cognitive outcomes

Cognitive outcome assessments of the four domains included complex attention measured by the TMT-A, executive function by the TMT-B and FAS, memory by the Word List Delayed Recall, and language by the Verbal Fluency Test Category (12, 13, 28-31). Global cognition was also measured using the MoCA.

Statistics

Z-scores normalized by mean and standard deviation (SD) of the normative data were derived from the raw scores of the cognitive tests, as described in Supplementary Table S1 (12, 13). PSCI was measured by global z, MoCA z-score, and z-scores of the four cognitive domains assessed. Global z was defined as the average of the four cognitive domains, which were measured by the z-score of the single completed cognitive test, except for executive function, measured by two tests where the average z-score was used. The z-scores were implemented with lower z-scores indicating poorer outcomes.

PSCI was analyzed with mixed-effects linear regression with global z, MoCA, and z-scores of four cognitive domains – attention, executive function, memory, and language – as dependent variables one at a time. The independent variables were the vascular risk factors (hypertension, hypercholesterolemia, smoking, diabetes mellitus, atrial fibrillation, coronary heart disease, previous stroke) examined one at a time, follow-up time and the interaction between the vascular risk factor and follow-up time (model 1). We adjusted for age, education, and sex. The results for model 1 were presented as the estimates with mean and 95% confidence intervals (CI). In order to perform a hypothesis test for the effect of each vascular risk factor and follow-up time in model 1, the analyses were also performed with follow-up time (model 2) as well as with the vascular risk factor (model 3) as the independent variable. Hypothesis tests for the effects of vascular risk factors and follow-up times in model 1 were conducted by likelihood ratio tests comparing model 1 and model 2, as well as comparing model 1 and model 3. These results were presented as the test statistics with degrees of freedom and p-value. Mixed-effects linear regression models were preferred since a mixed-effects linear regression model minimizes bias by handling missing data in an appropriate way under a missing at random assumption, while a complete case analysis would have been unbiased only under the stricter missing completely at random assumption (32). There were approximately 5-25% missing for the variables for PSCI, however, this is handled appropriate with mixed-effects linear regression models. Imputation of outcome measures was done as described in Supplementary section.

Sensitivity analyses with the exclusion of patients deceased at 18 months, as well as with exclusion of pre-stroke dementia defined as pre-stroke GDS 4–7, were performed to explore whether this affected the outcome. To assess the robustness of the results, we also performed unadjusted analyses and analyses adjusted for age, education, sex, pre-stroke mRS, and NIHSS altogether. An illustration of the statistical model for the mixed-effects linear regressions for model 1 is presented in Supplementary Figure S1.

Vascular risk factors, follow-up time, and sex were analyzed as categorical variables, while global z, MoCA z-score, z-scores of the cognitive domains, age, education, mRS, and NIHSS were analyzed as continuous variables. Complete case analyses were used for vascular risk factors, age, education, and sex, while available case analyses were used for global z, MoCA, z-scores of the cognitive domains, pre-stroke mRS, and NIHSS. Confounders were included as fixed effects, while subject and hospital were included as random effects.

Due to multiple hypotheses, we considered two-tailed p-values <0.01 as statistically significant. Data were analyzed using SPSS 25 and STATA 16.0.

Results

Baseline characteristics

Of the 815 patients enrolled in the Nor-COAST study, 700 were assessed at the 3 month follow-up and 599 assessed at the 18-month follow-up. Of the 599 patients assessed at the 18-month follow-up, 10 were not assessed at the 3 month follow-up. Of the 710 patients assessed at either 3 or 18 months, 75 were excluded due to missing cognitive data, and this resulted in a study sample of 635 patients (Figure 1). Of the 635 patients enrolled in the study, 21 were deceased at 18 months.

The mean age of the patients was 71.6 years (SD 11.7); 42% were females; the mean for years of education was 12.4 years (SD 3.8); and mean NIHSS score at admittance was 3.8 (SD 4.8). The baseline characteristics of the patients are shown in Table 1. Excluded patients had a mean age of 80.2 years (SD 9.0), 55% were females, their mean education was 10.3 years (SD 3.0), and their mean NIHSS score at admittance was 7.7 (8.5). The numbers of patients completing cognitive tests for the cognitive domains, with mean z-score of the tests and proportions with z-score <-1.5, are shown in Supplementary Table S2.

Impairments in global cognition and the cognitive domains

Regardless of vascular risk factors, the global scores and the four cognitive domains (attention, executive function, memory, language) were impaired in terms of z-score < 0 at 3 and 18 months. In patients with vascular risk factors, MoCA and attention were the most severely impaired, while language was the least severely impaired. In contrast, patients without vascular risk factors showed a more equally distributed severity of impairments across global measures and cognitive domains (Figures 2 and 3, panels A–G; Supplementary Table S3).

Differences in cognitive function

Atrial fibrillation was associated with poorer language at 18 months, and coronary heart disease was associated with poorer performance on the MoCA at 18 months (Figure 3, panel E; Figure 2, panel F; and Supplementary Table S3). Previous stroke was associated with poorer global z and attention at both 3 and 18 months (Figures 2 and 3, panel G; Supplementary Table S3).

Course of cognition

In patients without atrial fibrillation, attention improved from 3 to 18 months, and in patients without coronary heart disease, executive function improved from 3 to 18 months (Figure 3, panels E and F; Supplementary Table S3). Language improved from 3 to 18 months in patients with hypercholesterolemia, diabetes mellitus, or coronary heart disease and in non-smokers and patients without hypertension, atrial fibrillation, or previous stroke (Figure 3, panel A–G; Supplementary Table S3).

Sensitivity analyses

The results were essentially the same for sensitivity analyses; for unadjusted analyses; analyses excluding patients deceased at 18 months (n=21) adjusted for age, education, and sex; analyses excluding patients with pre-stroke dementia (n=25) adjusted for age, education,

and sex; and analyses adjusting for age, education, sex, pre-stroke mRS and NIHSS altogether (Supplementary Figures S2–S9; Supplementary Tables S4–S7). The exceptions were that the improvement in attention for patients without atrial fibrillation did not reach statistical significance for exclusion of pre-stroke dementia; the improvement in executive function in patients without coronary heart disease did not reach statistical significance for analyses with the exclusion of deceased patients, exclusion of pre-stroke dementia, and analyses adjusted for age, education, sex, pre-stroke mRS and NIHSS; the effect of previous stroke did not reach statistical significance for global z for analyses adjusted for age, education, sex, pre-stroke mRS and NIHSS; the improvement in language in non-smokers did not reach statistical significance for analyses with the exclusion of deceased patients and analyses adjusted for age, education, sex, pre-stroke mRS and NIHSS.

The numbers of patients with the different vascular risk factors included in the analyses are shown in Supplementary Table S3.

Discussion

We identified impairments in the global measures and all the assessed cognitive domains regardless of pre-stroke vascular risk factors in this observational study of stroke survivors. Coronary heart disease and previous stroke were associated with poorer global cognition, previous stroke with poorer attention, and atrial fibrillation with poorer language. We found improvement in attention in patients without atrial fibrillation and in executive function in patients without coronary heart disease.

Our findings of poorer cognition in patients with atrial fibrillation, coronary heart disease, and previous stroke align with Lo et al.'s findings of associations between cognition and diabetes mellitus, previous stroke, hypertension, atrial fibrillation, and smoking, respectively (2). We were unable to measure exposure to pre-stroke vascular risk factors over time, and

this could explain our lack of a finding for hypertension in our study population with its relatively high average age. Although it has been shown that mid-life hypertension and smoking are associated with cognitive decline, late-life hypertension alone might not be associated (3, 4, 6, 7). Atrial fibrillation, coronary heart disease, and previous stroke can be seen as risk factors that have already exerted an influence on the functioning of the heart, brain, or other organs, indicating a long-lasting and severe exposure to vascular risk factors that may explain our findings.

Although a stroke lesion is focal, we found the most severe global cognitive impairment in patients with pre-stroke vascular risk factors, which might indicate that vascular risk factors contribute to decline in global, rather than in focal, cognitive function. The MoCA, followed by attention, were the most severely impaired regardless of vascular risk factors. The MoCA measures a broad spectrum of domains and is a global assessment (23). Attention should probably be seen as an expression of global rather than focal cognition (33). Therefore, our results emphasize the global cognitive impairment seen after a stroke. Lacking a stroke-free control group, we were unable to evaluate whether cognition is more severely impaired in those who have suffered a stroke than in the background population. A recent study found no differences in cognitive function between patients with minor stroke and those with myocardial infarction one year after the vascular event (34). Additionally, in our study population comprising both first-ever and recurrent strokes, an evaluation of the effects of recurrent strokes is limited.

Memory was severely impaired regardless of vascular risk factors, with no progression over time, which may indicate a neurodegenerative component compatible with Alzheimer's disease (AD), especially for the oldest age groups, as AD is more strongly associated with memory impairment than vascular cognitive impairment is (3). As neurodegenerative processes typically develop slowly, we might have captured a decline in memory with a

longer follow-up time. Although the results for both global cognition and cognitive domains remained almost the same when patients with pre-stroke dementia were excluded, we were unable to determine the impact of neurodegenerative components on PSCI. Vascular factors are also shown to be established risk factors for cognitive decline in Alzheimer's disease (35), and the global impairments seen in AD might be related to vascular risk factors.

Poorer language skills were identified in patients with atrial fibrillation, which is probably related to focal cortical lesions in the dominant hemisphere (2). Regardless of vascular risk factors, there was an improvement in language from 3 to 18 months, which aligns with the findings of Maas et al. of good prognoses in patients with post-stroke aphasia (36). The improvement we found is more likely attached to the improvement in language in the entire stroke population we have shown in a previous work (13). Most patients in Norway with aphasia after suffering a stroke receive speech rehabilitation from a speech therapist according to the Norwegian guidelines for stroke treatment (37). However, we had no data on rehabilitation and we were unable to conclude whether the improvement was due to natural brain regeneration or rehabilitation.

In previous publications, we have shown that about half of stroke survivors experience PSCI, and most have mild neurocognitive disorders (12, 13). We found improvement in attention and executive function in patients without vascular risk factors. Studies focusing on the prevention of PSCI and improvement in PSCI and studies designed to prevent deterioration of PSCI over time are critically important. Cochrane reviews have identified a lack of knowledge on the effects of cognitive rehabilitation for attention and executive function in stroke populations and call for more research to clarify the impact of cognitive rehabilitation on PSCI (38, 39). Our findings of improvements in a subgroup support the need for such research.

Poorer prognoses in patients with pre-stroke vascular risk factors indicate a need for a preventive vascular approach to keep these risk factors at a minimum. There is a lack of knowledge about which vascular risk factors are most important for the prognosis of PSCI, and intervention on single vascular risk factors may not be effective in preventing PSCI. In both a general and a stroke population, the presence of several vascular risk factors is shown to be associated with a higher risk of dementia than only one or two such factors (40-42).

However, as previous randomized controlled studies with low power and short follow-up time (43, 44), have failed to show effect on cognitition after stroke, the role of multifactorial interventions in preventing PSCI is still unclear. A systematic review concluding that recurrent stroke rather than vascular risk factors is the explanation for incident dementia (41, 45) aligns with our findings of the most severe impairments in global cognitive measures and attention in patients with previous stroke. This emphasizes the critical need to prevent recurrent stroke in order to prevent cognitive impairment.

This study has several strengths. Its first is a large sample size and multicenter design with longitudinal cognitive assessments of most cognitive domains in both the early period and long-term after a stroke. A second strength is a study population with similar baseline characteristics to a Norwegian stroke population, although patients with more severe strokes were unable to complete the entire test battery and, thereby, less likely to contribute to this study's findings (46, 47). Third, standardization with z-scores and minimization of selection bias by using mixed-effects linear regression models.

The study also has several limitations. First, the lack of a control group results in a descriptive study not designed to study causality, where adjustment for several confounders could result in overadjustment (48). Second, we lack Norwegian normative data. Third, all the cognitive domains except executive function are measured by only one cognitive test, and

a cognitive test for visuospatial function beyond this subdomain in MoCA is lacking. Fourth, the inclusion of patients in the acute phase of stroke when most of the population have temporarily elevated blood pressure limited the definition of hypertension to "use of antihypertensive medication," and this might introduce a misclassification bias. The result, therefore, should be interpreted with caution.

Conclusion

Our findings of severely impaired global cognitive function indicate that a focal stroke lesion may initiate pathophysiological processes leading to global cognitive impairment. The poorer prognoses of PSCI in patients with vascular risk factors emphasize the need for further research focusing on the effectiveness of a complex intervention targeting all risk factors to prevent PSCI, preferably with a randomized controlled design.

Acknowledgments

We thank all patients for their contributions as well as the Nor-COAST research group and the dedicated study staff at St. Olavs hospital, Haukeland University Hospital, Ålesund Hospital, Vestre Viken Hospital Trust, and Oslo University Hospital. We also thank Jonas Ravndal Kildal for contributing with graphing in Python (x,y).

Sources of funding

The Nor-COAST study is funded by the Norwegian Health Association, and additional funding was provided by the Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Science, NTNU-Norwegian University of Science and Technology. The authors are funded elsewhere: SA by the Liaison Committee for Education, Research and Innovation in Central Norway.

Conflict of Interest

IS and ABK have been investigators in the drug trial Boehringer-Ingelheim 1346.0023, and ABK

has also been an investigator for Roche BN29553; otherwise, the authors declare that they have no competing interests.

Authors' contributions

IS manages the Nor-COAST study and developed the idea for the design of the present study. SA, IS, and BF were responsible for the analysis plan and writing the present report. SA and SL planned the statistical analyses and SA performed them. MNG was responsible for the workup with categorization of the vascular risk factors. RMK, HIH, and HE were responsible for collecting data at their respective hospitals. ABK and RSE contributed to the analysis plan. All authors interpreted the results, read, and approved the final manuscript.

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Figures and tables

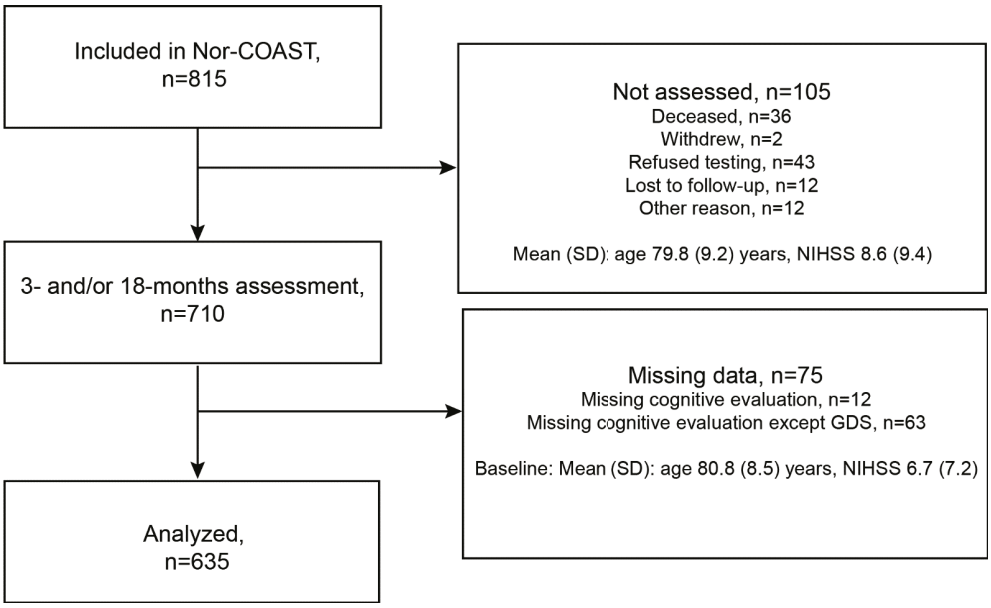


Figure 1. Flow chart of patients included in the study

Table 1. Baseline characteristics				
Demographics		N = 635		
	Mean age, years (SD)		71.6	(11.7)
	Female sex, n (%)		266	(42)
	Mean education, years (SD)		12.4	(3.8)
Vascular risk factors, n (%)				
	Hypertension, n (%)	N = 635	460	(72)
	Hypercholesterolemia, n (%)	N = 635	216	(34)
	Smoking, n (%)	N = 631	121	(19)
	Diabetes mellitus, n (%)	N = 635	145	(18)
	Mean BMI, kg/m^2 (SD)	N = 600	26.1	(4.2)
	Atrial fibrillation, n (%)	N = 635	145	(23)
	Coronary heart disease, n (%)	N = 635	112	(18)
	Previous stroke, n (%)	N = 635	112	(18)
Stroke subtype, n (%)		N = 635		
	Cerebral infarction		582	(92)
	Cerebral hemorrhage		53	(8.3)
TOAST classification*, n (%)		N = 564		
	Large-vessel disease		140	(25)
	Cardioembolic disease		153	(27)
	Small-vessel disease		135	(24)
	Other etiology		17	(3.0)
	Undetermined etiology		119	(21)
Thrombolysis, n (%)		N = 629	153	(24)

Thrombectomy, n (%)		N = 635	12	(1.9)
Pre-stroke GDS (1–7), n (%)		N = 629		
	GDS = 1–2 (Normal cognition)		568	(90)
	GDS = 3 (Mild Neurocognitive Disorder)		36	(5.7)
	GDS = 4–7 (Major Neurocognitive Disorder)		25	(4.0)
Assessments				
	NIHSS (0–42) at admittance, mean (SD)	N = 618	3.8	(4.8)
	Pre-stroke mRS (0–6), mean (SD)	N = 631	0.78	(1.0)
	mRS (0–6) at discharge, † mean (SD)	N = 633	2.1	(1.3)
	Barthel Index (0–100) at discharge, † mean (SD)	N = 633	89	(19)

SD = Standard deviation, BMI = Body mass index, TIA = Transient ischemic attack, TOAST = Trial of Org 10172 in Acute Stroke Treatment, GDS = Global Deterioration Scale, NIHSS = National Institutes of Health Stroke Scale, mRS = modified Rankin Scale

*TOAST modification (13); Undetermined etiology of TOAST probable (15), first classified as TOAST possible, (15) then as TOAST likely (16) where patients with findings of carotid stenosis <50% were classified as large artery disease. Finally, TOAST modified was developed by merging TOAST probable, TOAST possible, and TOAST likely.

†at discharge or day 7 if length of stay extends beyond 7 days

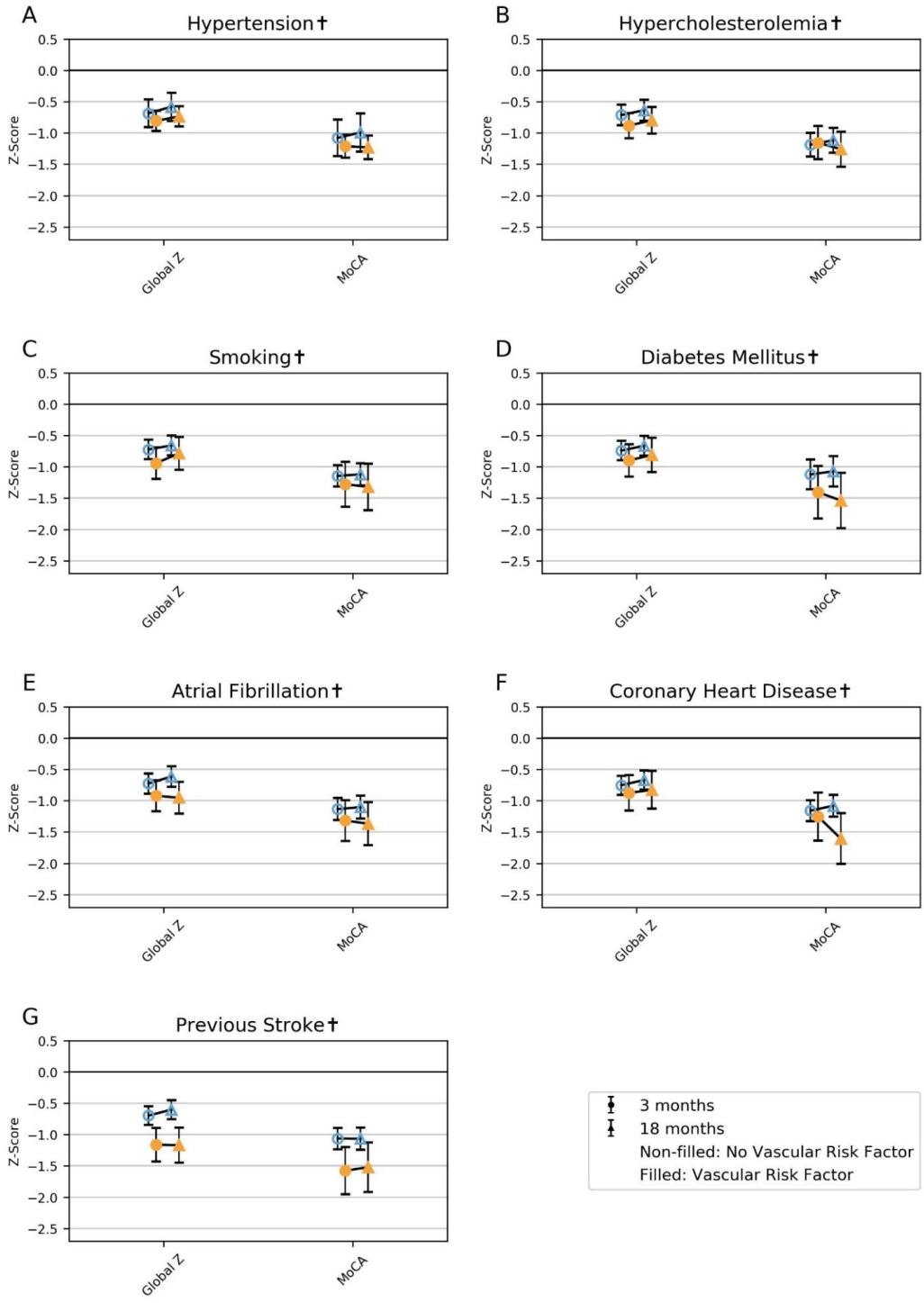

A
Hypertension†
B
Hypercholesterolemia†
C
Smoking†
D
Diabetes Mellitus†
E
Atrial Fibrillation†
F
Coronary Heart Disease†
G
Previous Stroke†
Z-Score
0.5
0.0
−0.5
−1.0
−1.5
−2.0
−2.5
Global Z
MoCA
3 months
18 months
Non-filled: No Vascular Risk Factor
Filled: Vascular Risk Factor

Figure 2. Mean z-score with 95% CI for the global cognitive measures for the different vascular risk factors at 3- and 18-months post-stroke in model 1

MoCA = Montreal Cognitive Assessment

†=Adjusted for age, education, and sex

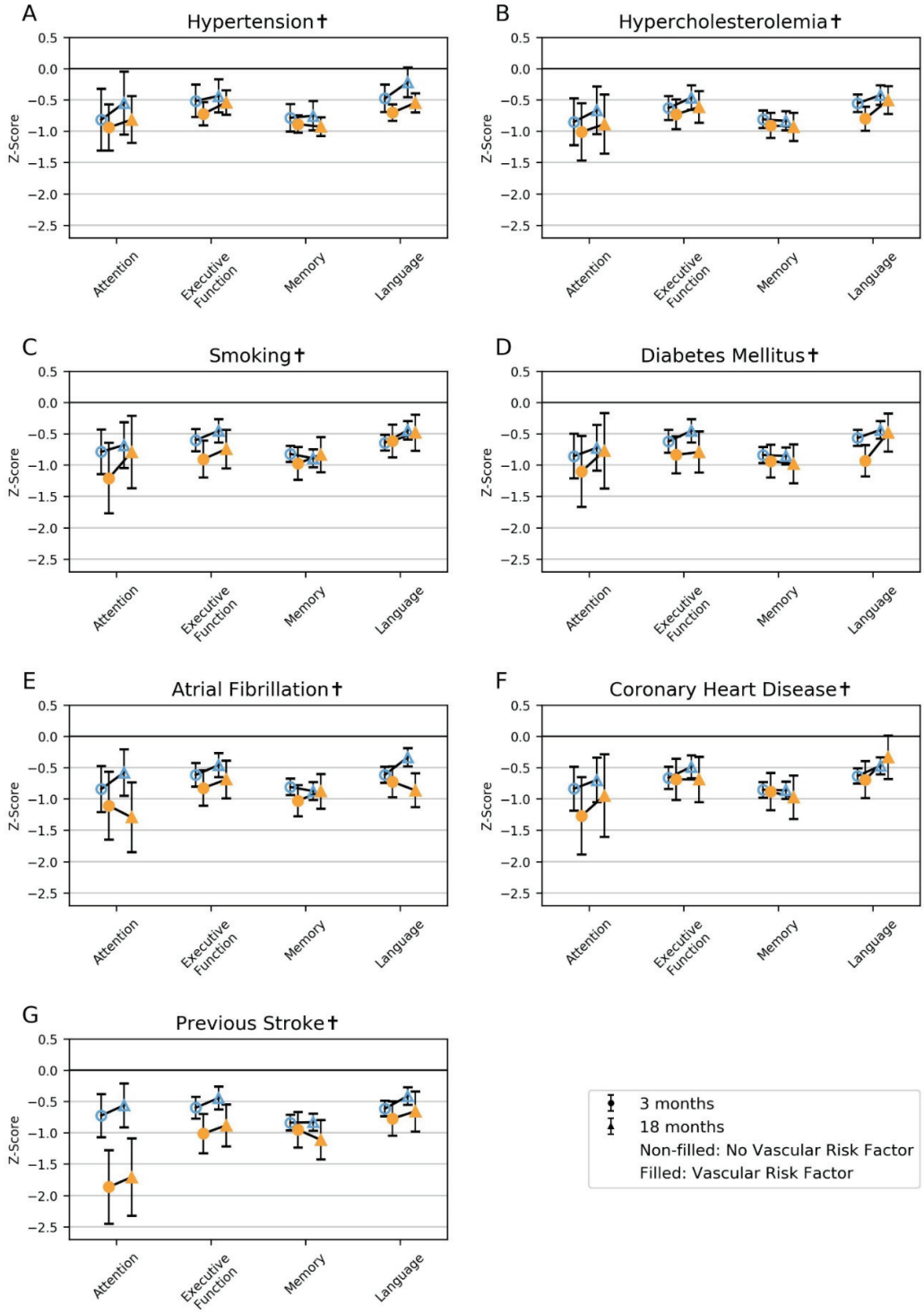

A
Hypertension†
B
Hypercholesterolemia†
C
Smoking†
D
Diabetes Mellitus†
E
Atrial Fibrillation†
F
Coronary Heart Disease†
G
Previous Stroke†
Z-Score
0.5
0.0
−0.5
−1.0
−1.5
−2.0
−2.5
Attention
Executive Function
Memory
Language
3 months
18 months
Non-filled: No Vascular Risk Factor
Filled: Vascular Risk Factor

Figure 3. Mean z-score with 95% CI for the cognitive domains for the different vascular risk factors at 3- and 18-months post-stroke in model 1

†=Adjusted for age, education, and sex

Supplementary Material Paper 1

SUPPLEMENTARY MATERIAL

Impact of different methods defining post-stroke neurocognitive disorder: The Nor-COAST study

Definition of vascular risk factors

Hypertension was defined as pre-stroke use of antihypertensive medication. Hypercholesterolemia was defined as pre-stroke use of lipid-lowering medication or total cholesterol ≥6.2 mmol/L and/or low density lipoprotein ≥4.1 mmol/L at hospital admittance for stroke [1, 2]. Diabetes mellitus was defined as a history of diabetes mellitus from medical records and/or pre-stroke use of antidiabetic medication and/or HbA1c≥6.5% at admittance for stroke. Coronary heart disease was defined as a history of coronary heart disease according to medical records. Atrial fibrillation was defined as a history of permanent or paroxysmal atrial fibrillation or atrial flutter detected in electrocardiogram and described in medical records and/or permanent or paroxysmal atrial fibrillation or atrial flutter detected in electrocardiogram and/or telemetry during hospital stay. Previous stroke or TIA was defined as a history of previous stroke or TIA from medical records.

Statistics

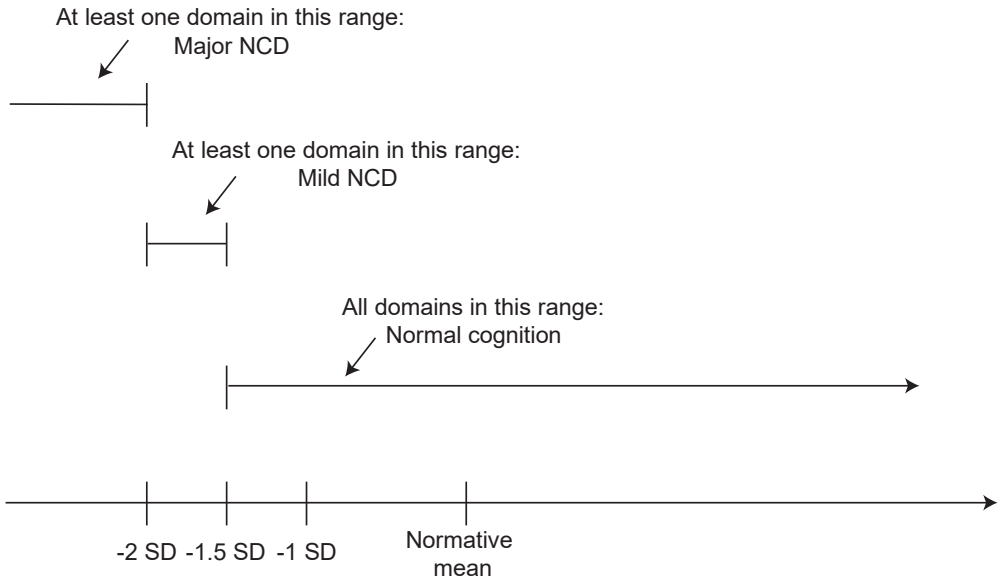
The strength of agreement for Cohen's kappa was interpreted as suggested by Altman [3] as poor (<0.20), fair (0.21 to 0.40), moderate (0.41 to 0.60), good (0.61 to 0.80), very good (>0.80). For a 2x2 table, positive agreement is defined as $n_{22}/[n_{22}+(n_{12}+n_{21})/2]$, and negative agreement is defined as $n_{12}/[n_{12}+(n_{12}+n_{21})/2]$, as row 1 and column 1 in the data represent negative ratings and row 2 and column 2 represent positive ratings [4]. Positive and negative ratings have a similar interpretation as sensitivity and specificity for a diagnostic test [4].

Imputation

Single items missing in the Montreal Cognitive Assessment (MoCA) [5] total scores were imputed by the mean of the available MoCA items for the same participant; this was done for one participant with one missing item. For the 21 participants assessed by Telephone-MoCA [6], 8 of 30 points that could not be assessed by telephone were imputed by the mean of the available MoCA items for the same participant. Among them, three had one missing item in addition to the 8 points not assessed. For the 13 participants able to start but not completing the Trail Making Test A [7] due to cognitive impairment and for the 88 participants starting but not complete the Trail Making Test B [7] due to cognitive impairment, the tests' results were set as equal to the time of the interruption of the tests, which was 300 seconds for both [8]. Other missing data were not imputed but treated as missing. Imputation was done according to the plan developed before the analysis was performed.

Supplemental figures and tables

Model A*



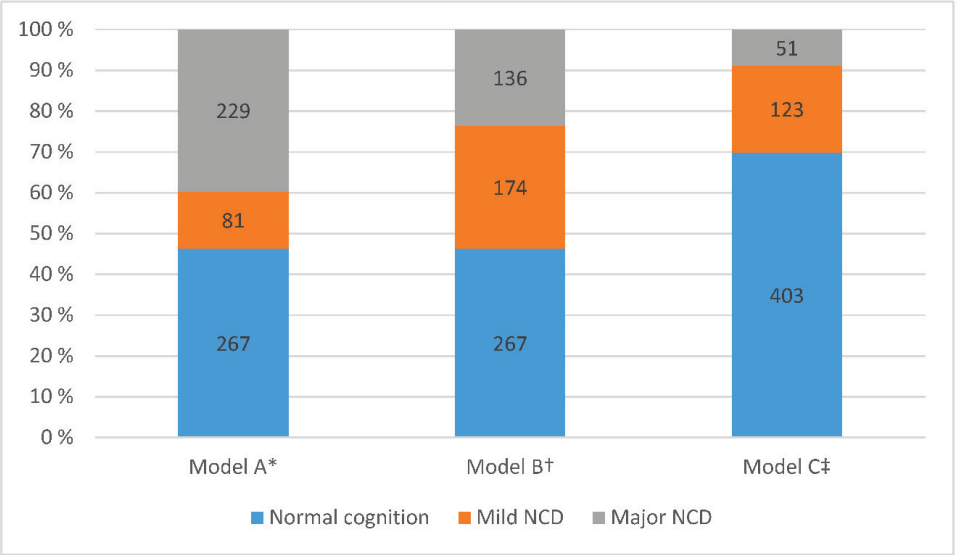
Supplementary Figure S1. Illustration of Model A based on neuropsychology alone.

NCD = Neurocognitive disorder, SD = Standard deviation

*Model A: Normal cognition defined as score ≥ -1.5 SD for all cognitive domains; mild NCD defined as score in the range of -1.5 to -2 SD for at least one cognitive domain; and major NCD defined as a score ≤ -2 SD for at least one cognitive domain.

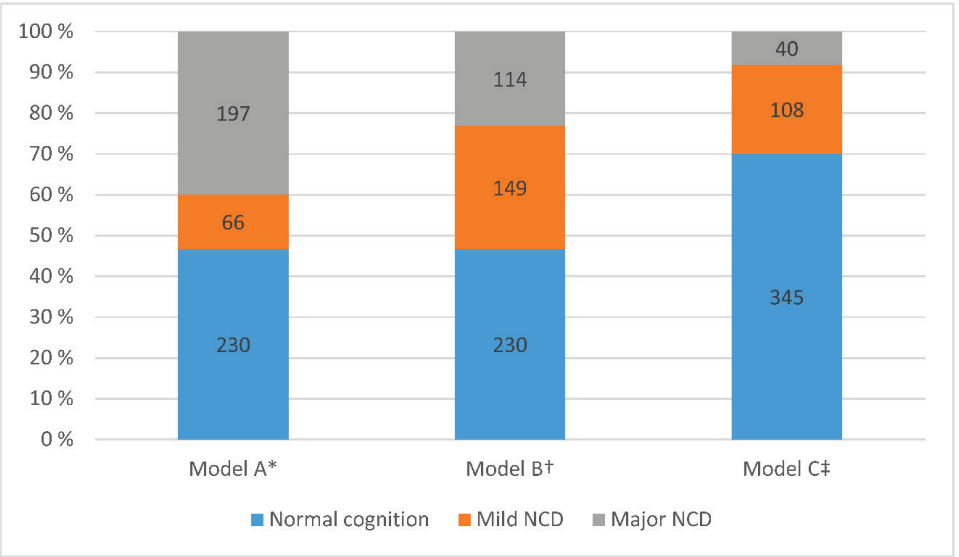
Supplementary Table S1. Normative data for the neuropsychological test battery	
Neuropsychological Test	**Normative data**
Trail Making Test A (TMT-A) and B (TMT-B)	For participants ages 18–59 years or >80 years: Trail Making Test A and B: Normative data stratified by age and education [9] For participants ages 60–79 years: Age-, Sex-, and Education-Specific Norms for an Extended CERAD Neuropsychological Assessment Battery–Results From the Population-Based LIFE-Adult-Study [10]
Verbal Fluency Test Letters (FAS)	Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming [11]
Verbal Fluency Test Category (animals)	For participants aged 18–59 years or >80 years: Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming [11] For participants ages 60–79 years: Age-, Sex-, and Education-Specific Norms for an Extended CERAD Neuropsychological Assessment Battery–Results From the Population-Based LIFE-Adult-Study [10]
Word List Recall	For participants ages < 60 years: Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery [12] For participants ages 60–79 years: Age-, Sex-, and Education-Specific Norms for an Extended CERAD Neuropsychological Assessment Battery–Results From the Population-Based LIFE-Adult-Study [10] For participants ages > 80 years: CERAD-NP battery: Age-, gender- and education-specific reference values for selected subtests. Results of the German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe) [13]
Montreal Cognitive Assessment (MoCA)	Montreal Cognitive Assessment: Normative data from a large Swedish population-based cohort [14]

Supplementary Table S2. Comparison of Model A and Model B for the three different levels of Model C				
Model C = normal cognition				
Model B	**Model A** Normal cognition, n	Mild NCD, n	Major NCD, n	Total, n (%)
Normal cognition, n	242	0	0	241(60)
Mild NCD, n	0	50	71	122 (30)
Major NCD, n	0	7	33	40 (10)
Total (n, %)	241 (60)	55 (14)	107 (26)	403
Model C = mild NCD				
Model B	**Model A** Normal cognition, n	Mild NCD, n	Major NCD, n	Total, n (%)
Normal cognition, n	22	0	0	22 (17)
Mild NCD, n	0	10	41	51 (40)
Major NCD, n	0	9	46	55 (43)
Total, n (%)	22 (17)	19 (15)	87 (68)	128
Model C = major NCD				
Model B	**Model A** Normal cognition, n	Mild NCD, n	Major NCD, n	Total, n (%)
Normal cognition, n	3	0	0	3 (4.4)
Mild NCD, n	0	0	2	2 (2.9)
Major NCD, n	0	7	56	63 (93)
Total, n (%)	3 (4.4)	7 (10)	58 (85)	68
NCD = Neurocognitive disorder				



Supplementary Figure S2. Proportion of participants with normal cognition, mild- and major NCD three months post-stroke; participants with pre-stroke major NCD[§] excluded, N=577.

NCD = Neurocognitive disorder
*Model A: Normal cognition defined as score ≥-1.5 SD for all cognitive domains; mild NCD defined as score in the range of -1.5 to -2 SD for at least one cognitive domain; and major NCD defined as a score ≤ -2 SD for at least one cognitive domain.
†Model B: Normal cognition defined as score ≥-1.5 SD for all cognitive domains; NCD defined as score <-1.5 SD for at least one cognitive domain; major NCD defined as having post-stroke NCD with dependency in instrumental activities of daily living (I-ADL), defined as the need for assistance in managing one's finances and/or medications. Mild NCD was post-stroke NCD without impairments in I-ADL.
‡Model C: Evaluation based on Global Deterioration Scale (GDS); normal cognition defined as a GDS score of 1–2; mild NCD defined as a GDS score of 3; and major NCD defined as a GDS score of 4–7.



Supplementary Figure S3. Proportion of participants with normal cognition, mild- and major NCD three months post-stroke; participants with previous stroke excluded, N=493.

NCD = Neurocognitive disorder
*Model A: Normal cognition defined as score ≥-1.5 SD for all cognitive domains; mild NCD defined as score in the range of -1.5 to -2 SD for at least one cognitive domain; and major NCD defined as a score ≤ -2 SD for at least one cognitive domain.
†Model B: Normal cognition defined as score ≥-1.5 SD for all cognitive domains; NCD defined as score <-1.5 SD for at least one cognitive domain; major NCD defined as having post-stroke NCD with dependency in instrumental activities of daily living (I-ADL), defined as the need for assistance in managing one's finances and/or medications. Mild NCD was post-stroke NCD without impairments in I-ADL.
‡Model C: Evaluation based on Global Deterioration Scale (GDS); normal cognition defined as a GDS score of 1–2; mild NCD defined as a GDS score of 3; and major NCD defined as a GDS score of 4–7.

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Supplementary Material Paper 2

Supplementary Material

1 Definitions of vascular risk factors

Hypertension was defined as pre-stroke use of antihypertensive medication.

Hypercholesterolemia was defined as pre-stroke use of lipid-lowering medication or total cholesterol ≥6.2 mmol/L and/or low-density lipoprotein ≥ 4.1 mmol/L at hospital admittance for stroke (1, 2).

Diabetes mellitus was defined as a history of diabetes mellitus identified in the patient's medical records and/or pre-stroke use of antidiabetic medication and/or HbA1c ≥ 6.5% at admittance for stroke.

Coronary heart disease was defined as a history of coronary heart disease according to medical records.

Atrial fibrillation was defined as a history of permanent or paroxysmal atrial fibrillation or atrial flutter detected on an electrocardiogram and described in medical records and/or permanent or paroxysmal atrial fibrillation or atrial flutter detected on an electrocardiogram and/or telemetry during hospital stay.

Previous stroke or TIA was defined as a history of previous stroke or TIA identified in medical records.

2 TOAST classification as TOAST modified

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (3), used to classify etiological stroke subtypes in the present study, generates a large group in the category undetermined aetiology (UD) (4-6). The TOAST classification is conservative and may underscore clinically relevant risk factors for ischemic stroke, e.g., carotid stenosis is a risk factor even if it is under 50%, which is the limit set by the TOAST criteria for classification as large artery disease (LAD) (7). Furthermore, in regard to the classification of cardiac emboli as the etiology, atrial fibrillation is often underdiagnosed due to a brief monitoring period (48 hrs) (8).

To achieve an etiology as clinically relevant as possible for ischemic strokes, we aimed to identify the most-likely stroke etiology even in the group of the TOAST classification labelled UD. Therefore, experienced stroke physicians first applied the original TOAST criteria and classified these according to TOAST *probable* (3). The results for TOAST *probable* are shown in Figure S1; 232 (41%) ischemic strokes were classified as UD.

Based on collected data; including previous medical history, electrocardiograms, telemetry, transthoracic and transesophageal ultrasound, and information from MRI and CT scans, we performed a stepwise classification of the UD group (3, 9), first into TOAST *possible,* as described by Adams et al (3), and the details described in Figure S1; 189 (34%) ischemic strokes were still UD. Next, these UD patients were classified as TOAST *likely* (9), where participants with findings of carotid stenosis < 50% or plaques were classified as having LAD (Figure S1). In this last step, the UD group was reduced to 119 (21%). The final

TOAST classification in the present study, TOAST *modified*, was developed by merging TOAST *probable*, TOAST *possible* and TOAST *likely*.

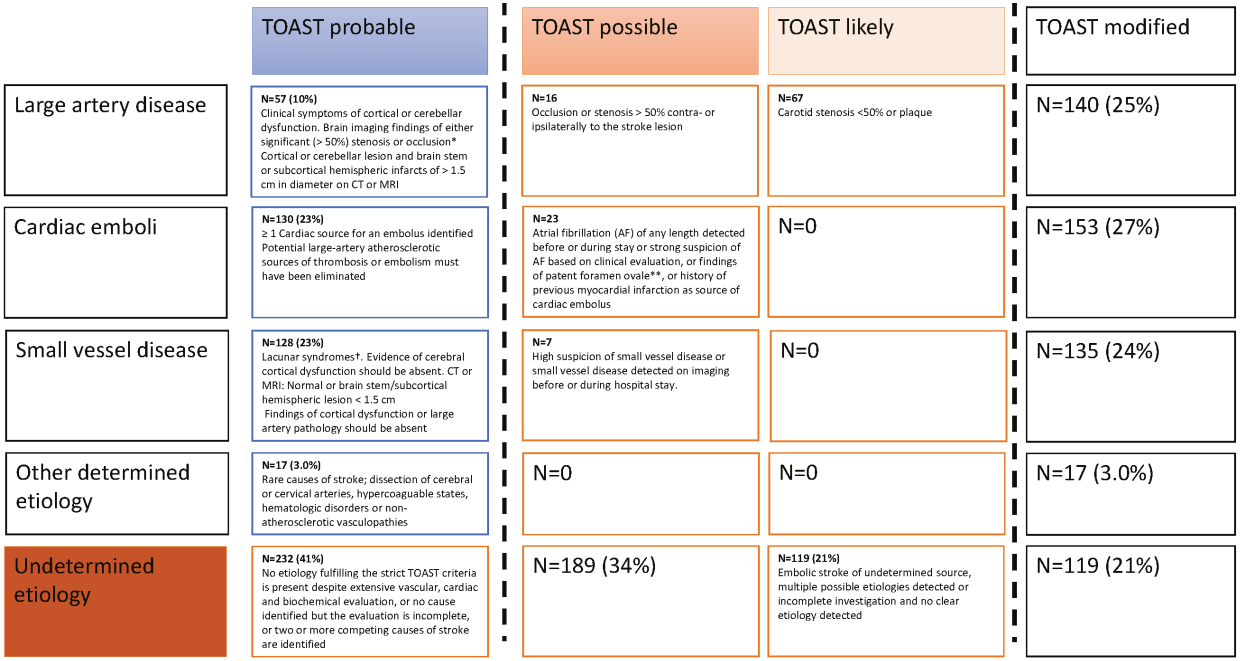

Figure S1. TOAST classification. First classified as TOAST *probable* based on original classification (3), then undetermined etiology (UD) of TOAST *probable* was categorized as TOAST *possible,* also based on original classification (3); those still categorized as UD were then classified as TOAST *likely* (9); finally, these were merged as TOAST *modified.*

*of a major cerebral artery or cortical branch of an artery

†most frequently being pure motor hemiparesis, pure sensory hemiparesis, ataxic hemiparesis, sensorimotor stroke, and dysarthria-clumsy hand syndrome

**on transesophageal ultrasound

3 Definition of post-stroke cognitive impairment (PSCI) according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders criteria

Cognitive status was dichotomized into normal cognition and cognitive impairment; cognitive impairment comprised both mild and major neurocognitive disorders (NCD) and the cut-off for cognitive impairment was defined according to the cut-off for mild NCD in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for mild and major neurocognitive disorders (10), as described in previous work in the Nor-COAST study (11). Five of six cognitive domains defined in DSM-5 were assessed; social cognition was not assessed. Complex attention was measured by Trail Making Test A (12); executive function by Trail Making Test B (12) and Verbal Fluency Test Letters (FAS) (13, 14); memory by Word List Memory and Recall Test (15); language by Verbal Fluency Test Category (animals) (16); and perceptual-motor function by the visuospatial/executive section of the Montreal Cognitive Assessment (MoCA), version 7.3 at 3 months and version 7.1 at 18 months (17). The probability for post-stroke cognitive impairment (PSCI), defined as mild as well as major neurocognitive disorder according to DSM-5 criteria, was based on performance on cognitive tests, and participants scoring < -1.5 SD in at least one cognitive domain were identified as having PSCI. To include participants who were unable to complete the whole test battery and to minimize bias from missing data, cognitive performance was based on MoCA scores for participants completing MoCA only and for those with incomplete cognitive testing but normal scores on completed tests.

4 4. Imputation of outcome measures

To minimize bias from excluded participants, imputation was performed as described in previous work (11) and in the following. Single items missing in the MoCA total scores were imputed by the mean of the available MoCA items for the same participant (n=1 at 3 months and n=0 at 18 months). For participants assessed by Telephone-MoCA , 8 of 30 points that could not be assessed by telephone and these 8 points were imputed by the mean of the available MoCA items for the same participant (n=20 at 3 months, where 3 had missing items in addition to the 8 points not assessed, n=25 at 18 months, where 5 had missing items in addition to the 8 points not assessed). For those participants who were able to start but not complete TMT-A (n=13 at 3 months and n=8 at 18 months) and TMT-B (n=87 at 3 months and n=53 at 18 months) due to cognitive impairment, the tests' results were set as equal to the time at the interruption of the tests, which was 300 seconds for both tests (11, 18). For global z, we imputed missing values on the domain z-scores using the mean z-scores from the other domains for the same participant at the same time point if z-scores were available for at least three of five domains (n=117 at 3 months and n=126 at 18 months). Other missing data were not imputed but treated as missing.

Supplementary Table S1. References for the normative data used for the cognitive test battery	
Cognitive Test	**Normative data**
Trail Making Test A (TMT-A) and B (TMT-B)	Participants ages 18–59 years or >80 years: Trail Making Test A and B: Normative data stratified by age and education (19) Participants ags 60–79 years: Age-, Sex-, and Education-Specific Norms for an Extended CERAD Neuropsychological Assessment Battery–Results From the Population-Based LIFE-Adult-Study (20)
Verbal Fluency Test Letters (FAS)	Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming (21)
Verbal Fluency Test Category (animals)	Participants ages 18–59 years or >80 years: Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming (21) Participants ages 60–79 years: Age-, Sex-, and Education-Specific Norms for an Extended CERAD Neuropsychological Assessment Battery–Results From the Population-Based LIFE-Adult-Study (20)
Word List Recall	Participants ages < 60 years: Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery (22) Participants ages 60–79 years: Age-, Sex-, and Education-Specific Norms for an Extended CERAD Neuropsychological Assessment Battery–Results From the Population-Based LIFE-Adult-Study (20) Participants ages > 80 years: CERAD-NP Battery: Age-, gender- and education-specific reference values for selected subtests. Results of the German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe) (23)
Montreal Cognitive Assessment (MoCA)	Montreal Cognitive Assessment: Normative data from a large Swedish population-based cohort (24)

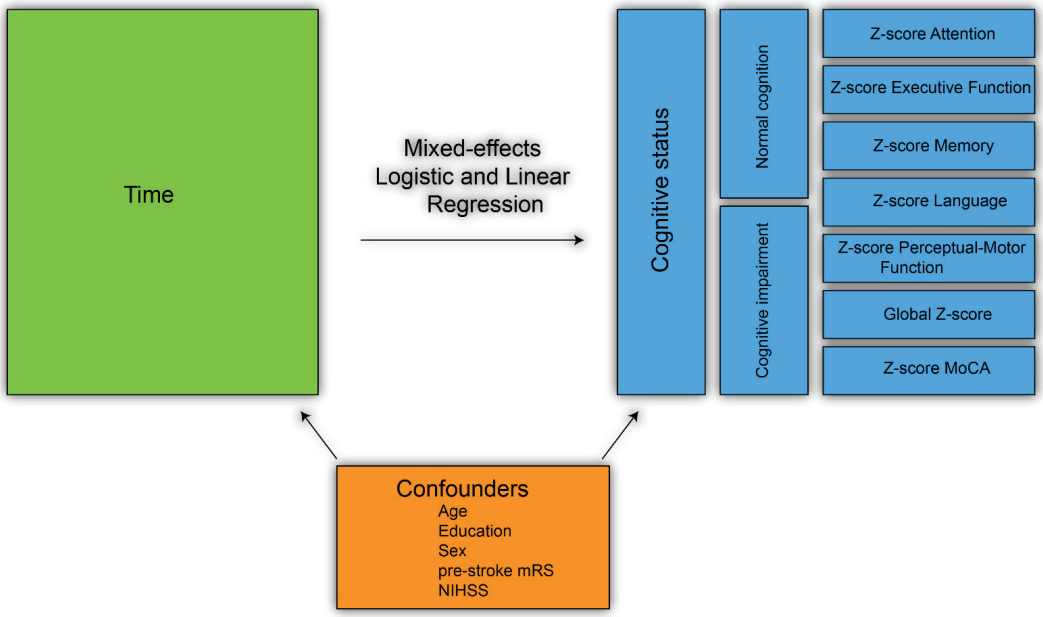

Figure S2. Illustration of the mixed-effects logistic and linear regression for model 1

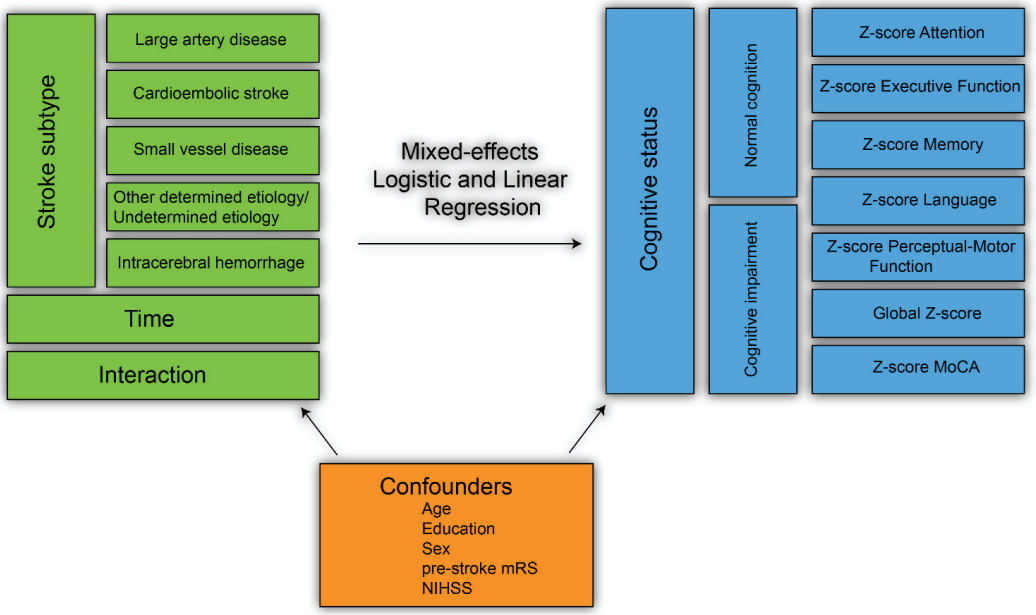

Figure S3. Illustration of the mixed-effects logistic and linear regression for model 2

Table S2. Participants' performance on the cognitive domains								
	3 months				18 months			
	N	Mean z-score (SD)		n with z<-1.5 (%)	N	Mean z-score (SD)		n with z<-1.5 (%)
Attention	548	-0.99	(2.9)	124 (23)	440	-0.57	(2.4)	68 (15)
Executive function	543	-0.69	(1.5)	122 (22)	436	-0.45	(1.4)	85 (19)
Memory	479	-0.87	(1.4)	148 (31)	353	-0.76	(1.3)	94 (27)
Language	468	-0.64	(1.2)	101 (22)	328	-0.38	(1.4)	65 (20)
Perceptual-motor function	568	0.058	(1.1)	64 (11)	468	-0.14	(1.3)	73 (16)
Global z	544	-0.63	(1.2)	99 (18)	438	-0.46	(1.1)	55 (13)
MoCA	588	-1.2	(2.1)	205 (35)	493	-0.95	(2.1)	153 (31)
SD=Standard Deviation, MoCA=Montreal Cognitive Assessment								

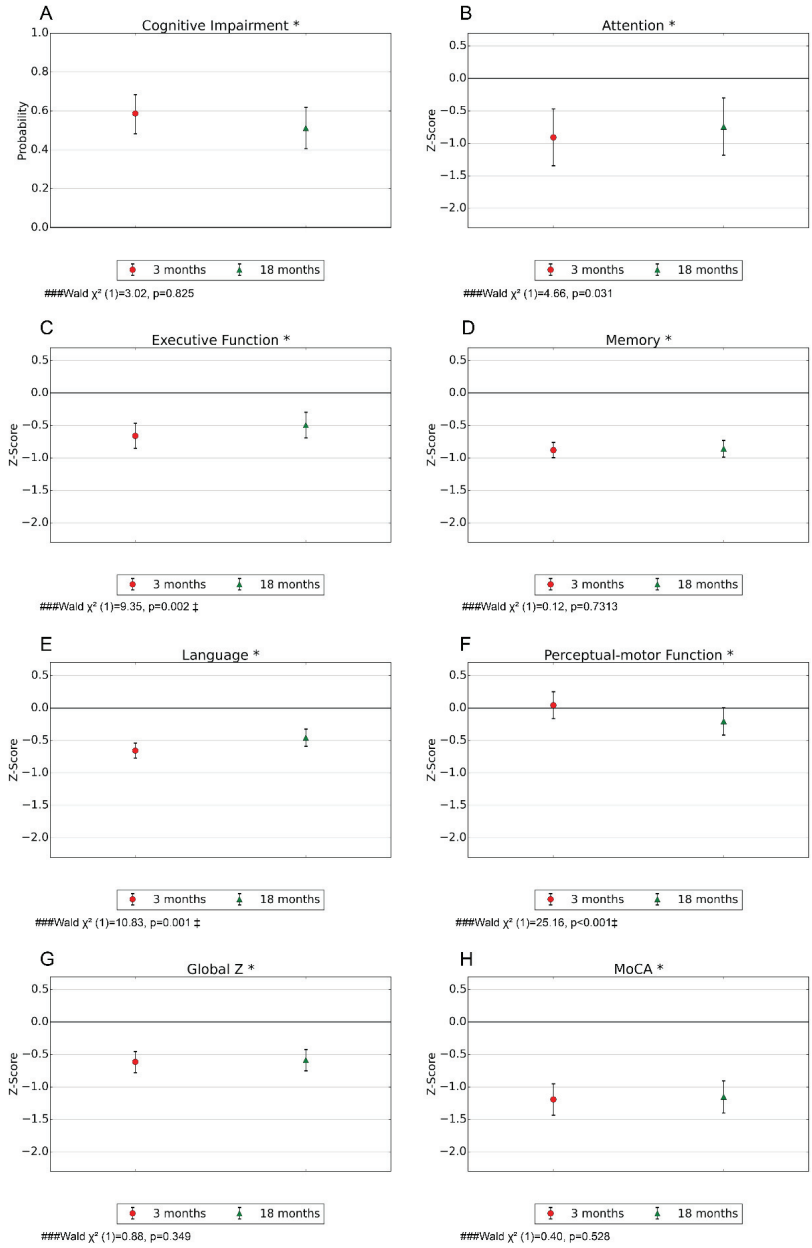

Figure S4. Sensitivity analyses without adjustment: probability for cognitive impairment according to DSM-5 criteria and mean z-scores for the cognitive domains with 95% confidence intervals at 3 and 18 months post-stroke for model 1

MoCA = Montreal Cognitive Assessment

*unadjusted analysis

Wald $\chi^2(1)$ = Wald χ^2 with one degree of freedom; test of whether there is an effect of time

‡ = $p<0.01$

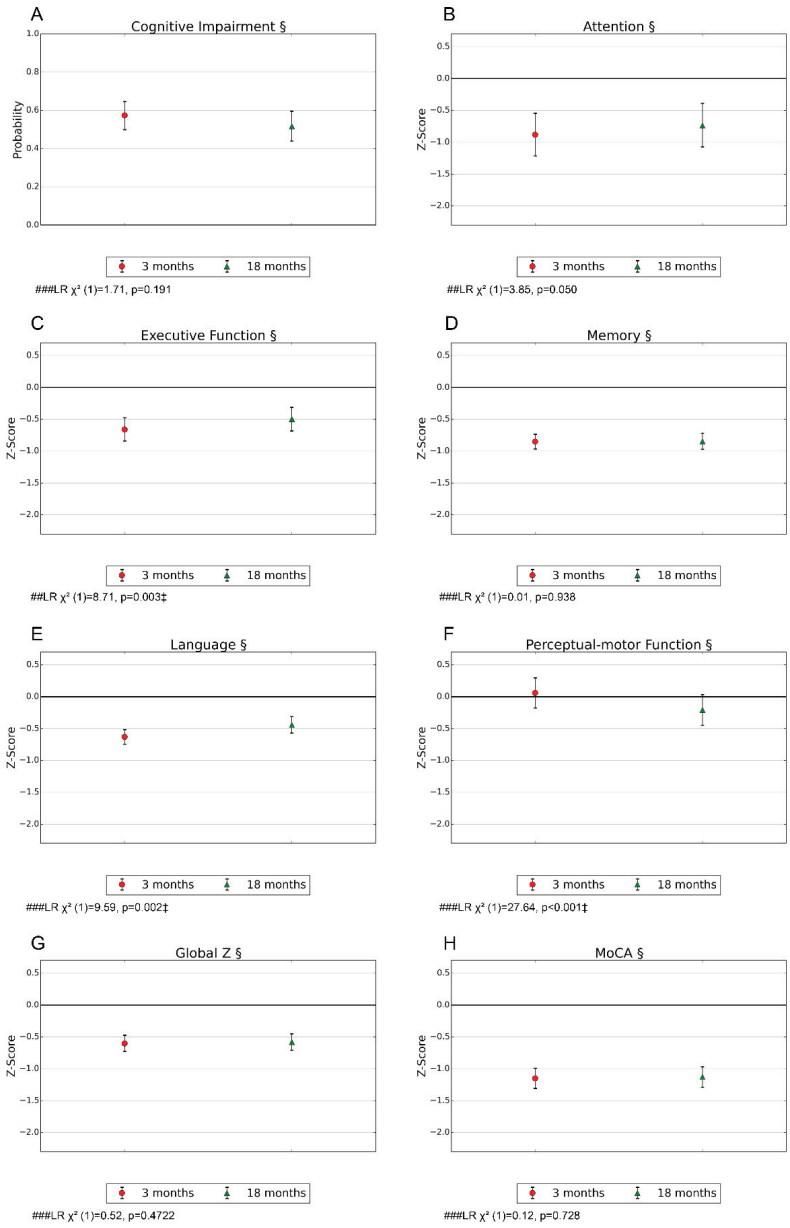

Figure S5. Sensitivity analyses with exclusion of participants deceased at 18 months: probability for cognitive impairment according to DSM-5 criteria and mean z-scores for the cognitive domains with 95% confidence intervals at 3 and 18 months post-stroke for model 1 adjusted for age, education, and sex

MoCA = Montreal Cognitive Assessment

§exclusion of participants deceased at 18 months, adjusted for age, education and sex

LR $\chi^2(1)$ = Likelihood ratio test model 1 vs a model with only age, education and sex as confounders, with one degree of freedom; hypothesis test of whether there is an effect of time

‡ = $p<0.01$

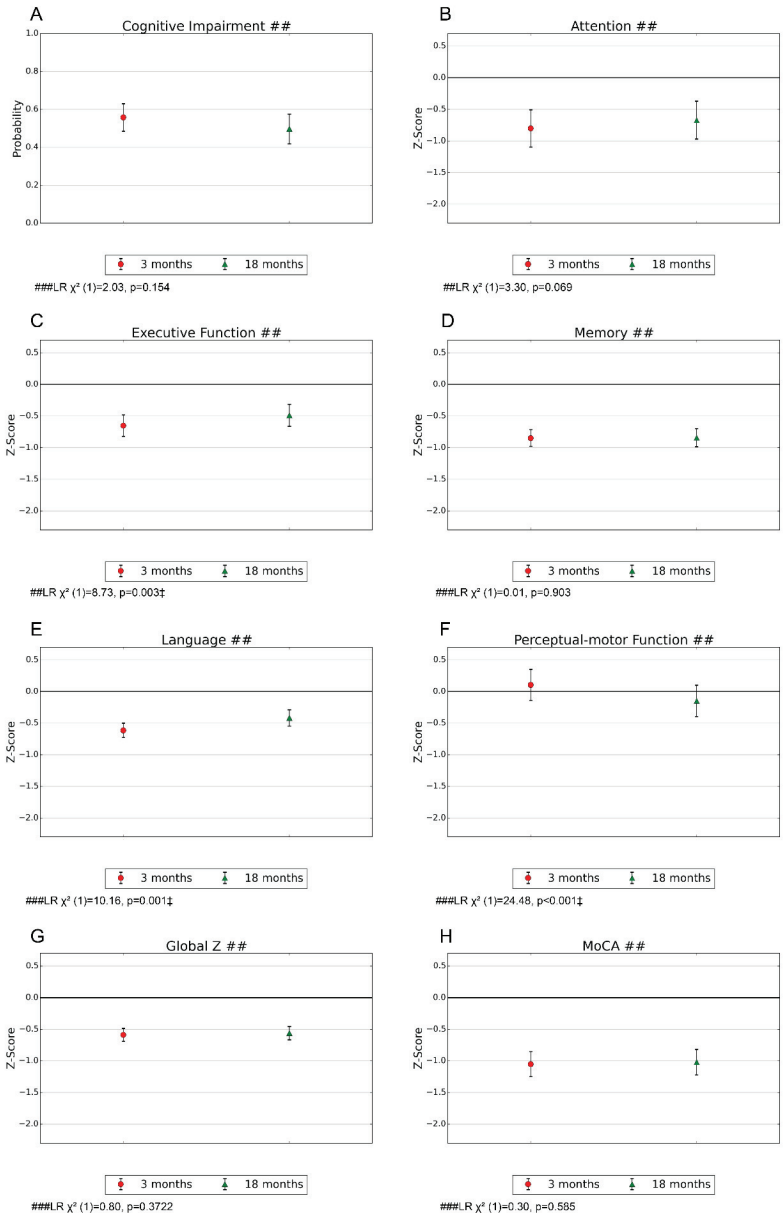

Figure S6. Sensitivity analyses with exclusion of participants with pre-stroke dementia: probability for cognitive impairment according to DSM-5 criteria and mean z-scores for the cognitive domains with 95% confidence intervals at 3 and 18 months post-stroke for model 1 for analyses adjusted for age, education, and sex

MoCA = Montreal Cognitive Assessment

exclusion of participants with pre-stroke dementia, defined as pre-stroke Global Deterioration Scale 4-7, adjusted for age, education, and sex

LR $\chi^2(1)$ =Likelihood ratio test model 1 vs a model with only age, education, and sex as confounders, with one degree of freedom; hypothesis test of whether there is an effect of time

‡ = $p<0.01$

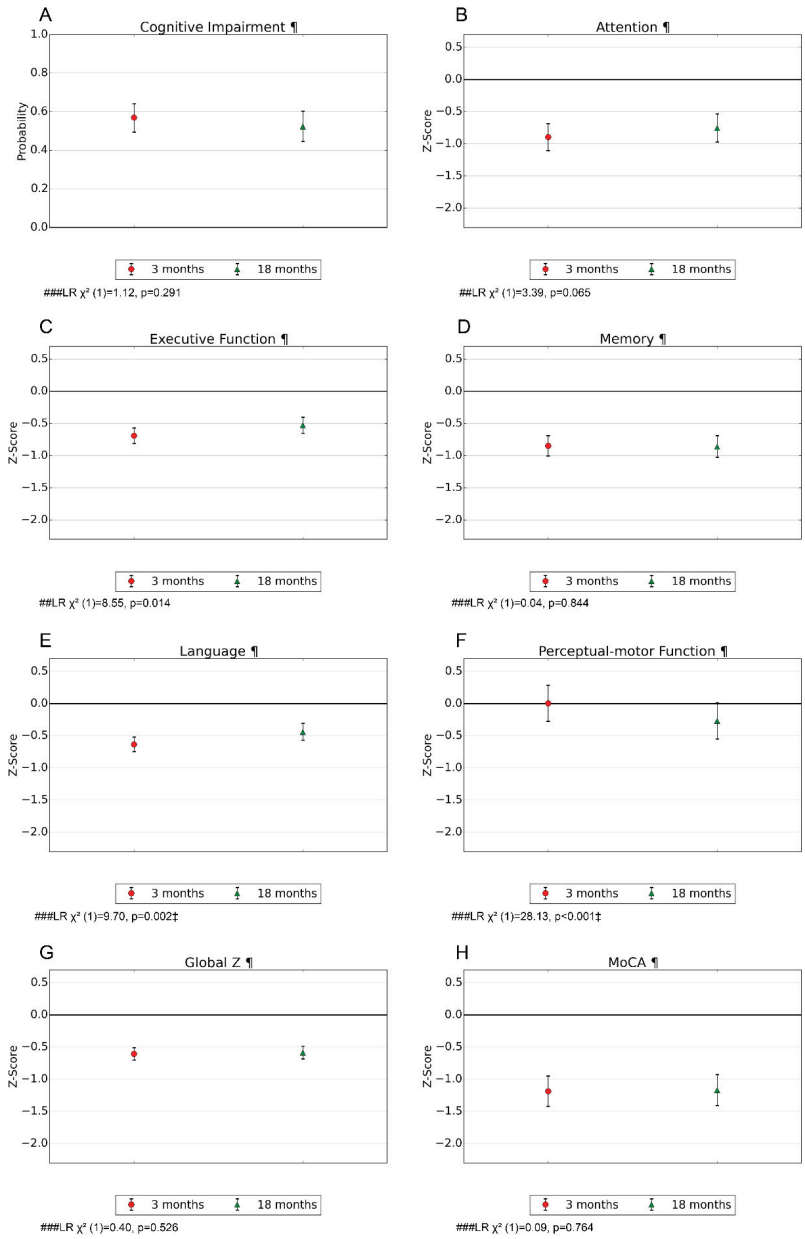

Figure S7. Sensitivity analyses with adjustment for age, education, sex, pre-stroke mRS, NIHSS: probability for cognitive impairment according to DSM-5 criteria and mean z-scores for the cognitive domains with 95% confidence intervals at 3 and 18 months post-stroke for model 1

MoCA = Montreal Cognitive Assessment

¶ adjusted for age, education and sex, pre-stroke modified Rankin Scale (mRS), National Institutes of Health Stroke Scale (NIHSS)

LR $\chi^2(1)$ = Likelihood ratio test model 1 vs a model with only age, education,sex, pre-stroke mRS, and NIHSS as confounders, with one degree of freedom; hypothesis test of whether there is an effect of time

‡ = $p<0.01$

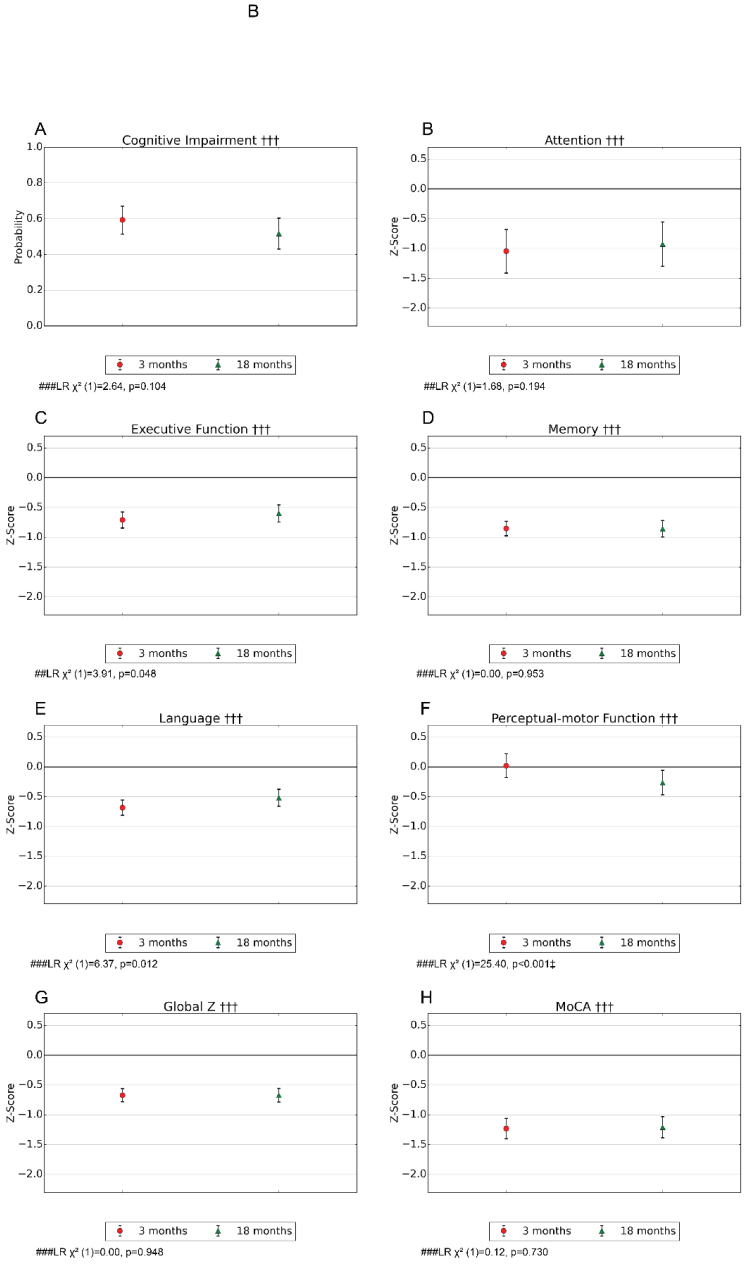

Figure S8. Sensitivity analyses with adjustment for age, education, sex, and location of symptoms: probability for cognitive impairment according to DSM-5 criteria and mean z-scores for the cognitive domains with 95% confidence intervals at 3 and 18 months post-stroke for model 1

MoCA = Montreal Cognitive Assessment

††† adjusted for age, education, sex, and location of symptoms

LR $\chi^2(1)$ = Likelihood ratio test model 1 vs a model with only age, education, sex and location of symptoms as confounders, with one degree of freedom; hypothesis test of whether there is an effect of time

‡ = $p<0.01$

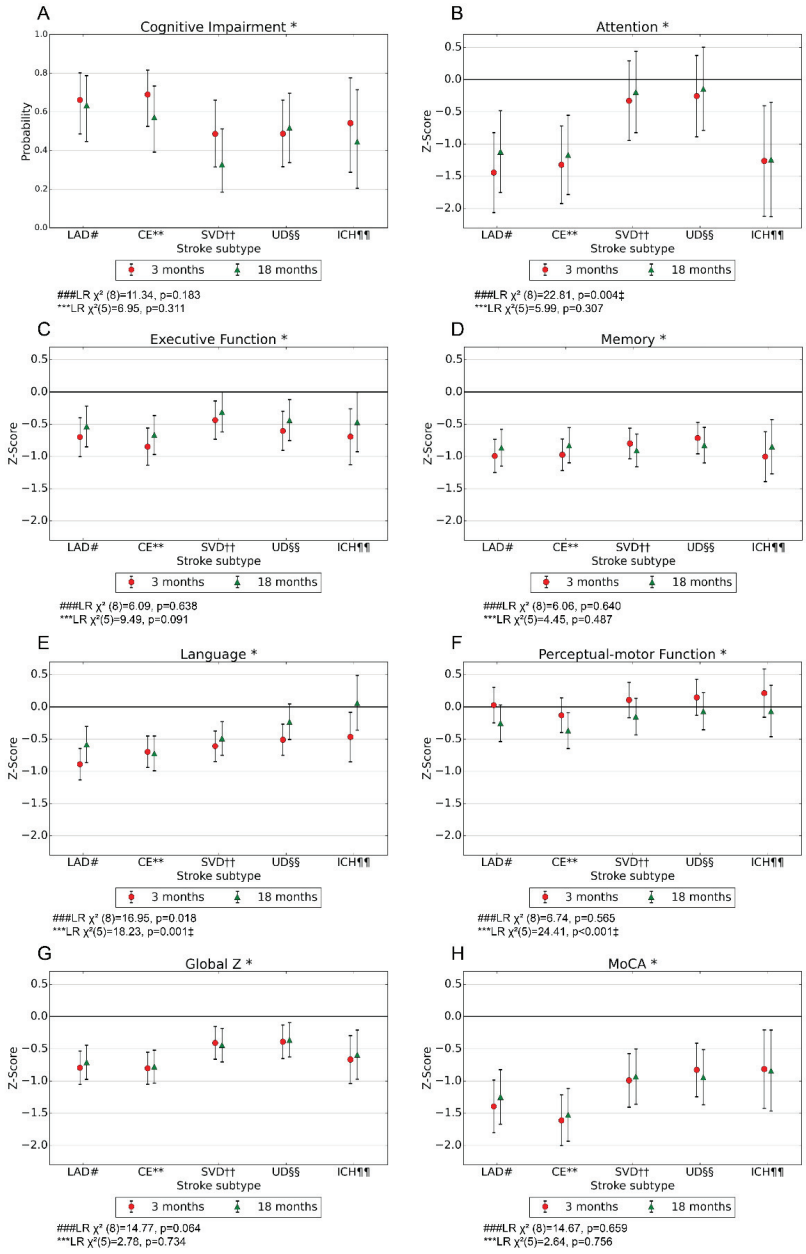

Figure S9. Sensitivity analyses without adjustment: probability for PSCI according to DSM-5 criteria and mean z-scores for the cognitive domains with 95% confidence intervals at 3 and 18 months post-stroke for model 2

MoCA = Montreal Cognitive Assessment

*unadjusted analysis

#LAD = Large artery disease

**CE = Cardiac emboli

††SVD = Small vessel disease

§§UD = Undetermined and other determined strokes

¶¶ICH = Intracerebral hemorrhage

LR $\chi^2(8)$ = Likelihood ratio test model 1 vs model 2 with 8 degrees of freedom; hypothesis test of whether there is an effect of stroke subtype

*** LR $\chi^2(5)$ =Likelihood ratio test model 2 vs model 3 with 5 degrees of freedom; hypothesis test of whether there is an effect of time for at least one stroke subtype

‡ = $p<0.01$

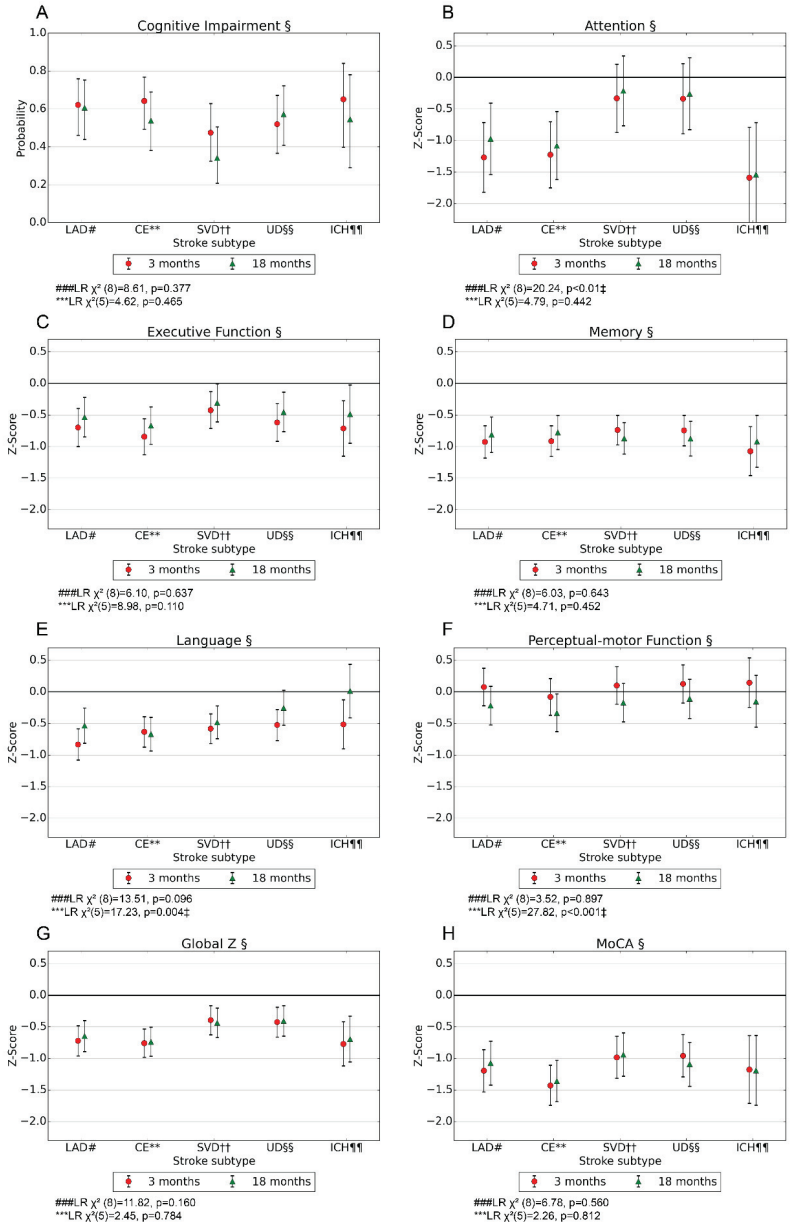

Figure S10. Sensitivity analyses with exclusion of participants deceased at 18 months: probability for cognitive impairment according to DSM-5 criteria and mean z-scores for the cognitive domains with 95% confidence intervals at 3 and 18 months post-stroke for model 2 for analyses adjusted for age, education, and sex

MoCA = Montreal Cognitive Assessment

§exclusion of participants deceased at 18 months, adjusted for age, education, and sex

#LAD = Large artery disease

**CE = Cardiac emboli

††SVD = Small vessel disease

§§UD = Undetermined- and other determined strokes

¶¶ICH = Intracerebral hemorrhage

LR $\chi^2(8)$ = Likelihood ratio test model 1 vs model 2 with 8 degrees of freedom; hypothesis test of whether there is an effect of stroke subtype

*** LR $\chi^2(5)$ = Likelihood ratio test model 2 vs model 3 with 5 degrees of freedom; hypothesis test of whether there is an effect of time for at least one stroke subtype

‡ = $p<0.01$

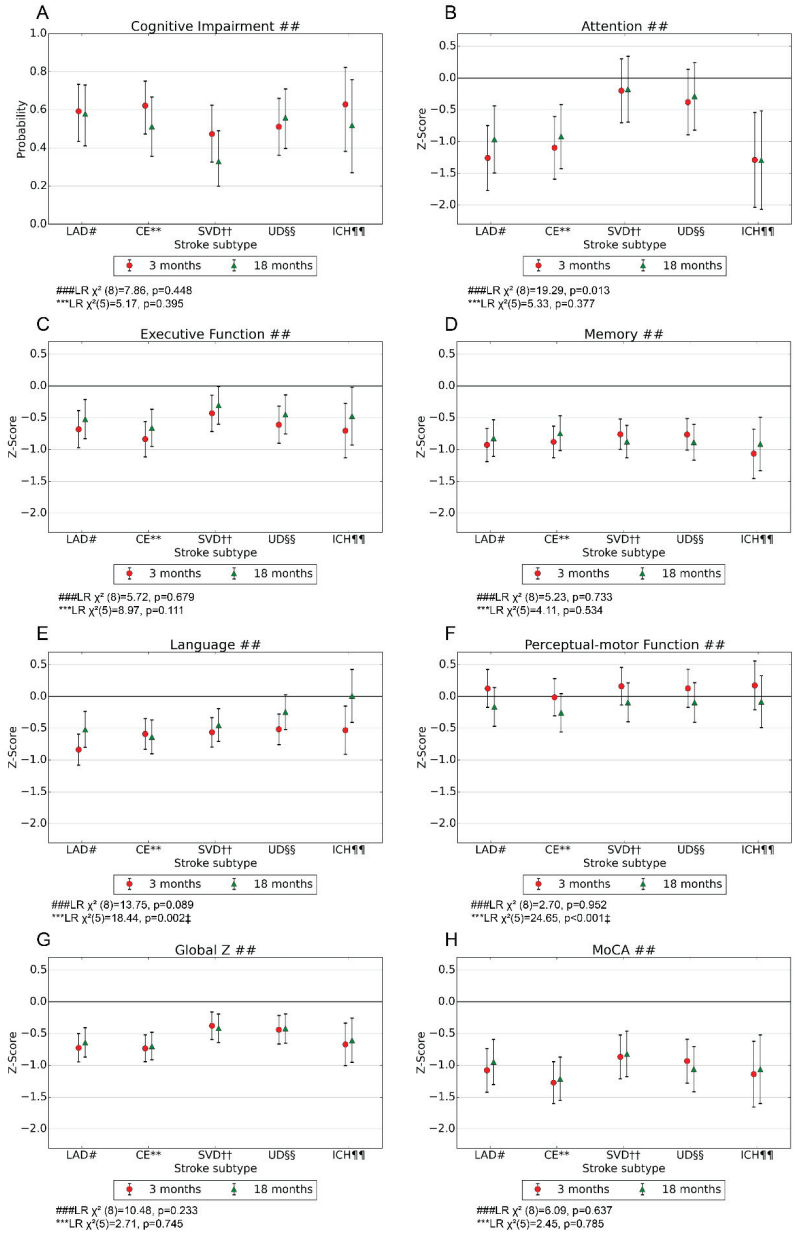

Figure S11. Sensitivity analyses with exclusion of participants with pre-stroke dementia: probability for cognitive impairment according to DSM-5 criteria and mean z-scores for the cognitive domains with 95% confidence intervals at 3 and 18 months post-stroke for model 2 for analyses adjusted for age, education, and sex

MoCA = Montreal Cognitive Assessment

exclusion of participants with pre-stroke dementia, defined as pre-stroke Global Deterioration Scale 4–7, adjusted for age, education, and sex

#LAD = Large artery disease

**CE = Cardiac emboli

††SVD = Small vessel disease

§§UD = Undetermined and other determined strokes

¶¶ICH = Intracerebral hemorrhage

LR $\chi^2(8)$ =Likelihood ratio test model 1 vs model 2 with 8 degrees of freedom; hypothesis test of whether there is an effect of stroke subtype

*** LR $\chi^2(5)$ = Likelihood ratio test model 2 vs model 3 with 5 degrees of freedom; hypothesis test of whether there is an effect of time for at least one stroke subtype

‡ = $p<0.01$

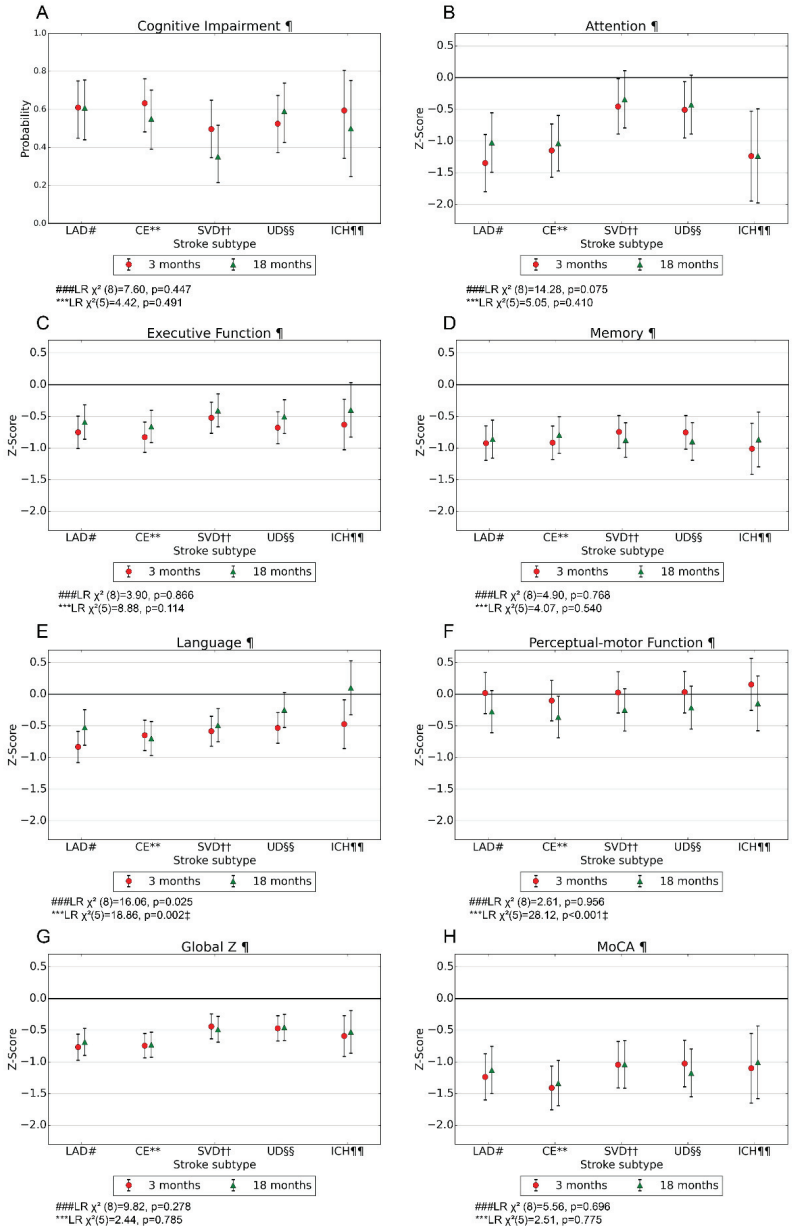

Figure S12. Sensitivity analyses with adjustment adjusted for age, education, sex, pre-stroke mRS and NIHSS: Probability for cognitive impairment according to DSM-5 criteria and mean z-scores for the cognitive domains with 95% confidence intervals at 3 and 18 months post-stroke for model 2

MoCA = Montreal Cognitive Assessment

¶ adjusted for age, education and sex, pre-stroke modified Rankin Scale (mRS), and National Institutes of Health Stroke Scale (NIHSS)

#LAD = Large artery disease

**CE = Cardiac emboli

††SVD = Small vessel disease

§§UD = Undetermined and other determined strokes

¶¶ICH = Intracerebral hemorrhage

LR $\chi^2(8)$ = Likelihood ratio test model 1 vs model 2 with 8 degrees of freedom; hypothesis test of whether there is an effect of stroke subtype

*** LR $\chi^2(5)$ = Likelihood ratio test model 2 vs model 3 with 5 degrees of freedom; hypothesis test of whether there is an effect of time for at least one stroke subtype

‡ = $p<0.01$

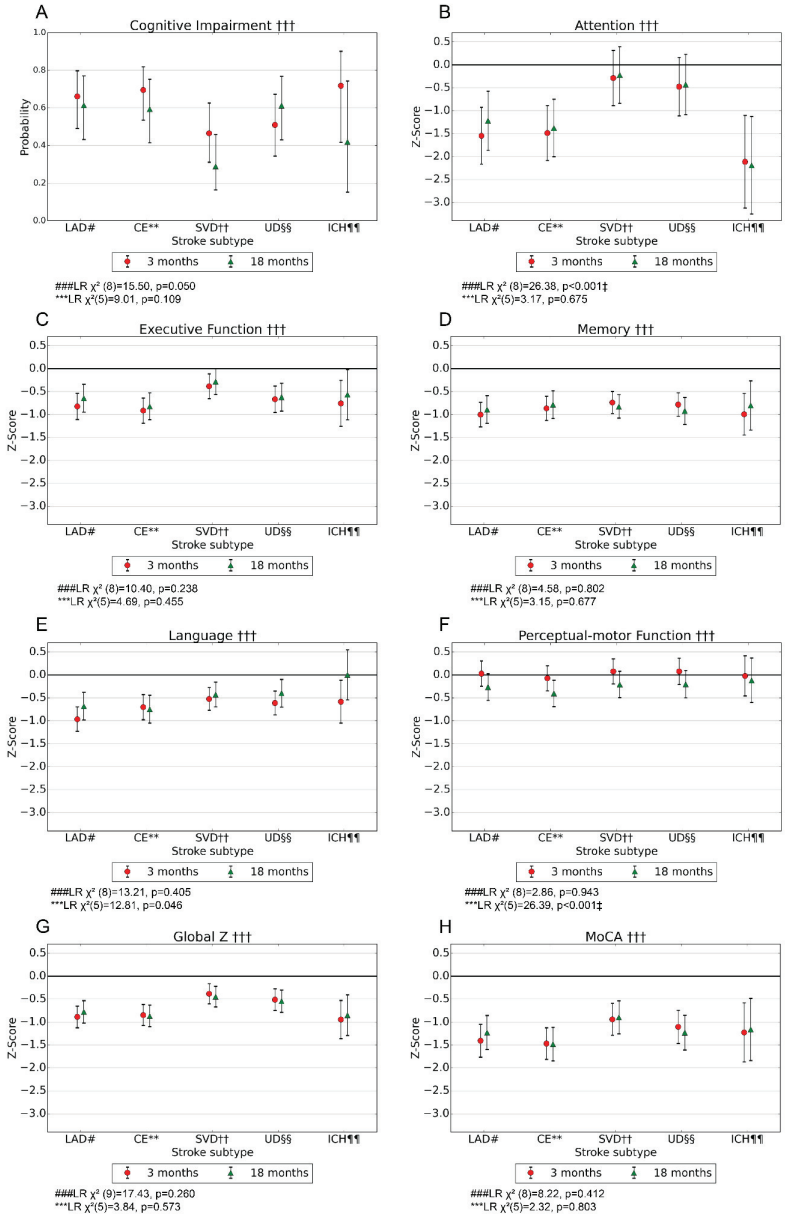

Figure S13. Sensitivity analyses with adjustment for age, education, sex and location of symptoms: probability for cognitive impairment according to DSM-5 criteria and mean z-scores for the cognitive domains with 95% confidence intervals at 3 and 18 months post-stroke for model 2

MoCA = Montreal Cognitive Assessment

††† adjusted for age, education and sex, and location of symptoms

#LAD = Large artery disease

**CE = Cardiac emboli

††SVD = Small vessel disease

§§UD = Undetermined and other determined strokes

¶¶ICH = Intracerebral hemorrhage

LR $\chi^2(8)$ = Likelihood ratio test model 1 vs model 2 with 8 degrees of freedom; hypothesis test of whether there is an effect of stroke subtype

*** LR $\chi^2(5)$ = Likelihood ratio test model 2 vs model 3 with 5 degrees of freedom; hypothesis test of whether there is an effect of time for at least one stroke subtype

‡ = $p<0.01$

Table S3. Numbers of participants of different stroke subtypes included in the analyses								
			Stroke subtype					
			LAD	CE	SVD	UD	ICH	Total
Probability for cognitive impairment	Unadjusted analyses and analyses adjusted for age, education, and sex	3 months	130	147	129	131	52	589
		18 months	110	121	110	110	45	496
	Analyses adjusted for age, education, and sex, exclusion of deceased (n=20)	3 months	125	142	126	126	50	569
		18 months	110	120	110	110	45	495
	Analyses adjusted for age, education, and sex, exclusion of pre-stroke dementia (n=20)	3 months	124	140	126	128	51	569
		18 months	107	116	108	109	44	484
	Analyses adjusted for age, education, sex, pre-stroke mRS, and NIHSS	3 months	125	143	126	129	50	573
		18 months	108	119	108	108	42	485
	Analyses adjusted for age, education, sex, and location of symptoms	3 months	110	120	116	107	35	488
		18 months	93	97	98	90	29	407
Attention	Unadjusted analyses and analyses adjusted for age, education, sex, pre-stroke mRS, and NIHSS	3 months	124	136	126	118	50	548
		18 months	93	108	104	96	39	440

	Analyses adjusted for age, education, and sex, exclusion of deceased (n=18)	3 months	112	133	123	114	48	530
		18 months	93	108	104	96	39	440
	Analyses adjusted for age, education, and sex, exclusion of pre-stroke dementia (n=13)	3 months	114	132	124	116	49	535
		18 months	92	106	103	96	39	436
	Analyses adjusted for age, education, sex, pre-stroke mRS, and NIHSS	3 months	115	132	123	116	48	534
		18 months	91	107	102	94	38	432
	Analyses adjusted for age, education, sex, and location of symptoms	3 months	99	113	113	96	33	454
		18 months	76	85	92	79	24	356
Executive function	Unadjusted analyses and analyses adjusted for age, education, and sex	3 months	117	133	125	119	49	543
		18 months	93	106	103	96	38	436
	Analyses adjusted for age, education, and sex, exclusion of deceased (n=17)	3 months	111	131	122	115	47	526
		18 months	93	106	103	96	38	436
	Analyses adjusted for age, education, and sex, exclusion of pre-stroke dementia (n=10)	3 months	113	130	124	117	49	533
		18 months	91	104	102	96	38	431

	Analyses adjusted for age, education, sex, pre-stroke mRS, and NIHSS	3 months	112	130	122	117	48	529
		18 months	91	105	101	94	37	428
	Analyses adjusted for age, education, sex, and location of symptoms	3 months	98	109	112	97	32	448
		18 months	76	83	91	79	22	351
Memory	Unadjusted analyses and analyses adjusted for age, education, and sex	3 months	99	110	114	112	44	479
		18 months	71	78	95	75	34	353
	Analyses adjusted for age, education, and sex, exclusion of deceased (n=15)	3 months	95	108	111	108	42	464
		18 months	71	78	95	75	34	353
	Analyses adjusted for age, education, and sex, exclusion of pre-stroke dementia (n=10)	3 months	95	107	113	111	43	469
		18 months	70	77	93	75	34	349
	Analyses adjusted for age, education, sex, pre-stroke mRS, and NIHSS	3 months	96	107	112	110	42	467
		18 months	69	77	93	73	33	345
	Analyses adjusted for age, education, sex, and location of symptoms	3 months	86	81	100	89	28	384
		18 months	59	58	73	56	17	263

Language	Unadjusted analyses and analyses adjusted for age, education, and sex	3 months	105	104	111	106	42	468
		18 months	69	77	81	70	31	328
	Analyses adjusted for age, education, and sex, exclusion of deceased (n=15)	3 months	101	102	108	102	40	453
		18 months	69	77	81	70	31	328
	Analyses adjusted for age, education, and sex, exclusion of pre-stroke dementia (n=9)	3 months	101	101	110	105	42	459
		18 months	67	76	80	70	31	324
	Analyses adjusted for age, education, sex, pre-stroke mRS, and NIHSS	3 months	100	103	108	104	41	456
		18 months	67	76	79	68	30	320
	Analyses adjusted for age, education, sex and location of symptoms	3 months	86	81	100	89	28	384
		18 months	59	58	73	56	17	263
Perceptual-motor function	Unadjusted analyses and analyses adjusted for age, education, and sex	3 months	125	140	129	123	51	568
		18 months	104	113	108	103	40	468
	Analyses adjusted for age, education, and sex, exclusion of deceased (n=20)	3 months	120	135	126	118	49	548
		18 months	104	113	108	103	40	468

	Analyses adjusted for age, education, and sex, exclusion of pre-stroke dementia (n=19)	3 months	119	133	126	121	50	549
		18 months	102	109	106	102	39	458
	Analyses adjusted for age, education, sex, pre-stroke mRS, and NIHSS	3 months	122	136	126	121	49	554
		18 months	102	111	106	101	38	458
	Analyses adjusted for age, education, sex, and location of symptoms	3 months	105	114	116	101	34	470
		18 months	87	90	96	85	24	382
Global z	Unadjusted analyses and analyses adjusted for age, education, and sex	3 months	117	132	126	119	50	544
		18 months	93	107	104	96	38	438
	Analyses adjusted for age, education, and sex, exclusion of deceased (n=16)	3 months	112	130	123	115	48	528
		18 months	93	107	104	96	38	438
	Analyses adjusted for age, education, and sex, exclusion of pre-stroke dementia (n=11)	3 months	113	129	125	117	49	533
		18 months	91	105	103	96	38	433
	Analyses adjusted for age, education, sex, pre-stroke mRS, and NIHSS	3 months	114	129	123	117	48	531
		18 months	91	106	102	94	37	430

	Analyses adjusted for age, education, sex, and location of symptoms	3 months	98	108	113	97	33	449
		18 months	76	84	92	79	22	353
MoCA	Unadjusted analyses and analyses adjusted for age, education, and sex	3 months	130	147	129	130	52	588
		18 months	109	120	110	110	44	493
	Analyses adjusted for age, education, and sex, exclusion of deceased (n=20)	3 months	125	142	126	125	50	568
		18 months	109	120	110	110	44	493
	Analyses adjusted for age, education, and sex, exclusion of pre-stroke dementia (n=20)	3 months	124	140	126	127	51	568
		18 months	106	116	108	109	43	482
	Analyses adjusted for age, education, sex, pre-stroke mRS, and NIHSS	3 months	125	143	126	128	50	572
		18 months	107	118	108	108	41	482
	Analyses adjusted for age, education, sex, and location of symptoms	3 months	110	120	116	106	35	487
		18 months	92	97	98	90	28	405

LAD = Large artery disease, CE = cardioembolic strokes, SVD = small vessel disease, UD = undetermined and other etiology, ICH = intracerebral hemorrhage, MoCA = Montreal Cognitive Assessment, mRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale

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Supplementary Material Paper 3

SUPPLEMENTARY MATERIAL

Imputation of cognitive outcome measures

To minimize selection bias from excluded patients, imputation of cognitive outcome measures was performed as described in previous work in the Nor-COAST study and in the following [1, 2]. Single items missing in the MoCA total scores were imputed by the mean of the available MoCA items for the same patient (n= 2 at 3 months follow-up and n=4 at 18 months follow-up). For patients assessed with telephone-MoCA [3] , 8 of 30 points of MoCA could not be assessed by telephone, and these 8 points were imputed by the mean of the available MoCA items for the same patient (n=21 at 3 months follow-up of whom 3 patients had one single item missing in MoCA in addition to the 8 points not assessed, and n=25 at 18 months follow-up of whom 6 patients had items missing in MoCA in addition to the 8 points not assessed). For the patients able to start but not completing the TMT-A (n=14 at 3 months follow-up, and n=8 at 18 months follow-up) and TMT-B (n=91 at 3 months follow-up, and n=57 at 18 months follow-up) due to cognitive impairment, the tests' results were set as equal to the time of the interruption of the tests, which was 300 seconds for both [1, 2, 4]. For the global z, we imputed missing values on the domains z-scores using the mean z-scores from the other domains for the same patient on the same time point, if z-scores were available for at least 2 of 4 domains (n=129 at 3 months follow-up, and n=127 at 18 months follow-up). Other missing data were not imputed but treated as missing.

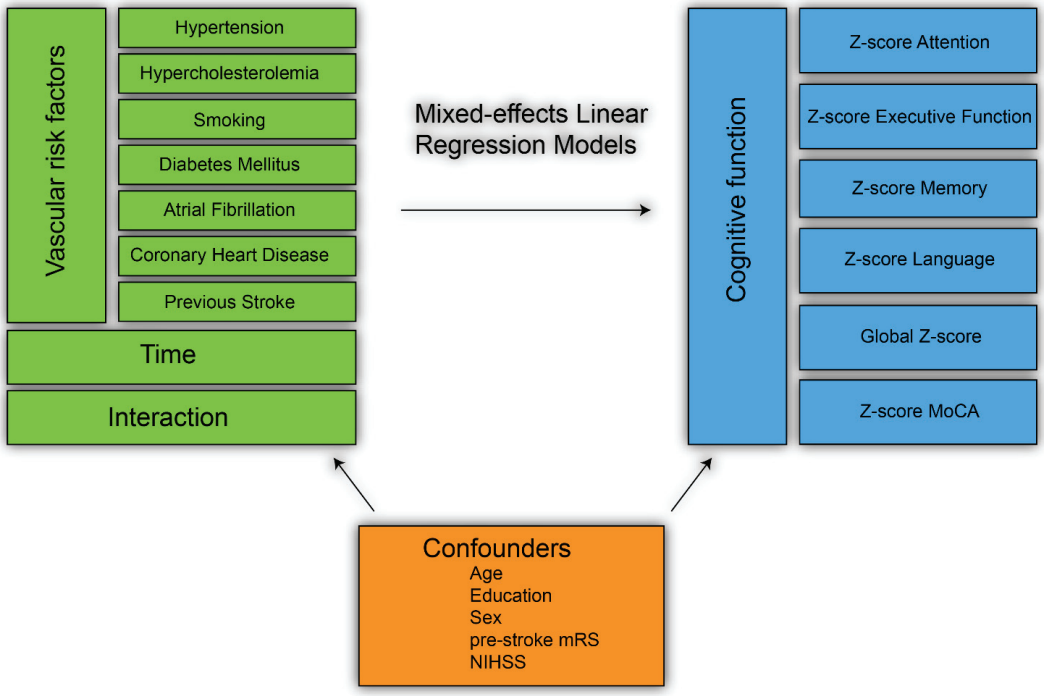

Figure S1. Illustration of the mixed-effects linear regression for model 1.

The outcome variables of cognitive function as well as the vascular risk factors were analyzed one at a time. Follow-up time and the interaction between the vascular risk factor and follow-up time were included in all analyses. The main analyses were adjusted for age, education, and sex. Also, unadjusted analyses were performed as well as analyses adjusted for age, education, sex, pre-stroke mRS, and NIHSS altogether.

Supplementary Table S1. Normative data for the cognitive test battery	
Cognitive Test	**Normative data**
Trail Making Test A (TMT-A) and B (TMT-B)	For patients ages 18–59 years or >80 years: Trail Making Test A and B: Normative data stratified by age and education [5] For patients ages 60–79 years: Age-, Sex-, and Education-Specific Norms for an Extended CERAD Neuropsychological Assessment Battery–Results From the Population-Based LIFE-Adult-Study [6]
Word List Recall	For patients ages < 60 years: Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery [7] For patients ages 60–79 years: Age-, Sex-, and Education-Specific Norms for an Extended CERAD Neuropsychological Assessment Battery–Results From the Population-Based LIFE-Adult-Study [6] For patients ages > 80 years: CERAD-NP battery: Age-, gender- and education-specific reference values for selected subtests. Results of the German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe) [7]
Verbal Fluency Test Letters (FAS)	Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming [8]
Verbal Fluency Test Category (animals)	For patients aged 18–59 years or >80 years: Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming [8] For patients ages 60–79 years: Age-, Sex-, and Education-Specific Norms for an Extended CERAD Neuropsychological Assessment Battery–Results From the Population-Based LIFE-Adult-Study [6]
Montreal Cognitive Assessment (MoCA)	Montreal Cognitive Assessment: Normative data from a large Swedish population-based cohort [9]

Table S2. Patients' performance on the global measures and cognitive domains										
	3 months					18 months				
	N	Mean z-score (SD)		n with z<-1.5 (%)		N	Mean z-score (SD)		n with z<-1.5 (%)	
Global z	560	-0.64	(1.26)	102	(18)	452	-0.47	(1.10)	59	(13)
MoCA	605	-1.18	(2.06)	211	(35)	508	-0.96	(2.08)	159	(27)
Attention	565	-1.00	(2.89)	129	(23)	454	-0.56	(2.42)	70	(15)
Executive function	558	-0.69	(1.48)	127	(23)	450	-0.46	(1.38)	89	(20)
Memory	492	-0.86	(1.37)	151	(31)	365	-0.79	(1.30)	94	(26)
Language	480	-0.63	(1.22)	103	(22)	339	-0.38	(1.39)	67	(20)
SD=Standard deviation, MoCA=Montreal Cognitive Assessment										

Table S3. Hypothesis test of whether there is an effect of the vascular risk factor and follow-up time in model 1 for the global measures and cognitive domains for the different vascular risk factors for analyses adjusted for age, education and sex								
		Hypertension	**Hypercholesterolemia**	**Smoking**	**Diabetes mellitus**	**Atrial fibrillation**	**Coronary heart disease**	**Previous stroke**
Global z	LR_{vasc} $\chi2(2)$, p-value	1.59, 0.452	2.39, 0.302	3.09, 0.214	1.39, 0.498	6.99, 0.030	1.02, 0.601	12.76, 0.002*
	LR_{time} $\chi2(2)$, p-value	5.56, 0.062	5.30, 0.071	6.75, 0.034	5.30, 0.071	8.24, 0.016	5.46, 0.065	6.40, 0.041
MoCA	LR_{vasc} $\chi2(2)$, p-value	1.71, 0.425	1.94, 0.379	0.90, 0.825	1.48, 0.478	1.75, 0.186	8.32, 0.004*	6.08, 0.108
	LR_{time} $\chi2(2)$, p-value	0.61, 0.738	1.90, 0.386	0.23, 0.891	1.12, 0.570	0.35, 0.840	6.61, 0.010	0.13, 0.936
Attention	LR_{vasc} $\chi2(2)$, p-value	1.24, 0.537	0.80, 0.669	3.70, 0.158	1.29, 0.524	8.77, 0.013	2.12, 0.347	16.20, <0.001*
	LR_{time} $\chi2(2)$, p-value	5.19, 0.075	4.63, 0.099	7.39, 0.025	5.38, 0.068	10.42, <0.01*	5.11, 0.078	4.41, 0.110
Executive function	LR_{vasc} $\chi2(2)$, p-value	2.37, 0.305	1.20, 0.550	4.30, 0.117	4.00, 0.135	2.50, 0.286	1.62, 0.445	8.06, 0.018
	LR_{time} $\chi2(2)$, p-value	8.77, 0.013	8.13, 0.017	7.87, 0.020	8.62, 0.013	8.10, 0.017	9.33, 0.009*	7.96, 0.019

Memory	LR_{vasc} $\chi2(2)$, p-value	1.52, 0.677	2.18, 0.537	2.26, 0.521	0.63, 0.889	3.27, 0.352	0.36, 0.948	2.62, 0.454
	LR_{time} $\chi2(2)$, p-value	0.42, 0.812	0.19, 0.908	2.23, 0.329	0.14, 0.931	2.31, 0.316	0.32, 0.854	1.14, 0.565
Language	LR_{vasc} $\chi2(2)$, p-value	5.53, 0.063	4.38, 0.112	0.20, 0.904	7.88, 0.019	12.80, 0.002*	1.26, 0.531	2.04, 0.361
	LR_{time} $\chi2(2)$, p-value	10.27, 0.006*	11.38, 0.003*	9.67, 0.008*	13.65, 0.001*	18.58, <0.001*	11.18, 0.004*	10.05, 0.007*

MoCA=Montreal Cognitive Assessment.
LR_{vasc} $\chi2(2)$ =Likelihood ratio test model 1 vs model 2, with two degrees of freedom; hypothesis test of whether there is an effect of the vascular risk factor.
LR_{time} $\chi2(2)$ =Likelihood ratio test model 1 vs model 3, with two degrees of freedom; hypothesis test of whether there is an effect of follow-up time.
*$p<0.01$

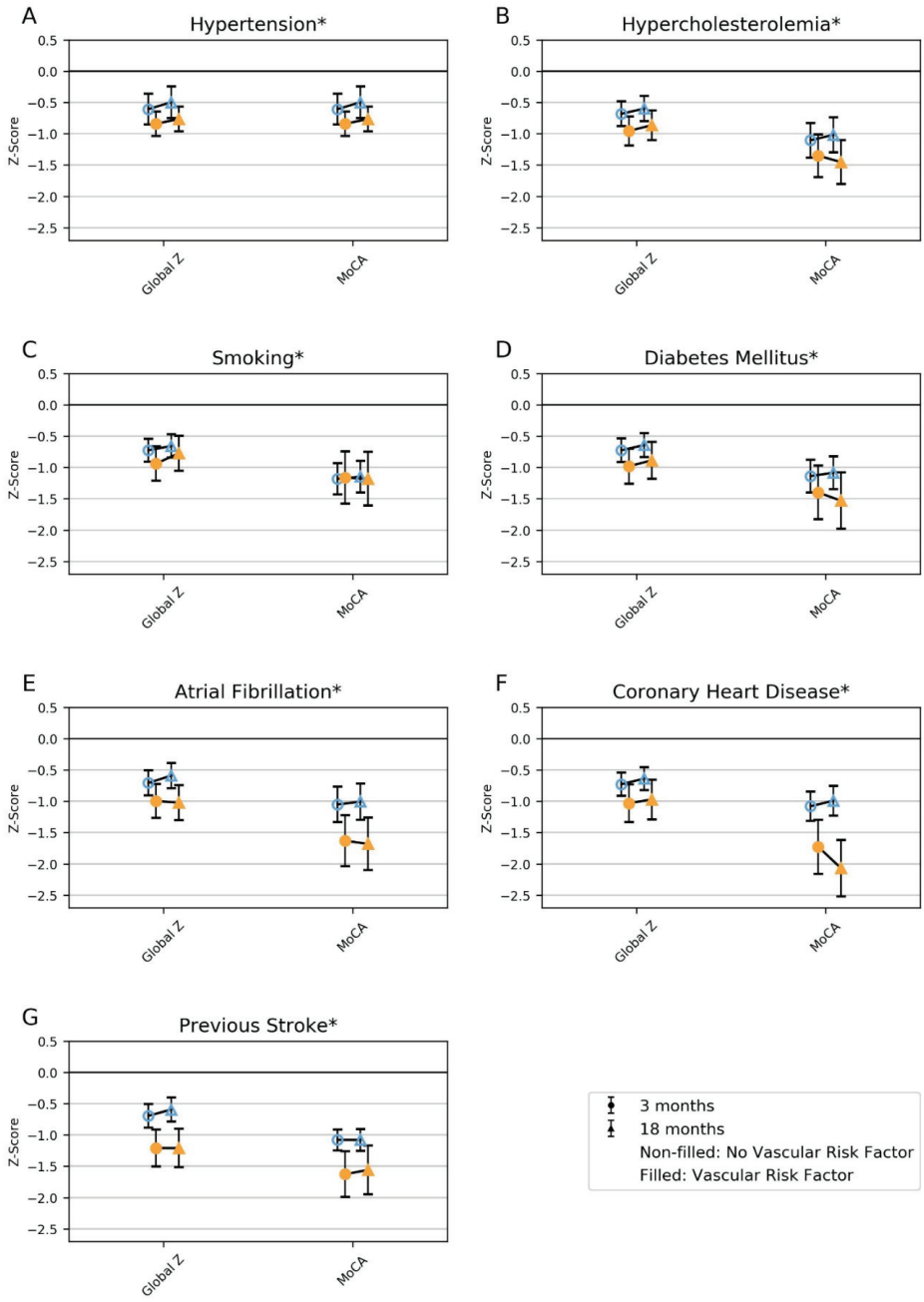

Figure S2. Sensitivity analyses without adjustment: Mean z-scores with 95% confidence intervals for for the global cognitive measures for the different vascular risk factors at 3- and 18-months post-stroke in model 1

MoCA = Montreal Cognitive Assessment

*unadjusted analysis

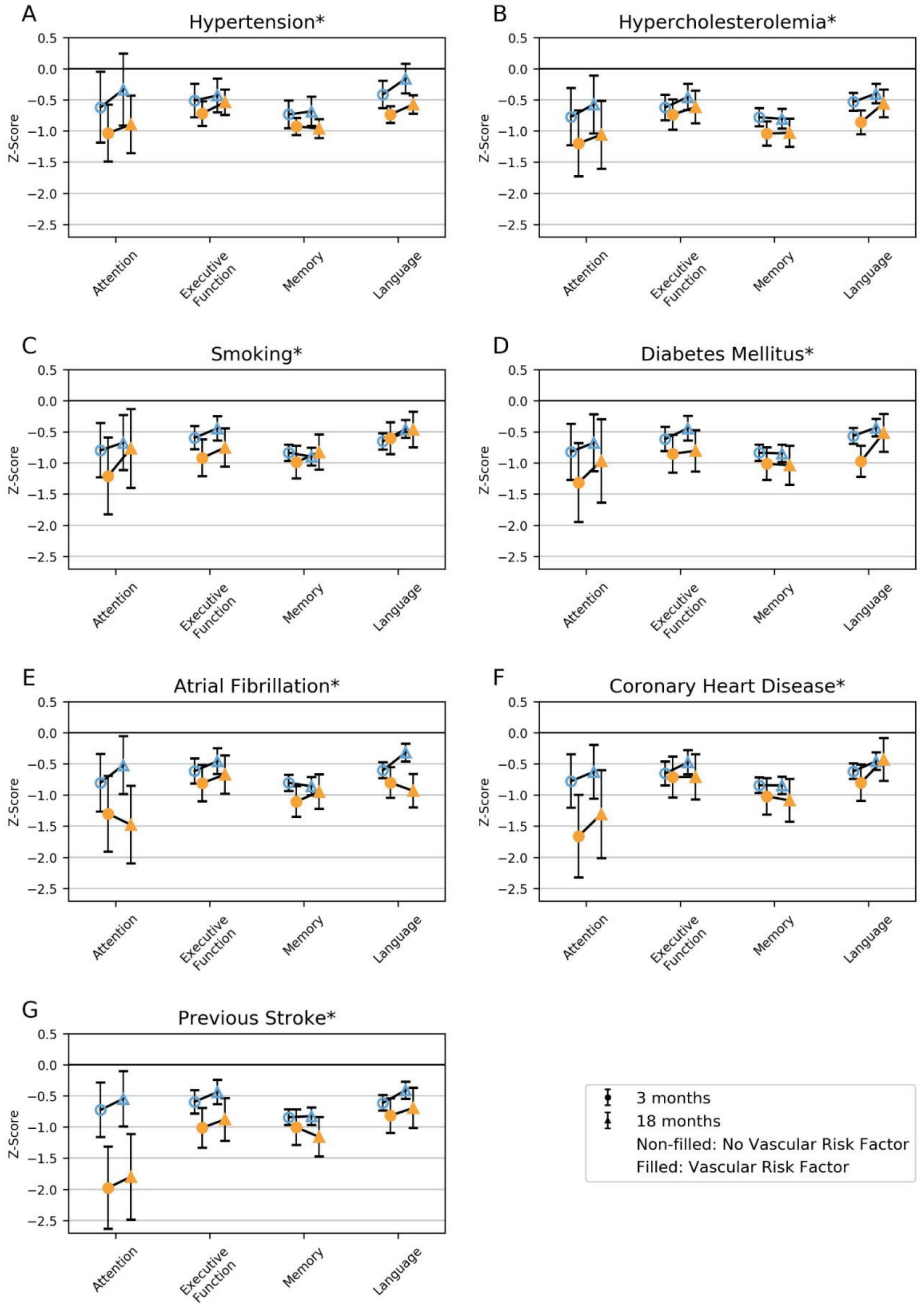

Figure S3. Sensitivity analyses without adjustment: Mean z-score with 95% CI for the cognitive domains for the different vascular risk factors at 3- and 18-months post-stroke in model 1

*unadjusted analysis

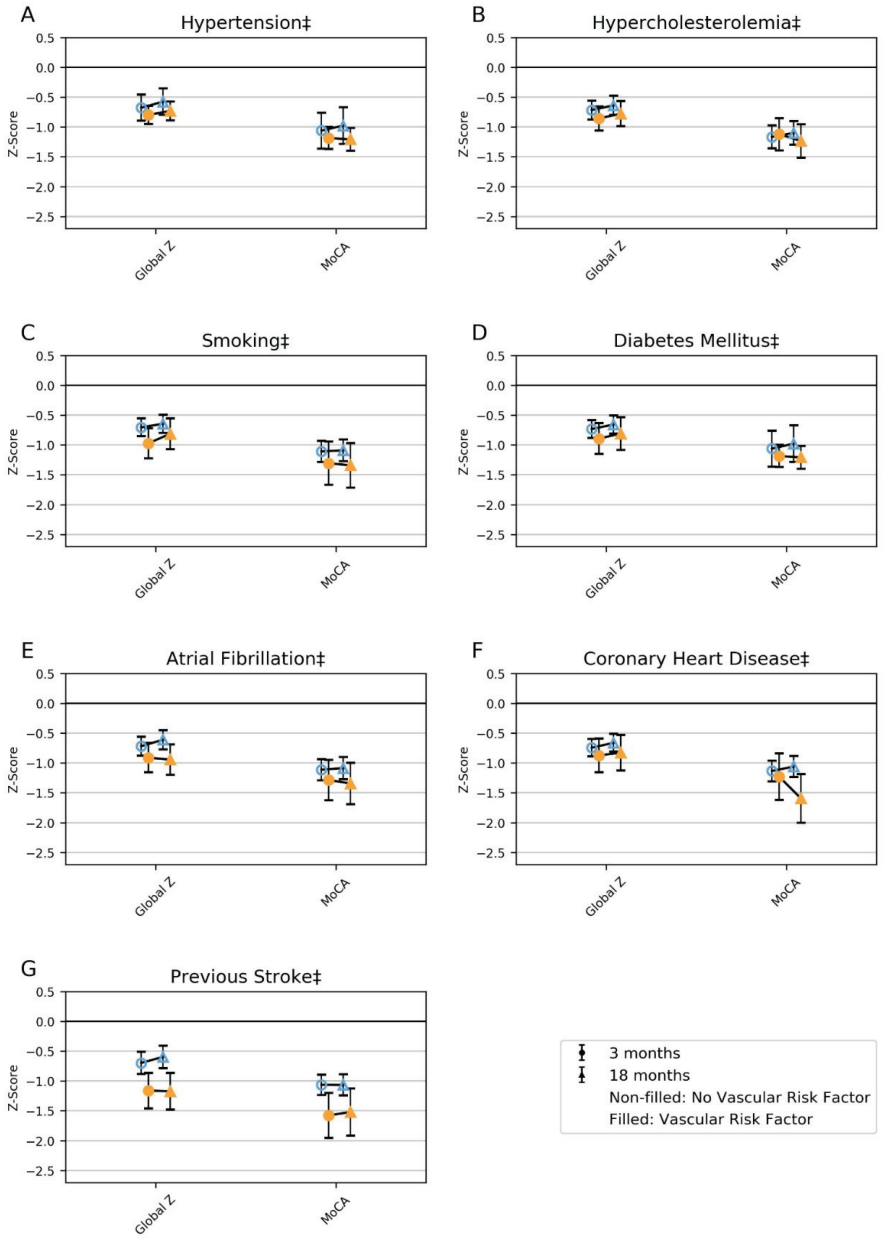

Figure S4. Sensitivity analyses with exclusion of patients deceased at 18 months: Mean z-scores with 95% confidence intervals for the global cognitive measures for the different vascular risk factors at 3- and 18-months post-stroke, adjusted for age, education and sex in model 1

MoCA = Montreal Cognitive Assessment

‡ exclusion of patients deceased at 18 months, adjusted for age, education, and sex

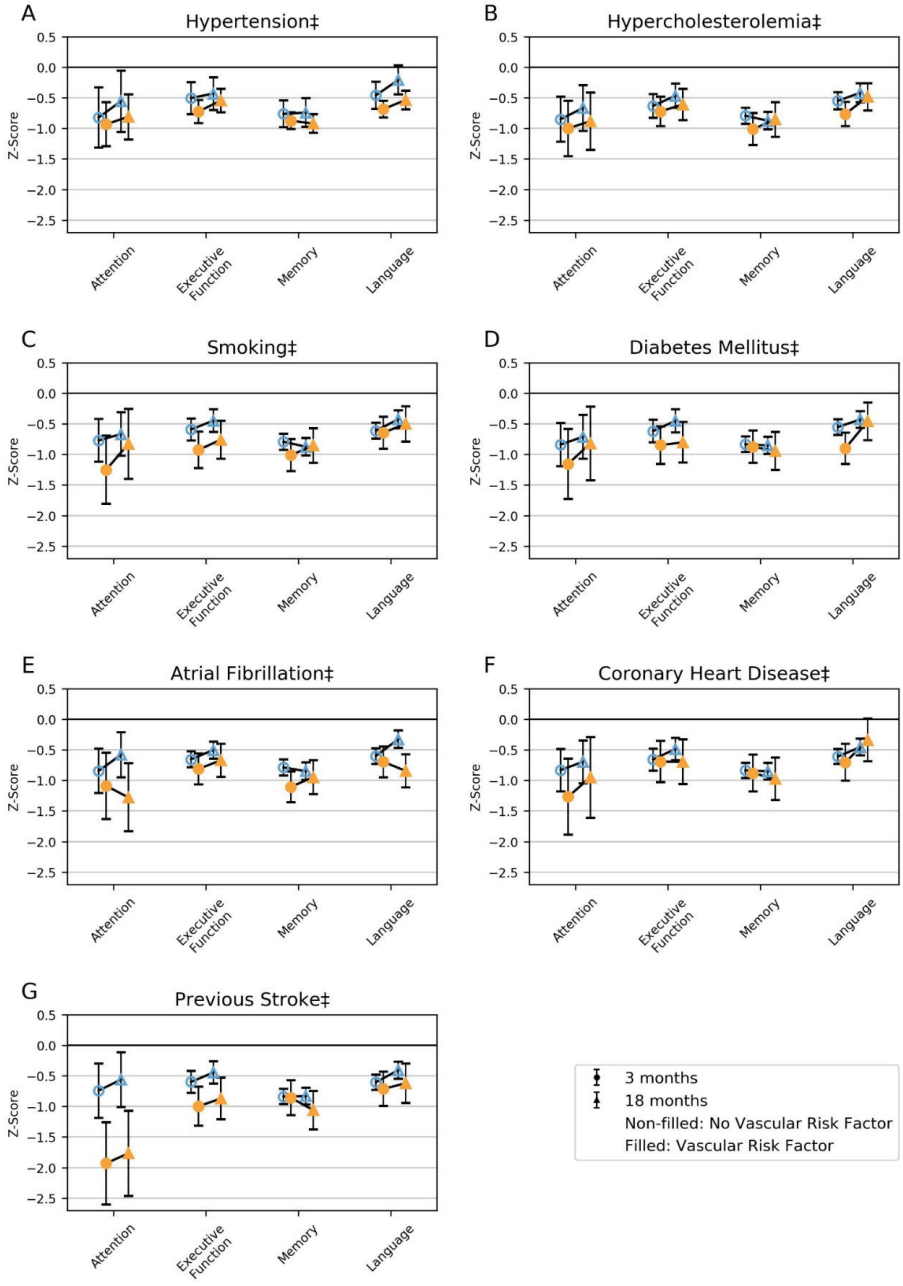

Figure S5. Sensitivity analyses with exclusion of patients deceased at 18 months: Mean z-scores with 95% confidence intervals for the cognitive domains for the different vascular risk factors at 3- and 18-months post-stroke, adjusted for age, education and sex in model 1

‡ exclusion of patients deceased at 18 months, adjusted for age, education, and sex

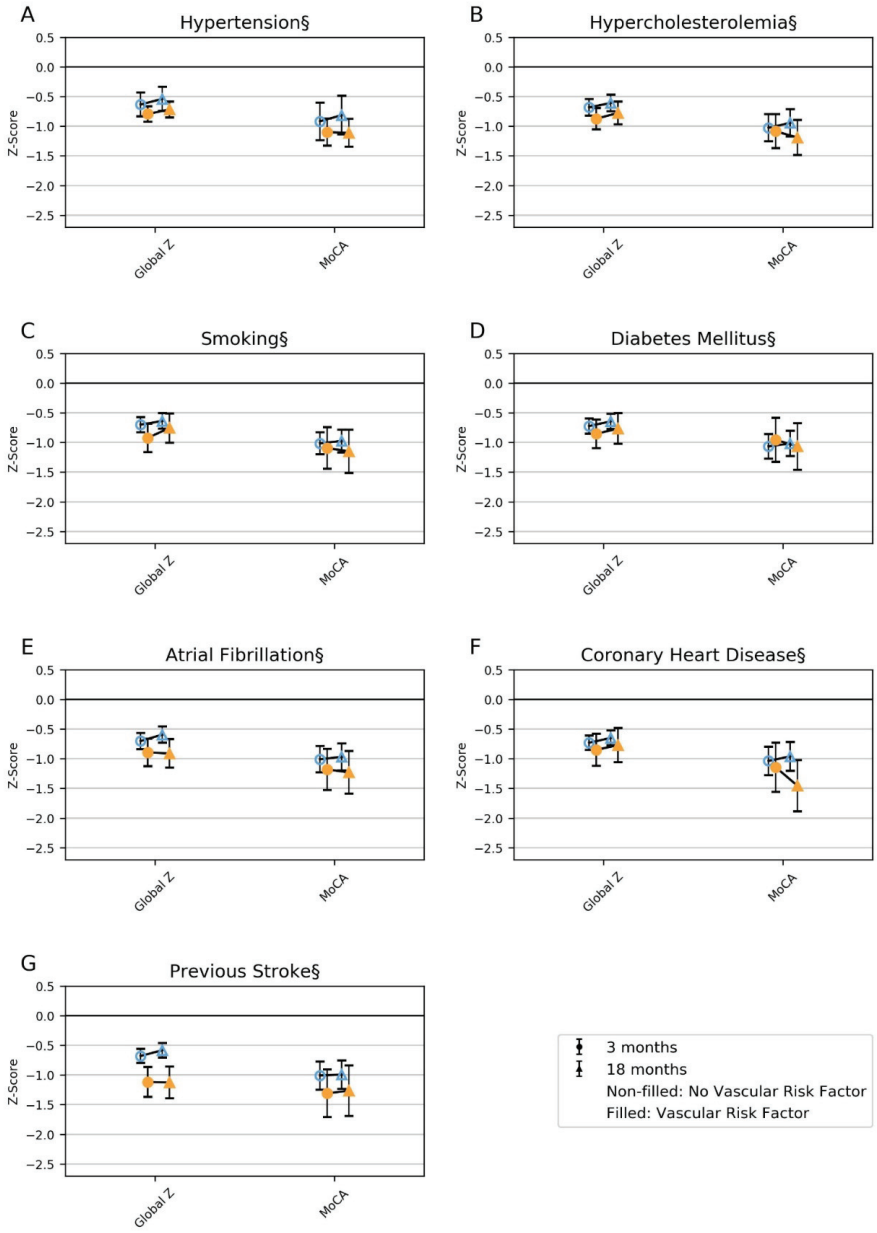

Figure S6. Sensitivity analyses with exclusion of patients with pre-stroke dementia: Mean z-scores with 95% confidence intervals for the global cognitive measures for the different vascular risk factors at 3- and 18-months post-stroke, adjusted for age, education and sex in model 1

MoCA = Montreal Cognitive Assessment

§ exclusion of patients with pre-stroke dementia, defined as pre-stroke Global Deterioration Scale 4-7, adjusted for age, education, and sex

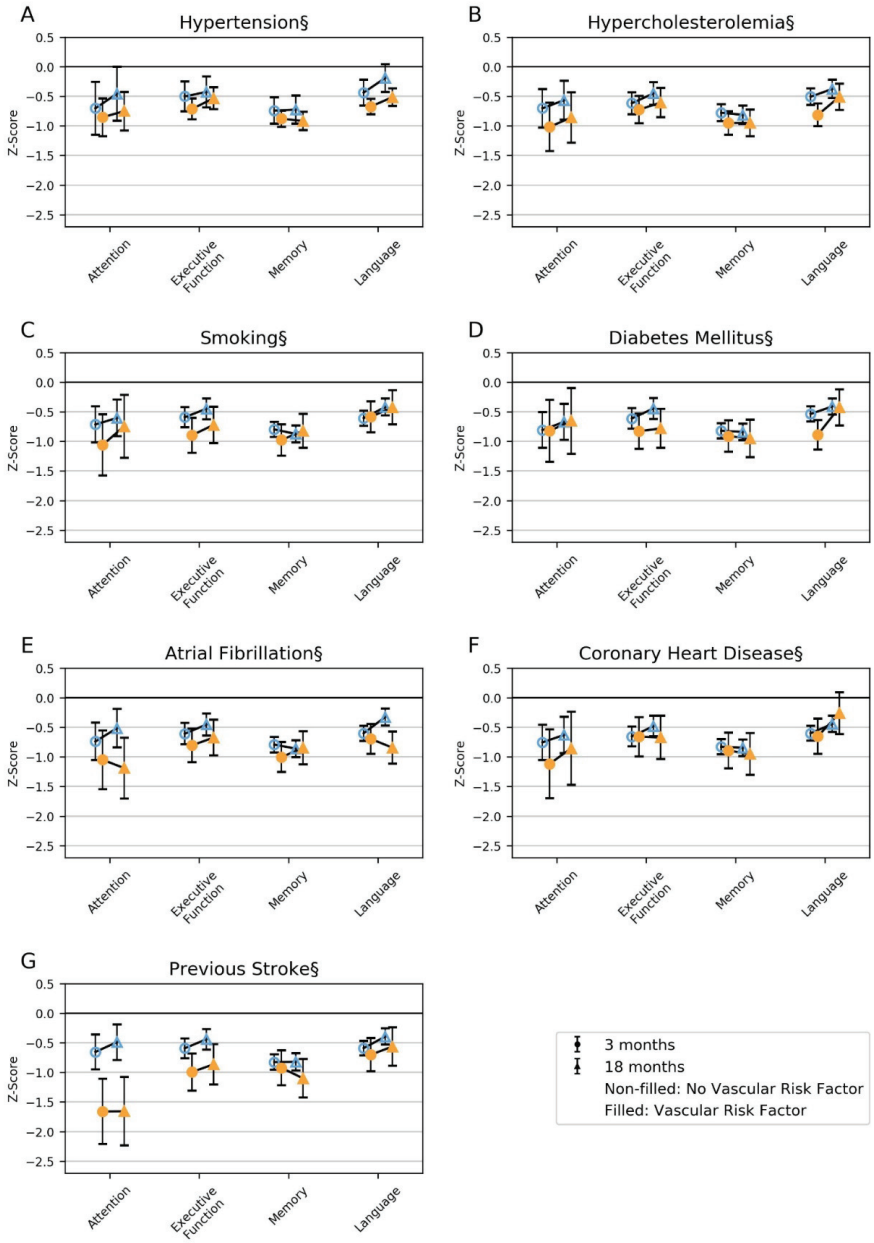

Figure S7. Sensitivity analyses with exclusion of patients with pre-stroke dementia: Mean z-scores with 95% confidence intervals for the cognitive domains for the different vascular risk factors at 3- and 18-months post-stroke, adjusted for age, education and sex in model 1

§ exclusion of patients with pre-stroke dementia, defined as pre-stroke Global Deterioration Scale 4-7, adjusted for age, education, and sex

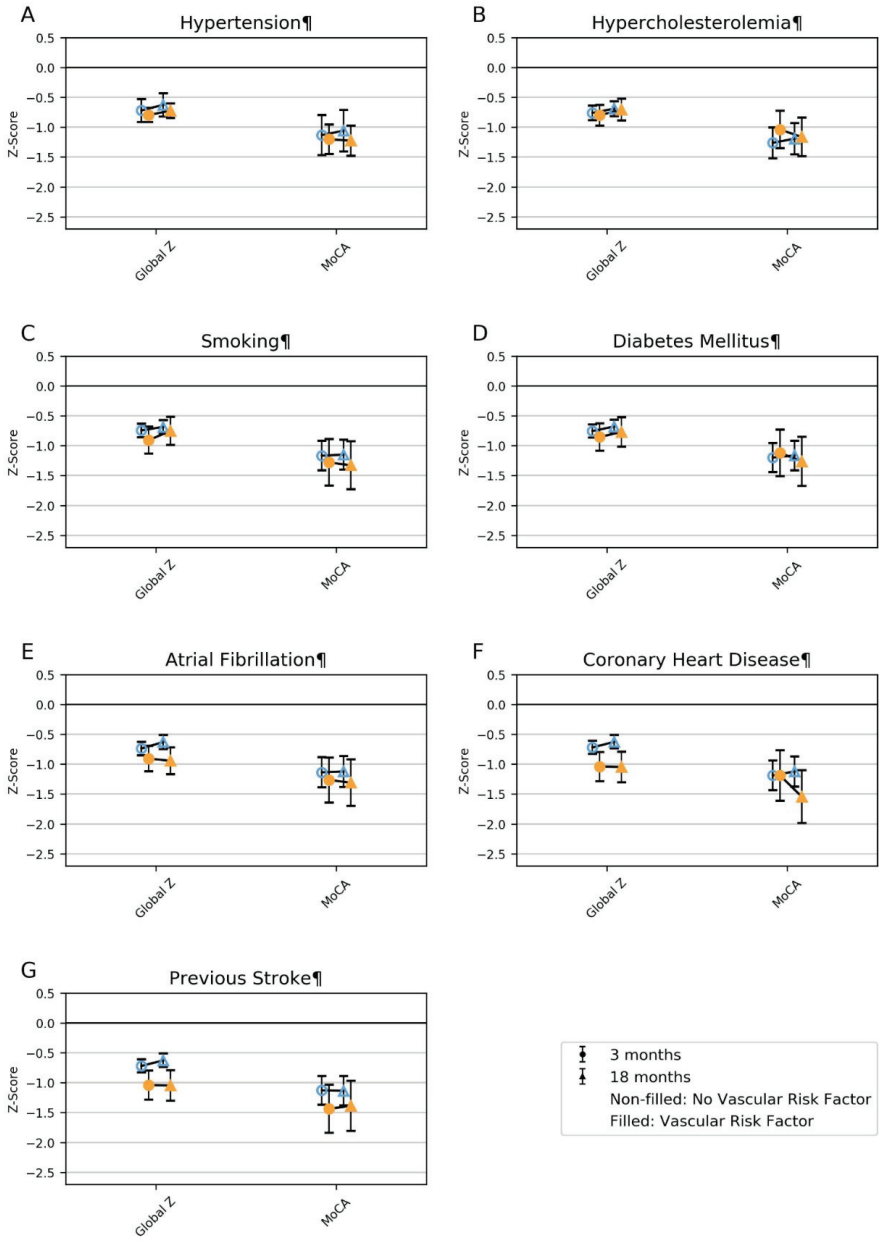

Figure S8. Sensitivity analyses with adjustment for age, education, sex, pre-stroke mRS, and NIHSS: Mean z-scores with 95% confidence intervals for the global cognitive measures for the different vascular risk factors at 3- and 18-months post-stroke in model 1

MoCA = Montreal Cognitive Assessment

¶ adjusted for age, education and sex, pre-stroke modified Rankin Scale (mRS), and National Institutes of Health Stroke Scale (NIHSS)

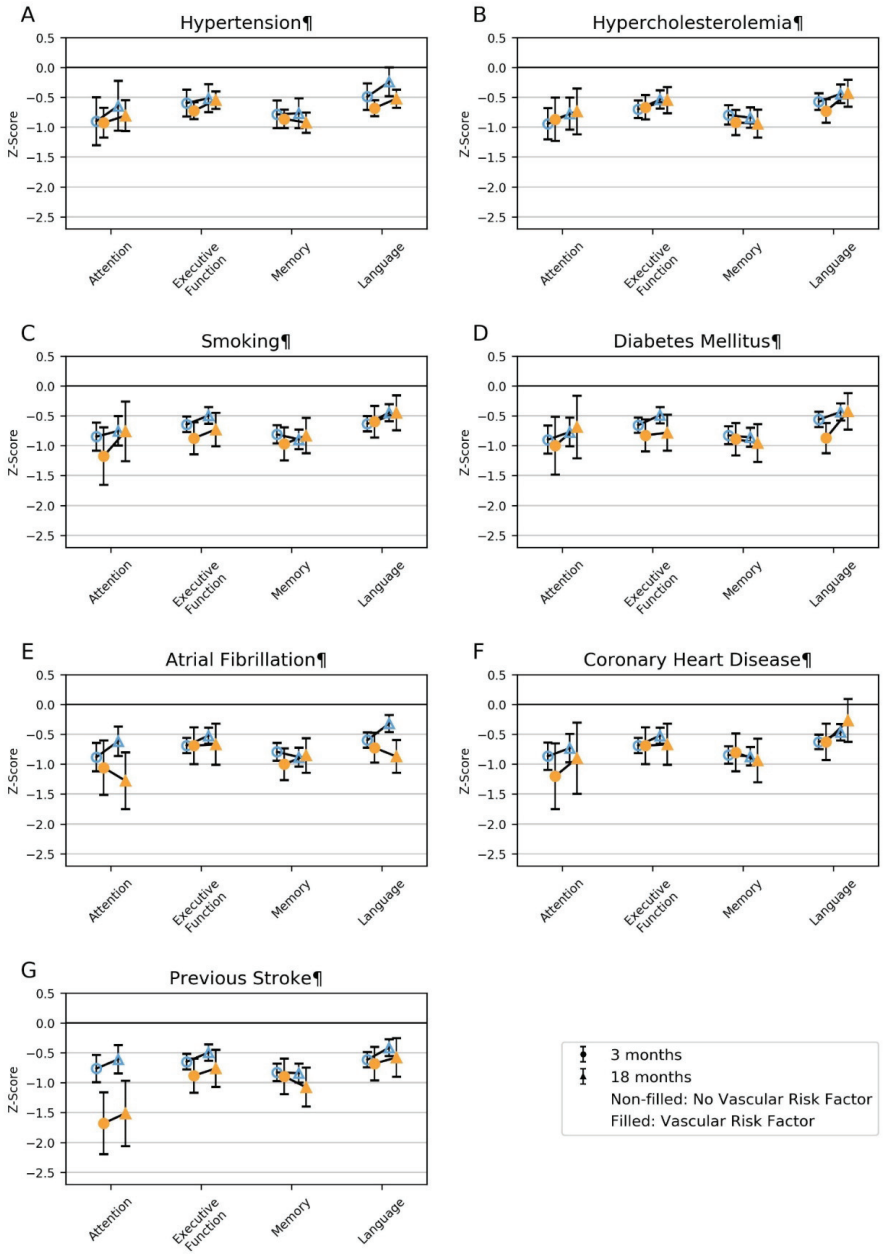

Figure S9. Sensitivity analyses with adjustment for age, education, sex, pre-stroke mRS, and NIHSS: Mean z-scores with 95% confidence intervals for the cognitive domains for the different vascular risk factors at 3- and 18-months post-stroke in model 1

¶ adjusted for age, education and sex, pre-stroke modified Rankin Scale (mRS), and, National Institutes of Health Stroke Scale (NIHSS)

Table S4. Hypothesis test of whether there is an effect of the vascular risk factor and follow-up time in model 1 for the global measures and cognitive domains for the different vascular risk factors for unadjusted analyses								
		Hypertension	**Hypercholesterolemia**	**Smoking**	**Diabetes mellitus**	**Atrial fibrillation**	**Coronary heart disease**	**Previous stroke**
Global z	LR_{vasc} $\chi2(2)$, p-value	4.89, 0.087	6.22, 0.045	3.02, 0.221	3.60, 0.165	10.68, 0.005*	4.95, 0.084	17.40, <0.001*
	LR_{time} $\chi2(2)$, p-value	6.29, 0.043	5.97, 0.050	7.64, 0.022	6.00, 0.050	9.07, 0.011	6.08, 0.048	7.21, 0.027
MoCA	LR_{vasc} $\chi2(2)$, p-value	8.60, 0.014	5.73, 0.057	0.11, 0.948	3.84, 0.147	10.54, 0.005*	20.77, <0.001*	10,89, 0.004
	LR_{time} $\chi2(2)$, p-value	0.73., 0.695	2.31, 0.315	0.26, 0.880	1.46, 0.481	0.55, 0.758	6.64, 0.036	0.27, 0.872
Attention	LR_{vasc} $\chi2(2)$, p-value	4.44, 0.109	3.89, 0.143	3.73, 0.155	3.14, 0.209	12.61, 0.002*	7.92, 0.019	18.07, <0.001*
	LR_{time} $\chi2(2)$, p-value	6.03, 0.049	5.38, 0.068	8.45, 0.015	6.19, 0.045	11.39, 0.003*	5.96, 0.051	5.25, 0.073
Executive function	LR_{vasc} $\chi2(2)$, p-value	2.48, 0.290	1.45, 0.484	5.09, 0.079	4.66, 0.097	2.26, 0.323	1.87, 0.393	8.19, 0.017
	LR_{time} $\chi2(2)$, p-value	8.96, 0.011	8.32, 0.016	8.14, 0.017	8.80, 0.012	8.31, 0.016	9.50, 0.009*	8.20, 0.017
Memory	LR_{vasc} $\chi2(2)$, p-value	3.90, 0.142	4.78, 0.093	2.44, 0.295	1.72, 0.424	4.92, 0.027	1.88, 0.170	3.54, 0.060

	LR_{time} $\chi2(2)$, p-value	0.41, 0.937	0.12, 0.944	2.32, 0.128	0.04, 0.998	2.16, 0.142	0.15, 0.696	1.07, 0.585
Language	LR_{vasc} $\chi2(2)$, p-value	9.35, 0.009*	7.26, 0.027	0.21, 0.901	9.32, 0.001*	16.14, <0.001*	1.96, 0.376	2.83, 0.243
	LR_{time} $\chi2(2)$, p-value	10.41, 0.006*	11.68, 0.003*	9.94, 0.007*	13.96, <0.001*	18.97, <0.001*	11.59, 0.003*	10.35, 0.006*

MoCA=Montreal Cognitive Assessment.
LR_{vasc} $\chi2(2)$ =Likelihood ratio test model 1 vs model 2, with two degrees of freedom; hypothesis test of whether there is an effect of the vascular risk factor.
LR_{time} $\chi2(2)$ =Likelihood ratio test model 1 vs model 3, with two degrees of freedom; hypothesis test of whether there is an effect of follow-up time.
*p<0.01

Table S5. Hypothesis test of whether there is an effect of the vascular risk factor and follow-up time in model 1 for the global measures and cognitive domains for the different vascular risk factors for analyses with exclusion of deceased at 18 months adjusted for age, education and sex								
		Hypertension	**Hypercholesterolemia**	**Smoking**	**Diabetes mellitus**	**Atrial fibrillation**	**Coronary heart disease**	**Previous stroke**
Global z	LR_{vasc} $\chi2(2)$, p-value	1.56, 0.458	2.39, 0.302	4.32, 0.116	1.42, 0.491	6.79, 0.034	1.09, 0.579	12.76, 0.002*
	LR_{time} $\chi2(2)$, p-value	5.27, 0.072	5.30, 0.071	6.65, 0.036	5.02, 0.081	7.95, 0.019	5.16, 0.076	6.40, 0.041
MoCA	LR_{vasc} $\chi2(2)$, p-value	1.63, 0.653	1.94, 0.380	1.41, 0.236	1.64, 0.651	1.62, 0.655	8.50, 0.014	6.08, 0.108
	LR_{time} $\chi2(2)$, p-value	0.63, 0.730	1.90, 0.386	0.13, 0.723	1.00, 0.608	0.35, 0.840	6.69, <0.01*	0.13, 0.936
Attention	LR_{vasc} $\chi2(2)$, p-value	1.21, 0.546	0.75, 0.687	4.24, 0.120	1.71, 0.425	5.59, 0.014	1.53, 0.466	14.09, 0.001*
	LR_{time} $\chi2(2)$, p-value	5.09, 0.079	4.51, 0.105	7.36, 0.025	5.33, 0.070	10.36, <0.001*	4.16, 0.125	4.31, 0.116
Executive function	LR_{vasc} $\chi2(2)$, p-value	2.59, 0.274	1.04, 0.595	4.93, 0.085	4.19, 0.123	2.55, 0.279	1.64, 0.442	7.20, 0.027
	LR_{time} $\chi2(2)$, p-value	8.51, 0.014	7.87, 0.020	7.55, 0.023	8.27, 0.016	7.79, 0.020	8.98, 0.011	7.69, 0.021

Memory	LR_{vasc} $\chi2(2)$, p-value	1.63, 0.442	0.71, 0.400	3.33, 0.189	0.28, 0.870	3.58, 0.167	0.40, 0.528	2.13, 0.144
	LR_{time} $\chi2(2)$, p-value	0.46, 0.796	0.18, 0.912	2.87, 0.090	0.28, 0.964	2.51, 0.285	0.35, 0.839	1.76, 0.184
Language	LR_{vasc} $\chi2(2)$, p-value	5.42, 0.067	3.41, 0.182	0.21, 0.900	7.12, 0.028	12.65, 0.002*	1.51, 0.470	1.43, 0.489
	LR_{time} $\chi2(2)$, p-value	9.50, 0.009*	10.48, 0.005*	8.83, 0.012	12.79, 0.002*	18.05, <0.001*	10.63, 0.005*	9.47, 0.009*

MoCA=Montreal Cognitive Assessment.
LR_{vasc} $\chi2(2)$ =Likelihood ratio test model 1 vs model 2, with two degrees of freedom; hypothesis test of whether there is an effect of the vascular risk factor.
LR_{time} $\chi2(2)$ =Likelihood ratio test model 1 vs model 3, with two degrees of freedom; hypothesis test of whether there is an effect of follow-up time.
*p<0.01

Table S6. Hypothesis test of whether there is an effect of the vascular risk factor and time in model 1 for the global measures and cognitive domains for the different vascular risk factors for analyses with exclusion of pre-stroke dementia adjusted for age, education and sex								
		Hypertension	**Hypercholesterolemia**	**Smoking**	**Diabetes mellitus**	**Atrial fibrillation**	**Coronary heart disease**	**Previous stroke**
Global z	LR_{vasc} $\chi2(2)$, p-value	2.30, 0.317	3.07, 0.215	3.41, 0.182	0.98, 0.612	6.02, 0.050	0.71, 0.701	13.93, <0.001*
	LR_{time} $\chi2(2)$, p-value	5.56, 0.062	5.53, 0.063	7.23, 0.027	5.47, 0.065	7.74, 0.021	5.48, 0.065	6.61, 0.037
MoCA	LR_{vasc} $\chi2(2)$, p-value	2.87, 0.239	3.00, 0.223	0.80, 0.670	1.03, 0.596	1.82, 0.402	6.92, 0.031	2.27, 0.321
	LR_{time} $\chi2(2)$, p-value	0.83, 0.662	2.25, 0.325	0.51, 0.776	1.08, 0.582	0.46, 0.793	5.27, 0.072	0.12, 0.941
Attention	LR_{vasc} $\chi2(2)$, p-value	1.64, 0.440	1.98, 0.372	2.17, 0.338	0.02, 0.988	7.54, 0.02	2.12, 0.347	15.70, <0.001*
	LR_{time} $\chi2(2)$, p-value	4.62, 0.099	3.79, 0.150	5.33, 0.070	3.87, 0.145	8.11, 0.017	5.11, 0.078	4.37, 0.113
Executive function	LR_{vasc} $\chi2(2)$, p-value	2.45, 0.294	1.24, 0.539	3.96, 0.138	3.80, 0.150	2.15, 0.342	1.57, 0.453	7.12, 0.028
	LR_{time} $\chi2(2)$, p-value	8.50, 0.014	7.78, 0.020	7.59, 0.023	8.26, 0.016	7.79, 0.020	9.12, 0.011	7.65, 0.022

Memory	LR_{vasc} $\chi2(2)$, p-value	1.91, 0.592	1.99, 0.575	2.68, 0.261	0.50, 0.918	3.15, 0.369	0.29, 0.962	2.44, 0.486
	LR_{time} $\chi2(2)$, p-value	†	0.22, 0.895	2.56, 0.278	0.15, 0.929	2.42, 0.490	0.17, 0.917	1.26, 0.532
Language	LR_{vasc} $\chi2(2)$, p-value	5.56, 0.062	6.48, 0.039	0.04, 0.980	7.71, 0.021	12.89, 0.002*	1.77, 0.412	0.94, 0.0624
	LR_{time} $\chi2(2)$, p-value	9.86, 0.007*	11.55, 0.003*	9.26, <0.001*	13.75, 0.001*	19.43, <0.001*	11.43, 0.003*	9.71, 0.008*

MoCA=Montreal Cognitive Assessment.
LR_{vasc} $\chi2(2)$ =Likelihood ratio test model 1 vs model 2, with two degrees of freedom; hypothesis test of whether there is an effect of the vascular risk factor.
LR_{time} $\chi2(2)$ =Likelihood ratio test model 1 vs model 3, with two degrees of freedom; hypothesis test of whether there is an effect of follow-up time.
*$p<0.01$
† calculations did not converge

Table S7. Hypothesis test of whether there is an effect of the vascular risk factor and follow-up time in model 1 for the global measures and cognitive domains for the different vascular risk factors for analyses adjusted for age, education, sex, pre-stroke mRS and NIHSS								
		Hypertension	**Hypercholesterolemia**	**Smoking**	**Diabetes mellitus**	**Atrial fibrillation**	**Coronary heart disease**	**Previous stroke**
Global z	LR_{vasc} $\chi2(2)$, p-value	0.71, 0.703	0.18, 0.913	2.15, 0.341	0.61, 0.738	6.45, 0.040	0.35, 0.841	8.50, 0.014
	LR_{time} $\chi2(2)$, p-value	5.09, 0.079	5.07, 0.079	6.14, 0.046	4.94, 0.085	7.89, 0.019	5.17, 0.076	6.10, 0.047
MoCA	LR_{vasc} $\chi2(2)$, p-value	0.99, 0.608	3.06, 0.217	0.77, 0.682	0.99, 0.608	0.89, 0.642	6.92, 0.031	2.30, 0.317
	LR_{time} $\chi2(2)$, p-value	0.52, 0.771	2.25, 0.324	0.21, 0.901	0.52, 0.771	0.16, 0.923	6.17, 0.046	0.12, 0.942
Attention	LR_{vasc} $\chi2(2)$, p-value	0.75, 0.686	0.13, 0.939	3.16, 0.207	0.82, 0.664	8.82, 0.012	1.37, 0.503	10.78, 0.005*
	LR_{time} $\chi2(2)$, p-value	4.70, 0.095	4.15, 0.125	6.76, 0.034	4.88, 0.087	10.73, 0.005*	4.43, 0.104	4.04, 0.133
Executive function	LR_{vasc} $\chi2(2)$, p-value	1.14, 0.767	0.17, 0.916	2.67, 0.263	3.04, 0.386	1.41, 0.494	0.93, 0.819	2.73, 0.435
	LR_{time} $\chi2(2)$, p-value	8.18, 0.043	7.72, <0.001*	7.54, 0.023	8.10, 0.018	7.55, 0.006*	8.32, 0.016	7.55, 0.056

Memory	LR_{vasc} $\chi2(2)$, p-value	1.17, 0.0558	1.01, 0.603	2.38, 0.304	0.33, 0.847	3.24, 0.176	0.36, 0.834	1.88, 0.390
	LR_{time} $\chi2(2)$, p-value	0.77, 0.680	0.46, 0.795	2.52, 0.283	0.45, 0.799	2.90, 0.234	0.75, 0.687	1.42, 0.491
Language	LR_{vasc} $\chi2(2)$, p-value	3.93, 0.139	2.28, 0.319	0.10, 0.951	6.31, 0.043	13.32, 0.001*	1.34, 0.511	0.83, 0.660
	LR_{time} $\chi2(2)$, p-value	9.63, 0.008*	10.88, 0.004*	8.90, 0.012	13.06, 0.002*	18.03, <0.001*	10.54, <0.01*	9.66, 0.008*

MoCA=Montreal Cognitive Assessment.
LR_{vasc} $\chi2(2)$ =Likelihood ratio test model 1 vs model 2, with two degrees of freedom; hypothesis test of whether there is an effect of the vascular risk factor.
LR_{time} $\chi2(2)$ =Likelihood ratio test model 1 vs model 3, with two degrees of freedom; hypothesis test of whether there is an effect of follow-up time.
*p<0.01

Table S8. Numbers of patients with the different vascular risk factors included in the analyses																								
			HTN			HC			S			DM			AF			CHD			PS			
			N	Y	T	N	Y	T	N	Y	T	N	Y	T	N	Y	T	N	Y	T	N	Y	T	
Global z	Unadjusted and adjusted for age, education, and sex	3 months	156	409	565	365	200	565	450	112	562	457	108	565	438	127	565	474	91	565	468	97	565	
		18 months	132	320	452	308	144	452	356	93	449	380	72	452	355	97	452	392	60	452	382	70	452	
	Exclusion of deceased (n=17) adjusted for age, education, and sex	3 months	152	396	548	357	191	548	435	110	545	445	103	548	461	87	548	461	87	548	455	93	548	
		18 months	132	320	452	308	144	452	356	93	449	380	72	452	392	60	452	392	60	452	382	70	452	
	Exclusion of pre-stroke dementia (n=12) adjusted for age, education, and sex	3 months	153	400	553	358	195	553	441	109	550	449	104	553	431	122	553	466	87	553	461	92	553	
		18 months	132	315	447	305	142	447	353	91	444	376	71	447	352	95	447	389	58	447	380	67	447	
	Adjusted for age, education, sex, pre-stroke mRS, and NIHSS	3 months	152	397	549	355	194	549	440	108	548	443	106	549	427	122	549	463	86	549	453	96	549	
		18 months	130	314	444	303	141	444	351	92	443	372	72	444	350	94	444	387	57	444	374	70	444	
MoCA	Unadjusted and adjusted for age, education, and sex	3 months	168	437	605	393	209	605	486	116	602	491	114	605	465	140	605	501	104	605	496	109	605	
		18 months	141	367	508	339	169	508	406	99	505	422	86	508	395	113	508	428	80	508	427	81	508	
	Exclusion of deceased (n=20) adjusted for age, education, and sex	3 months	162	423	585	385	200	585	469	113	582	478	105	583	485	100	585	486	97	583	483	102	585	
		18 months	141	367	508	339	169	369	406	99	505	415	81	496	428	80	508	421	75	496	427	81	508	
	Exclusion of pre-stroke dementia (n=22) adjusted for age, education, and sex	3 months	163	420	583	381	202	583	468	112	580	478	105	583	451	132	583	486	97	583	484	99	583	
		18 months	139	367	496	331	165	496	397	96	493	415	81	496	388	108	496	421	75	496	421	75	496	

	Adjusted for age, education, sex, pre-stroke mRS, and NIHSS	3 months	164	424	588	385	203	588	475	112	587	477	111	588	454	134	588	489	99	588	480	108	588
		18 months	138	659	497	331	166	497	398	98	496	412	85	497	388	109	497	420	77	497	416	81	497
Attention	Unadjusted and adjusted for age, education, and sex	3 months	155	410	565	367	198	565	452	110	562	155	410	565	437	128	565	473	92	565	469	96	565
		18 months	131	323	454	309	145	454	360	91	451	131	323	454	354	100	454	394	60	454	385	69	454
	Exclusion of deceased (n=18) adjusted for age, education, and sex	3 months	150	397	547	358	189	547	436	108	544	150	397	547	425	122	547	459	88	547	456	91	547
		18 months	131	323	454	309	145	454	360	91	451	131	323	454	354	100	454	394	60	454	385	69	454
	Exclusion of pre-stroke dementia (n=14) adjusted for age, education, and sex	3 months	153	398	551	358	193	551	442	106	548	153	398	551	428	123	551	464	87	551	461	90	551
		18 months	131	319	450	307	143	450	358	89	447	131	319	450	352	98	450	392	58	450	383	67	450
	Adjusted for age, education, sex, pre-stroke mRS, and NIHSS	3 months	151	399	550	357	193	550	441	107	548	151	399	550	428	122	550	463	87	550	455	95	550
		18 months	129	317	446	304	142	446	355	90	445	129	317	446	349	97	446	389	57	446	377	69	446
Executive function	Unadjusted and adjusted for age, education, and sex	3 months	151	407	558	358	200	558	445	110	555	450	108	558	432	126	558	468	90	558	450	108	558
		18 months	132	318	450	308	142	450	355	92	447	378	72	450	353	97	450	391	59	450	378	72	450
	Exclusion of deceased (n=17) adjusted for age, education, and sex	3 months	147	394	541	350	191	541	430	108	538	147	394	541	420	121	541	455	86	541	449	92	541
		18 months	132	318	450	308	142	450	355	92	447	132	318	450	353	97	450	391	59	450	380	70	450
	Exclusion of pre-stroke dementia (n=11) adjusted for age, education, and sex	3 months	149	398	547	352	195	547	436	106	542	443	104	547	426	121	547	461	86	547	456	91	547
		18 months	132	313	445	305	140	445	350	91	441	374	71	445	350	95	445	388	57	445	378	67	445

	Adjusted for age, education, sex, pre-stroke mRS, and NIHSS	3 months	148	395	543	349	194	543	436	106	542	437	106	543	422	121	543	458	85	543	437	106	543
		18 months	130	312	442	303	139	442	350	91	441	370	72	442	348	94	442	386	56	442	370	72	442
Memory	Unadjusted and adjusted for age, education, and sex	3 months	137	355	492	318	174	492	393	97	490	395	97	492	383	109	492	415	77	492	412	80	492
		18 months	110	255	365	251	114	365	287	75	362	307	58	365	288	77	365	317	48	365	306	59	365
	Exclusion of deceased (n=15) adjusted for age, education, and sex	3 months	133	344	477	311	166	477	380	95	475	384	93	477	373	104	477	403	74	477	401	76	477
		18 months	110	255	365	251	114	365	287	75	362	307	58	365	288	77	365	317	48	365	306	59	365
	Exclusion of pre-stroke dementia (n=10) adjusted for age, education, and sex	3 months	134	348	482	312	170	482	386	94	480	387	95	482	377	105	482	407	75	482	407	75	482
		18 months	110	251	361	248	113	361	284	74	358	305	56	361	285	76	361	315	46	361	305	56	361
	Adjusted for age, education, sex, pre-stroke mRS, and NIHSS	3 months	133	346	479	310	169	479	383	95	478	384	95	479	375	104	479	407	72	479	400	79	479
		18 months	108	249	357	246	111	357	282	74	356	299	58	357	283	74	357	312	45	357	298	59	357
Language	Unadjusted and adjusted for age, education, and sex	3 months	130	350	480	310	170	480	383	94	477	381	99	480	379	101	480	407	73	480	398	82	480
		18 months	101	238	339	230	109	339	267	69	336	284	55	339	262	77	339	294	45	339	287	52	339
	Exclusion of deceased (n=15) adjusted for age, education, and sex	3 months	126	339	465	303	162	465	370	92	462	370	95	465	369	96	465	395	70	465	387	78	465
		18 months	101	238	339	230	109	339	267	69	336	284	55	339	262	77	339	294	45	339	287	52	339
	Exclusion of pre-stroke dementia (n=9) adjusted for age, education, and sex	3 months	129	342	471	306	165	471	376	92	468	374	97	471	374	97	471	401	70	471	394	77	471
		18 months	101	234	355	228	107	335	265	67	332	281	54	335	259	76	335	292	43	335	286	49	335

	Adjusted for age, education, sex, pre-stroke mRS, and NIHSS	3 months	127	340	467	302	165	467	376	92	468	370	97	467	369	98	467	399	68	467	385	82	467
		18 months	99	232	331	225	106	331	265	67	332	276	55	331	262	77	339	289	42	331	279	52	331
HTN = Hypertension, HC = Hypercholesterolemia, S = Smoking, DM = Diabetes mellitus, AF = Atrial fibrillation, CHD = Coronary heart disease, PS = Previous stroke, N = No, Y = Yes, T = Total, MoCA= Montreal Cognitive Assessment, mRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale																							

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ISBN 978-82-326-6363-7 (printed ver.)
ISBN 978-82-326-5744-5 (electronic ver.)
ISSN 1503-8181 (printed ver.)
ISSN 2703-8084 (online ver.)

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