Participation after stroke

Towards personalized care

UMC Utrecht Brain Center

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Participatie na een beroerte

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(met een samenvatting in het Nederlands)

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door

Joris Anton de Graaf

geboren op 1 september 1991
te 's-Hertogenbosch

Promotoren:	Prof. dr. J.M.A. Visser-Meily
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Copromotor:	Dr. V.P.M. Schepers

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Contents

Chapter 1

General introduction

STROKE

Stroke is one of the leading causes of death and disability worldwide.[1] The incidence of stroke has increased over the last decades due to the aging population, and is expected to rise even further in the coming years.[2] In the Netherlands, about 45,000 people suffer a first stroke each year.[3] Due to major improvements in the acute treatment of stroke (such as intravenous thrombolysis, mechanical thrombectomy and implementation of stroke units), survival rates have increased and more people are able to return home after stroke.[4] However, this has also resulted in in more people that have to deal with the long term consequences of stroke, such as physical, emotional, and cognitive problems, causing considerable long term restrictions in social and community participation.[5] "How can we improve participation and integration into society among stroke survivors?" is therefore among the main research and development priorities in the European Stroke Action Plan for the years 2018 to 2030 composed by the European Stroke Organisation.[6]

PARTICIPATION

The International Classification of Functioning, Disability and Health (ICF, Figure 1.1) is a widely used framework, which can be used to describe the impact of stroke on the individual at three levels: body functions and structures, activities and participation, which are intertwined with personal factors (such as gender, age and personality traits) and environmental

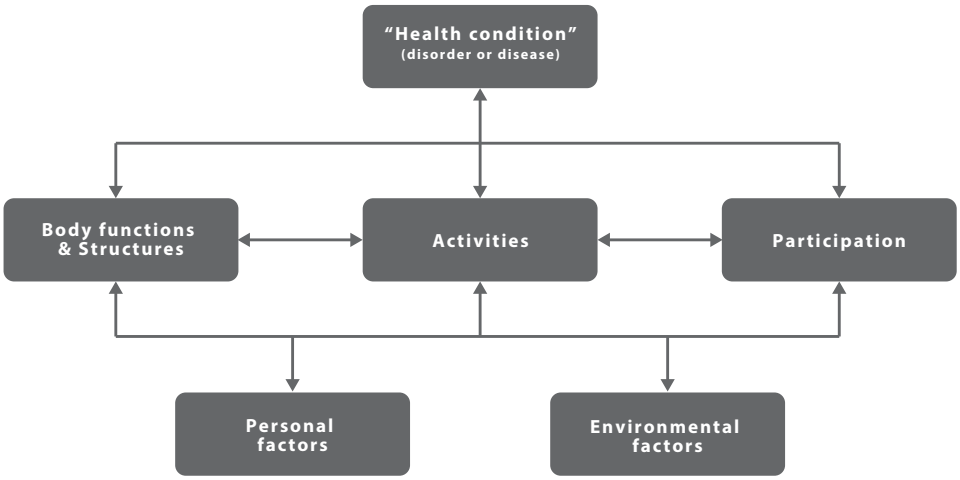

Figure 1.1: The International Classification of Functioning, Disability and Health (ICF), adapted from the World Health Organization (2001).[7]

factors (such as living situation and social support).[7] Participation has a central role in the ICF and is defined as "the person's involvement in a life situation",[7] including daily activities as well as social roles.[8] In comparison with the body functions and activities domains, participation is known to be more strongly influenced by cognitive functioning, personal factors and environmental factors[9] This may for example explain why many people experience long term restrictions in participation after stroke, despite good physical recovery or being independent in activities of daily living.[10]

RECOVERY AFTER STROKE

Stroke recovery is a highly heterogenous and complex process (including restitution, substitution and compensation) over time, which can be approached from various ICF levels. In general, recovery patterns of people with stroke differ greatly, varying from full recovery within hours or days to hardly any improvement in the long term after stroke.[11] Spontaneous neurological recovery (level of body functions) follows a nonlinear pattern over time, and mainly takes place in the first three months after stroke (Figure 1.2).[12] Improvement in functional outcome (level of activities) often exceeds this time window and is also observed after three months.[13]

Mirroring recovery of body functions and activities in the first months post-stroke, improvement in participation after stroke is mainly observed in the first six months up to one year after stroke.[14] Despite these improvements, many people with stroke experience persisting or increasing restrictions in participation after one year,[15,16] including the domains outdoor mobility, work, housekeeping and partner relationships.[10] Qualitative research suggest that participation after stroke is a long term dynamic and complex individual process, continuing beyond the "window of spontaneous neurological recovery",[17] but longitudinal cohort studies exploring the course of participation beyond the first year after stroke are scarce. Considering that participation after stroke is a crucial outcome in stroke rehabilitation, more insight into the long term course of participation over time after stroke is needed.[18]

PREDICTION OF STROKE OUTCOME

Nowadays, newly developed prediction models already support clinical decisions regarding discharge destination and stroke rehabilitation after hospital discharge in the very early phase after stroke.[17] Based on determinants on the level of body functions and activities measured

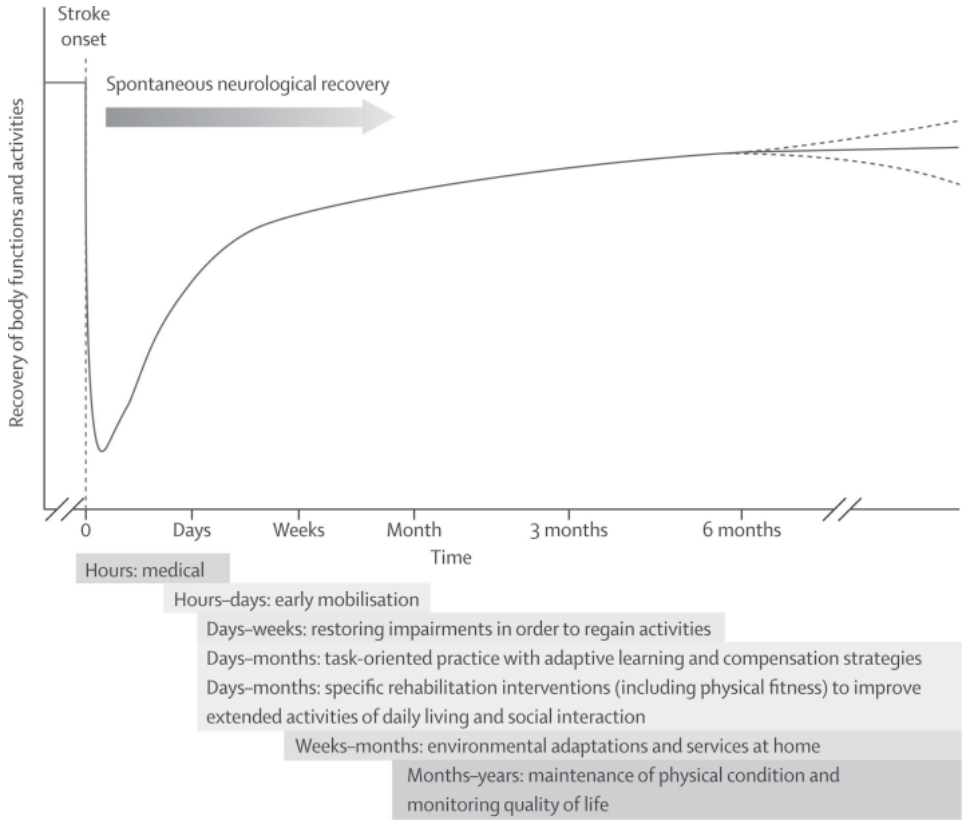

Figure 1.2: Hypothetical pattern of recovery after stroke, adapted from Langhorne et al. (2011).[13]

within 72 hours after stroke onset, such as stroke severity, degree of improvement in the first days after stroke and simple clinical bedside tests (such as finger extension and shoulder abduction), relatively accurate individual predictions of body functions and activities outcomes at six months after stroke can be made.[19,20] However, information on participation is limited in the acute phase after stroke, as restrictions in participation often manifest only after return to the home setting (when the impact of stroke on daily life becomes clearer).[17] Therefore, screening on restrictions in participation often takes place during follow-up assessments after stroke. These assessments are often limited to the first three months after stroke onset, so timely identification of those at risk for long term restrictions in participation is vital.[21] Unfortunately, current prediction models are not able to predict participation after stroke, possibly due to the multifactorial nature of participation (containing many different biopsychosocial determinants).[22]

PREDICTING PARTICIPATION

Several factors, including cognitive deficits,[23] emotional deficits, psychological factors,[24] functional dependency,[25] comorbidities,[26] stroke severity[18] and increasing age[18] have been associated with participation up to one year after stroke in previous literature. By early identification of determinants influencing the course of participation, persons with stroke at risk for long-term restrictions in participation may be selected timely and potentially modifiable determinants could be managed.

However, several limitations apply to the existing literature exploring determinants of participation after stroke: (1) prospective cohort studies are scarce (most studies use a cross-sectional design) and as a consequence the longitudinal association between determinants and participation remain largely unknown, (2) follow-up does often not exceed one year after stroke, (3) current study populations largely consist of people with stroke who are recruited via rehabilitation centers, while the majority of people with stroke are discharged home after hospitalization, (4) personal factors (such as psychological factors) are often overlooked as many studies have a biomedical approach,[18] despite existing scientific and clinical evidence on the importance of psychological factors after stroke,[24] and (5) the lack of consensus on the preferred participation measure after stroke hampers regular assessment of participation in clinical practice and clinical stroke trials limiting its usefulness.[8]

MEASURING PARTICIPATION

Participation is considered the cornerstone of successful rehabilitation after stroke.[17] Measuring participation provides clinicians with valuable person-centered information on the impact of stroke on daily life, and promotes individually tailored goal-setting and shared decision making during the rehabilitation process.[27] Furthermore, the course of participation seems to be a dynamic and complex individual process, emphasizing the need for a personalized approach in stroke rehabilitation.[17] Although participation is considered a pivotal outcome after stroke, participation measures are still underutilized in clinical care, stroke research and stroke audits.[18] Participation measures have been scarcely used in stroke research, accounting for less than 6% of stroke trials up to 2007.[28] Moreover, the huge heterogeneity in participation measures employed in clinical stroke trials limits the comparability and applicability of current study results even further.[29] And last but not least, participation measures are currently not part of the set of quality indicators in clinical stroke audits across Europe.[30]

OUTCOME MEASURES AFTER STROKE

In many countries, including the Netherlands,[4] the modified Rankin Scale (mRS) is the only instrument included in the set of quality indicators used in clinical stroke audits to evaluate stroke outcome after hospital discharge.[30] In the past, stroke outcomes were mainly focused on mortality and recurrence rates. The first application of a outcome measure to describe disability after stroke was the mRS in 1957.[31] As of today, the mRS is still the most commonly used outcome measure in clinical stroke trials[32] and clinical stroke audits,[30] despite its psychometric limitations and its limited scope (passing by relevant domains as cognition and social and emotional functioning).[33,34] More importantly, the mRS is a clinician-reported outcome measure, which may not capture all the aspects of outcome that are important for the patients themselves.[35] Therefore, stroke outcome collected directly from the patients themselves would give a better representation of the actual burden of stroke.

PATIENT-REPORTED OUTCOME MEASURES (PROMS)

During the last decade, the rise of the contemporary concepts of value-based healthcare[36] and positive health,[37] contributed to a shift from clinician-reported outcome towards a more holistic and patient-centered approach to measure stroke outcome. This led to many newly developed patient-reported outcome measures (PROMs), including many measures of participation and health-related quality of life (HRQoL) after stroke. HRQoL refers to the health aspects of the multidimensional concept of quality of life, and is considered to "reflect the impact of disease and treatment on disability and daily functioning".[38] Participation is considered an important subdomain of HRQoL.[39]

The EuroQol 5-dimensional 5-level questionnaire (EQ-5D-5L), the Patient Reported Outcomes Measurement Information System 10-Question Global Health Short Form (PROMIS-10), the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-Participation) and the Stroke Impact Scale 3.0 (SIS) are currently among the most widely used and most promising PROMs to measure participation or HRQoL in current stroke research.[35]

The EQ-5D-5L has shown validity and reliability in stroke populations and is often used in cost-effectiveness analyses.[40] The use of the PROMIS-10 as part of the standard set of outcome measures after stroke has been recommended by an international expert panel (International Consortium for Health Outcomes Measurement), since it covers the majority of the domains of HRQoL considered most important by the expert panel.[41,42] However, the

clinical and research experience with the PROMIS-10 after stroke is limited and concerns have been raised about its practical implementation.[43,44]

Similarly, an expert panel in the Netherlands recently advocated the use of the USER-Participation to measure participation as part of a minimum dataset of outcome measures to monitor recovery in patients with acquired brain injury.[45] The USER-Participation has shown satisfactory validity and reliability in stroke patients in stroke rehabilitation settings,[46] but has currently not been validated in a hospital-based stroke population. Last but not least, the SIS is still one of the most commonly used HRQoL measures in stroke research,[8] being one of the first stroke-specific HRQoL measures that has been developed (dating back to the late 1990's).[47] However, concerns have been raised regarding its reliability and its factorial structure.[48]

In summary, despite the abundance of PROMs in the participation and HRQoL domain, the lack of consensus on the preferred PROM to use as outcome measure after stroke hampers its implementation in clinical practice, stroke audits and clinical trials. A systematic review of stroke-related randomized controlled trials (2002–2016) found that only 21% used PROMs, and in case a PROM was used, they most commonly measured physical function and emotional status, sometimes HRQoL, but rarely participation.[29] Further validation and comparison between promising and commonly used patient-reported participation and HRQoL measures are needed to boost implementation in clinical practice, clinical audits and stroke research.

AIMS

The general aim of this Thesis is to gain a better understanding of participation after stroke by answering the following research questions:

- How should we measure participation and HRQoL after stroke?
- What is the course of participation over time after stroke?
- What are the determinants of participation after stroke?

STUDY DESIGNS

In this Thesis, the data used to explore our research questions were partly gathered as part of this Thesis (Stroke Outcome Measures study) and partly extracted from already existing

databases (Restore4Stroke Cohort study and the RISE study). The Restore4Stroke cohort study was originally set up by Marloes van Mierlo,[49] and an extra follow-up assessment at four years after stroke was added by Britta Nijsse.[50] The RISE study was set up by Roderick Wondergem.[51]

The Stroke Outcome Measures study

In the cross-sectional Stroke Outcome Measures study data were collected in people with stroke three months after stroke onset. A total of 360 people with stroke were recruited from six hospitals in the Netherlands: Flevoziekenhuis (Almere), Franciscus Gasthuis (Rotterdam), Leiden University Medical Center (Leiden), Rijnstate (Arnhem), St. Antonius Hospital (Nieuwegein) and University Medical Center Utrecht (Utrecht).

People who had suffered a stroke and were admitted to one of the stroke units of the six participating hospitals were eligible for inclusion. This study is funded by the Stichting Kwaliteitsgelden Medisch Specialisten (SKMS) (grant number 46361589) and executed by order of the Werkgroep CVA Nederland (WCN) and the Netherlands Society of Rehabilitation Medicine (NSRM).

The Restore4Stroke Cohort study

In the multicentre prospective longitudinal Restore4Stroke Cohort study data was collected in people with stroke at stroke onset, two months, six months, one year, two years and four years after stroke.[49] A total of 395 people with stroke were recruited from six general hospitals in the Netherlands: St. Antonius hospital (Nieuwegein), Diakonessenhuis (Utrecht) Canisius Wilhelmina hospital (Nijmegen), Elisabeth hospital (Tilburg), TweeSteden hospital (Tilburg) and Catherina hospital (Eindhoven).

Patients were eligible if they had a clinically confirmed diagnosis of ischemic or hemorrhagic stroke, gave informed consent within seven days after symptom onset, and were at least 18-years old. Patients were excluded from the study if they (1) had a serious other condition that could interfere with study outcomes; (2) had been dependent in basic activities of daily living before the stroke occurred (defined by a Barthel Index score of ≤ 17);[52] (3) had insufficient command of Dutch language, based on clinical judgment; or (4) had suffered cognitive decline prior to the stroke (defined by a score of ≥ 1 on the Heteroanamnesis List Cognition).[53] This study is funded by the VSB foundation (grant number 89000004) and co-ordinated by ZonMw (Dutch Organization for Health Research and Development, grant number 842003005).

RISE study

In this prospective longitudinal cohort study data were collected in people with stroke within three weeks after discharge from inpatient care, six months after discharge from inpatient care and one year after discharge from inpatient care.[51] A total of 200 people with stroke were recruited from four hospitals in the Netherlands: Catharina Hospital (Eindhoven), Jeroen Bosch Ziekenhuis ('s-Hertogenbosch), Maxima Medisch Centrum (Veldhoven) and Sint-Jans Gasthuis (Weert).

Participants were deemed eligible to participate when: presenting with a clinically confirmed first-ever stroke, expected to return home (with or without inpatient rehabilitation before returning home), activities of daily living independent before stroke (Barthel index > 18),[52] > 18 years old, able to maintain a conversation (score > 4 on the Utrecht Communication assessment),[54] and at least able to walk with supervision when they returned home (Score ≥ 3 in the Functional Ambulation Categories).[55] Participants were excluded if their life expectancy was < 2 years. This study was funded by the Netherlands Organization for Scientific Research (NWO), Doctoral grant for Teachers, 023.003.136.

OUTLINE OF THIS THESIS

This Thesis is divided into two parts. The first part explores measurement properties of promising patient-reported outcomes to evaluate participation and HRQoL after stroke. The second part focuses on the course of participation over time, aims to identify determinants of participation and provides insights into the association between participation and HRQoL after stroke.

Part 1: Measuring participation and HRQoL after stroke

- **Chapter 2** describes the validity of the Restrictions scale of the USER-Participation in a hospital-based stroke population to evaluate participation three months after stroke (*Stroke Outcome Measures Study*).
- **Chapter 3** compares the measurement properties (including concurrent validity and discriminant ability) between the EQ-5D-5L and the PROMIS-10 to evaluate HRQoL three months after stroke (*Stroke Outcome Measures Study*).
- **Chapter 4** compares the validity of the EQ-5D-5L with and without an additional cognitive domain (EQ-5D-5L+C) at three months after stroke (*Stroke Outcome Measures Study*).

Part 2: Determinants and course of participation after stroke

- **Chapter 5** describes differences in participation outcome between people with stroke aged under and over 70 years old, and identifies predictors of participation in both age groups (*Restore4Stroke Cohort Study*).
- **Chapter 6** explores the course of participation from two months up to four years after stroke, and examines if psychological factors are determinants of the course of participation during this period (*Restore4Stroke Cohort Study*).
- **Chapter 7** provides insights into the preferred approach to measure cognitive functioning when exploring the association between cognitive functioning and participation in the long term after stroke (*Restore4Stroke Cohort Study extended*).
- **Chapter 8** examines the course of participation across distinct movement behavior patterns (sedentary exercisers, sedentary movers and sedentary prolongers), and investigates the longitudinal association between these movement behavior patterns and participation up to one year after stroke (*RISE study*).
- **Chapter 9** shows the predictive value of participation restrictions two months after stroke for HRQoL one year after stroke, and aims to unravel the longitudinal relationship between participation and HRQoL after stroke (*Restore4Stroke Cohort study*).

General discussion

- **Chapter 10** presents a general discussion of the main findings of the studies, methodological considerations and recommendations for clinical practice and future research.

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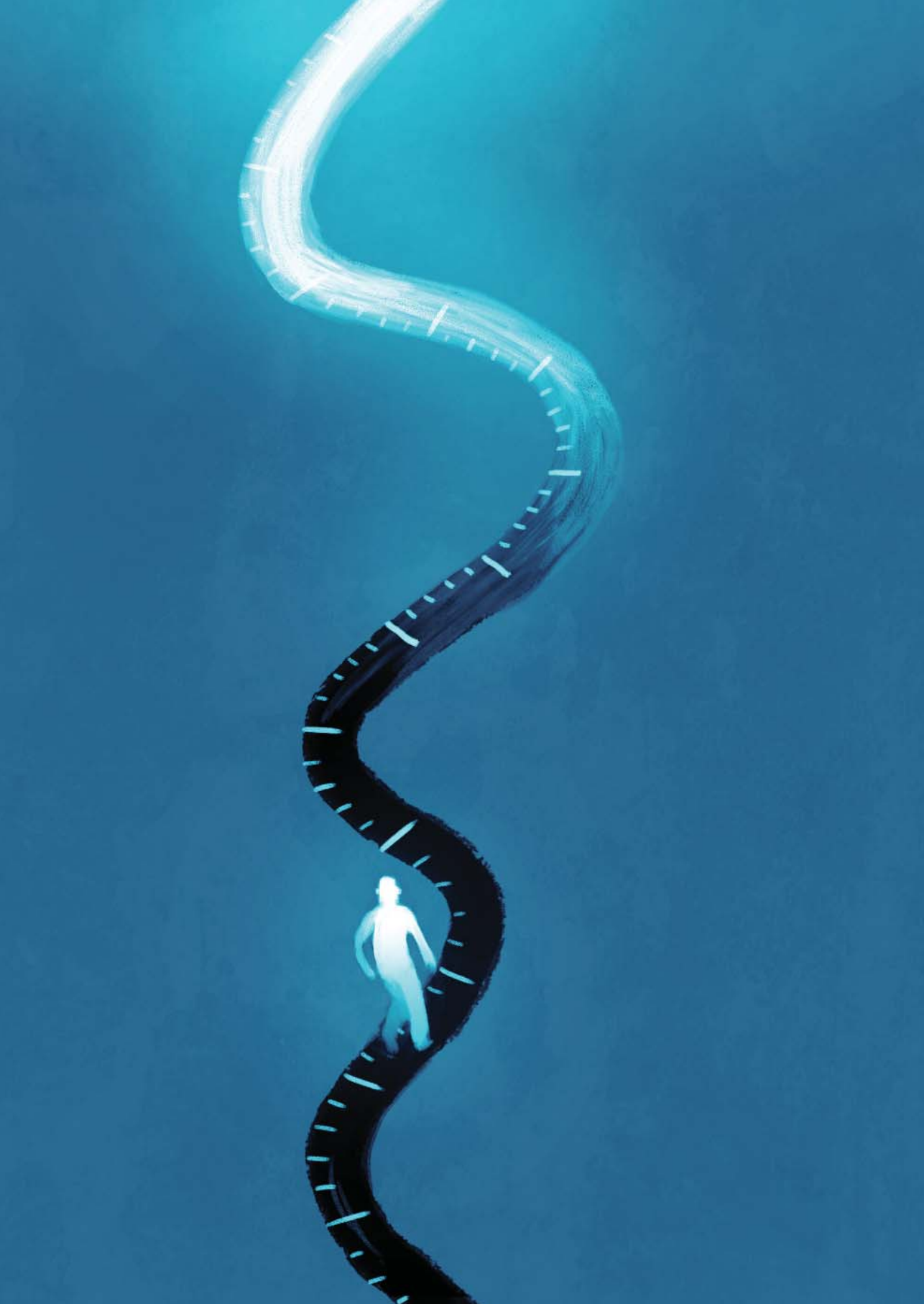

Part 1

Measuring participation and HRQoL after stroke

Chapter 2

Validity of the Utrecht Scale for Evaluation of Rehabilitation-Participation Restrictions scale in a hospital-based stroke population 3 months after stroke

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Abstract

Background: The Utrecht Scale for Evaluation of Rehabilitation-Participation Restrictions scale (USER-P-R) is a promising patient-reported outcome measure, but has currently not been validated in a hospital-based stroke population.

Objective: To examine psychometric properties of the USER-P-R in a hospital-based stroke population 3 months after stroke onset.

Methods: Cross-sectional study including 359 individuals with stroke recruited through 6 Dutch hospitals. The USER-P-R, EuroQol 5-dimensional 5-level questionnaire (EQ-5D-5L), Patient Reported Outcomes Measurement Information System 10-Question Global Health Short Form (PROMIS-10), modified Rankin Scale (mRS) and two items on perceived decrease in health and activities post-stroke were administered in a telephone interview 3 months after stroke. The internal consistency, distribution, floor/ceiling effects, convergent validity and discriminant ability of the USER-P-R were calculated.

Results: Of all participants, 96.9% were living at home and 50.9% experienced no or minimal disabilities (mRS 0–1). The USER-P-R showed high internal consistency (α = 0.90) and a non-normal left-skewed distribution with a ceiling effect (21.4% maximum scores). A substantial proportion of participants with minimal disabilities (mRS 1) experienced restrictions on USER-P-R items (range 11.9–48.5%). As hypothesized, the USER-P-R correlated strongly with the EQ-5D-5L (r = 0.67), PROMIS-10 (r = 0.66) and mRS (r = -0.71). The USER-P-R showed excellent discriminant ability in more severely affected individuals with stroke, whereas its discriminant ability in less affected individuals was moderate.

Conclusions: The USER-P-R shows good measurement properties and provides additional patient-reported information, proving its usefulness as an instrument to evaluate participation after 3 months in a hospital-based stroke population.

INTRODUCTION

Stroke is a major cause of morbidity and mortality worldwide.[1] Due to advances in acute stroke care, such as intra-arterial thrombectomy, more individuals nowadays survive this event, but they may have to deal with chronic impairments after stroke.[1] Stroke patients may experience restrictions across multiple participation domains, such as work and leisure activities. The International Classification of Functioning, Disability and Health (ICF) is a framework for the classification of health-related functional domains that defines participation restrictions as 'problems an individual may have in involvement in life situations'.[2] Measuring participation in daily and social activities after stroke provides clinicians with valuable person-centered information on the impact of stroke on daily life, and promotes individually tailored goal-setting and shared decision making during neurorehabilitation.[3]

Nevertheless, participation measures are not yet incorporated in current stroke audits or core outcome sets.[4] The modified Rankin Scale (mRS) remains the most commonly used assessment scale in clinical stroke care and stroke research, although it does not capture all aspects of outcome that are important to patients.[5] The use of patient-reported outcome measures (PROMs) in stroke care is increasing,[6] but most of these PROMs are health-related quality of life questionnaires (such as the EuroQol), which do not provide very specific information on participation in daily and social activities. In addition, the lack of consensus on the preferred participation measure may hamper regular assessment of participation.[7] Validation of participation measures commonly used for stroke patients, such as the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-Participation), could lead to further implementation of regular participation assessments in clinical stroke practice and stroke research.[6]

The USER-Participation is a suitable measure to capture the multidimensional concept of participation as described in the ICF, as the items of the USER-Participation are based on the Participation chapters of the ICF.[8] The USER-Participation is a commonly used tool throughout Dutch stroke care and provides relevant information for clinical purposes, for example supporting individually tailored goal-setting during rehabilitation after stroke.[9] Recently, an expert panel advocated the use of the USER-Participation to measure participation as part of a minimum dataset of outcome measures to monitor recovery in patients with acquired brain injury.[10] Feasibility of the USER-Participation in stroke rehabilitation patients has been shown,[11] and may further improve by reducing the length of the questionnaire and focusing on participation restrictions. The Restrictions scale of

the USER-Participation (USER-P-R) assesses restrictions of participation experienced, and comprises 11 items on restrictions experienced in e.g. work, household activities and social interaction.[12] Previous studies of the USER-P-R in stroke rehabilitation populations showed good internal consistency,[12–14] strong correlation with the ICF Measure of Activities and Participation-Screener (IMPACT-S)[12,13] and the Impact on Participation and Autonomy (IPA),[15] and better responsiveness than the Frenchay Activities Index and IMPACT-S.[8]

In summary, the USER-P-R is a promising PROM to evaluate participation restrictions, but has currently only been validated in stroke rehabilitation settings. However, most people with stroke return home directly after hospital discharge without referral for inpatient rehabilitation treatment. Further validation of the USER-P-R in hospital-based stroke populations is needed to expand its applicability to all people with stroke regardless of discharge destination. Therefore, we examined the internal consistency, convergent validity and discriminant validity of the USER-P-R in a hospital-based stroke population 3 months after stroke onset.

METHODS

Study design

This was a cross-sectional validation study. Recruitment took place in six Dutch hospitals between September 2017 and September 2018. Individuals who had suffered a stroke and were admitted to one of the participating hospitals were eligible for inclusion. No exclusion criteria were applied in this study. All eligible individuals received a letter informing them about this study, after which informed consent was acquired. The mRS[16] and all questionnaires[17,18] were administered by a trained stroke nurse or nurse practitioner in a telephone interview 3 months after stroke.[19] Proxy interviews were performed if the individual with stroke was not able to answer the phone. Demographic (sex, age, marital status, residency and level of education) and stroke-related information (type and localization of stroke, severity of stroke, and activities of daily living [ADL] dependency) were obtained from medical records by the stroke nurse. The Medical Ethics Committee of the University Medical Center Utrecht declared that the study did not need formal approval under Dutch law (2017-441C). All participating hospitals approved the study.

USER-Participation Restrictions scale

The USER-P-R consists of 11 items concerning difficulties experienced with vocational, leisure and social activities due to the stroke (for example, "Do you experience limitations due to your stroke in your daily life as regards household duties?").[12,20] For each item, four response categories are available: "not possible" (0), "with assistance" (1), "with difficulty" (2), and "without difficulty" (3). A "not applicable" option is available for all items, in case an activity is not performed for other reasons or a restriction is not attributed to the stroke. The total score of the Restrictions scale ranges from 0–100 and is based on applicable items. A higher score indicates a more favorable level of participation, i.e. fewer restrictions experienced.

Criterion measures

The EQ-5D-5L consists of 5 items, each covering a health-related quality of life (HRQoL) domain, namely mobility, self-care, daily activities (e.g. work, study, housework, family or leisure activities), pain or discomfort and anxiety or depression; each item is scored on a 5-point scale: (1) "no problems", (2) "slight problems", (3) "moderate problems", (4) "severe problems" and (5) "extreme problems/unable".[21] The item scores were converted into a total value score, using the EuroQol crosswalk index value calculator, in which a perfect health score is valued as a score of 100 and a health state worse than death is valued as a negative score, anchoring death at a score of 0.[22] The EuroQoL has shown validity and reliability in stroke populations and is often used in cost-effectiveness analyses.[23–26]

The PROMIS-10 consists of 10 items on physical, mental and social health and has been developed as a global health short-form questionnaire from the comprehensive PROMIS item banks.[27] One item regards social participation ("in general, please rate how well you carry out your usual social activities and roles, this includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend etc.") and is scored on a 5-point scale: (1) "poor", (2) "fair", (3) "good", (4) "very good" and (5) "excellent". The total score of the PROMIS-10 ranges from 0–100 (higher scores indicating better outcome). The PROMIS-10 has been recommended as a standard outcome measure after stroke by an international expert panel (International Consortium for Health Outcomes Measurement [ICHOM]).[28,29] The PROMIS-10 has shown acceptable measurement properties in the stroke population.[3,30,31]

The mRS is the most commonly used outcome measure in clinical stroke trials,[32] and its validity and reliability have been confirmed.[33] It measures disability due to stroke, incorpo-

rating body functions, activity and participation.[34] The mRS is a single ordinal seven-point scale (ranging from 0 to 6) that aims to categorize the level of disability after stroke.[21] The categories are "no symptoms" (mRS 0), "no significant disability, despite symptoms" (mRS 1), "slight disability" (mRS 2), "moderate disability: requires some help, able to walk" (mRS 3), "moderately severe disability: unable to walk, ADL dependent" (mRS 4), "severe disability: bedridden, requires constant nursing care" (mRS 5) and "death" (mRS 6). In the present study, mRS scores of 3, 4 and 5 were clustered because of the low numbers of participants in these categories.

Two self-developed items were used to evaluate patient-reported decrease in HRQoL associated with the onset of stroke. The first item asked participants to rate the decrease in health they experienced, associated with the onset of stroke. The second item asked participants to rate the decrease in activities they experienced, associated with the onset of stroke. The decrease experienced was measured on a 4-point response scale ("none", "little", "strong" and "very strong") for both items. The responses "strong" and "very strong" were clustered for both items afterwards, because few participants reported very strong decrease in health and activities.

Other measures

Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS) at hospital admission. Scores range from 0–42 and higher scores indicate more severe stroke.[35] ADL-dependency was assessed with the Barthel Index (BI) four days after stroke and at discharge from the hospital. Scores range from 0–20 and were dichotomized into "ADL dependent" (BI ≤ 17) and "ADL independent" (BI > 17). The BI is a validated measure often used in stroke research and practice.[36]

Statistical analysis

All analyses were conducted with IBM SPSS version 25 (IBM, Armonk, NY). Descriptive statistics were used to describe participant characteristics and dependent variables. Floor and ceiling effects were considered present if > 15% of participants achieved the worst (floor effect) or best score (ceiling effect).[37] Internal consistency was examined by calculating Cronbach's alpha; $\alpha > 0.70$ was considered acceptable.[38] The USER-P-R items were dichotomized to quantify the presence of persistent restrictions across mRS levels. "With difficulty," "with assistance," and "not possible" were defined as "restrictions" and "without difficulty" was defined as "no restrictions".

Bivariate associations between the USER-P-R, EQ-5D-5L (total score and the item score regarding daily activities), PROMIS-10 (total score and the item score regarding social participation) and mRS were tested using Spearman correlations. Correlation coefficients were interpreted as weak (0.10), moderate (0.30) or strong (0.50).[39] A strong correlation was hypothesized and, if present, interpreted as a positive finding (convergent validity).

The distribution of the USER-P-R total scores across different mRS levels and the patient-reported decrease in health and activities since stroke was graphically displayed in a boxplot. High variance of USER-P-R total scores within mRS levels was interpreted as a positive finding (i.e., showing potentially relevant additional information to evaluate participation after stroke). We explored the discriminant ability of the USER-P-R by comparing mean USER-P-R scores between adjacent mRS levels and adjacent levels of patient-reported decrease in health and activities post-stroke. Effect sizes were calculated (Hedges' *g*) and interpreted as weak (0.20), moderate (0.50) or strong (0.80).[40] An alpha < 0.05 was considered statistically significant.

RESULTS

Participant characteristics are presented in Table 2.1. A total of 360 participants were included in this study, 359 of whom completed the USER-P-R questionnaire and were available for

Table 2.1: Patient characteristics (n = 359)

Demographic factors (3 months after stroke)	
Sex (% male)	60.2
Age in years (at time of stroke)	70.0 (17.0)[a]
Marital status (% living together)	72.1
Residency (% living at home)	96.9
Stroke-related factors	
Ischemic stroke (%)	93.0
Left hemisphere (%)	46.2
Severity of stroke (NIHSS) at hospital admission (n = 242)	3.0 (4.0)[a]
No or minor stroke symptoms (% NIHSS ≤ 4)	68.0
Moderate to severe stroke symptoms (% NIHSS > 4)	32.0
ADL dependency (BI) 4 days after stroke (n = 275)	19.0 (4.0)[a]
% ADL-dependent (BI ≤ 17)	37.2
ADL dependency (BI) at discharge (n = 264)	20.0 (2.0)[a]
% ADL-dependent (BI ≤ 17)	23.6

Abbreviations: ADL, activities of daily living; BI, Barthel Index; NIHSS, National Institutes of Health Stroke Scale.
[a] Median (IQR, interquartile range).

analysis. A total of 143 participants (39.8%) were female and nearly all participants lived at home 3 months post-stroke. The majority of participants had suffered a mild ischemic stroke and most participants were ADL independent at discharge from the hospital.

The majority of participants had no significant disability (mRS 1) or slight disability (mRS 2), whereas only 12.1% of participants had moderate to severe disability (mRS 3–5) 3 months after stroke. Approximately one-third of participants did not report any decrease in health (36.7%) or in activities (33.1%) post-stroke (Table 2.2). The EQ-5D-5L showed a ceiling effect (21.2% maximum scores) and 41.8% did not experience any problems regarding daily activities. The PROMIS-10 was normally distributed (1.9% maximum scores) and few participants rated the item on social participation as "excellent" (3.9%) or "poor" (5.8%).

Table 2.2: Frequencies and descriptive statistics of the USER-Participation Restrictions scale

	n	Mean	± SD	Median	IQR	% maximum
USER-P-R total score	359	77.6	± 21.4	81.8	63.3–96.7	21.4
EQ-5D-5L total score	359	78.0	± 19.6	80.8	69.4–91.7	21.2
PROMIS-10 total score	359	54.3	± 18.5	55.0	42.5–65.0	1.9
USER-P-R total score across the different mRS levels						
mRS 0	47	94.8	± 12.6	100	96.3–100	70.2
mRS 1	135	89.3	± 11.6	92.6	83.3–100	28.1
mRS 2	134	70.3	± 16.8	71.8	58.1–81.8	4.5
mRS 3-5	43	45.1	± 19.5	46.7	33.3–60.0	0
USER-P-R total score across the different levels of patient-reported decrease in health and in activities						
No decrease in health	131	88.7	± 16.4	96.7	84.8–100	42.7
Little decrease in health	164	77.3	± 18.9	80.5	66.7–93.1	12.2
Strong decrease in health	64	55.7	± 19.4	53.9	44.7–68.9	1.6
No decrease in activities	118	91.1	± 13.7	96.8	87.6–100	48.7
Little decrease in activities	155	78.4	± 19.4	81.5	66.7–93.3	12.3
Strong decrease in activities	86	57.7	± 18.3	58.3	46.7–70.0	0

Abbreviations: IQR, interquartile range; mRS, Modified Rankin Scale; SD, standard deviation; USER-P-R, Utrecht Scale for Evaluation of Rehabilitation-Participation Restrictions scale.
Note: higher USER-P-R total scores indicate better participation outcome.

Internal consistency and distribution

The USER-P-R showed high internal consistency (Cronbach's alpha 0.90), and had a non-normal left-skewed distribution (skewness = -0.92, kurtosis = 0.23) with a ceiling effect (21.4% maximum scores). This ceiling effect in the USER-P-R mainly occurred in participants with no or no significant disabilities (mRS 0–1) 3 months after stroke and in participants

who did not report any decrease in health or activities post-stroke (Table 2.2). Participants with slight to severe disability (mRS 2–5) and participants who reported little to strong decreases in health and in activities post-stroke showed greater variation in USER-P-R scores compared to participants with no or no significant disability (mRS 0–1) and participants who did not report any decrease in health or activities post-stroke (Figure 2.1).

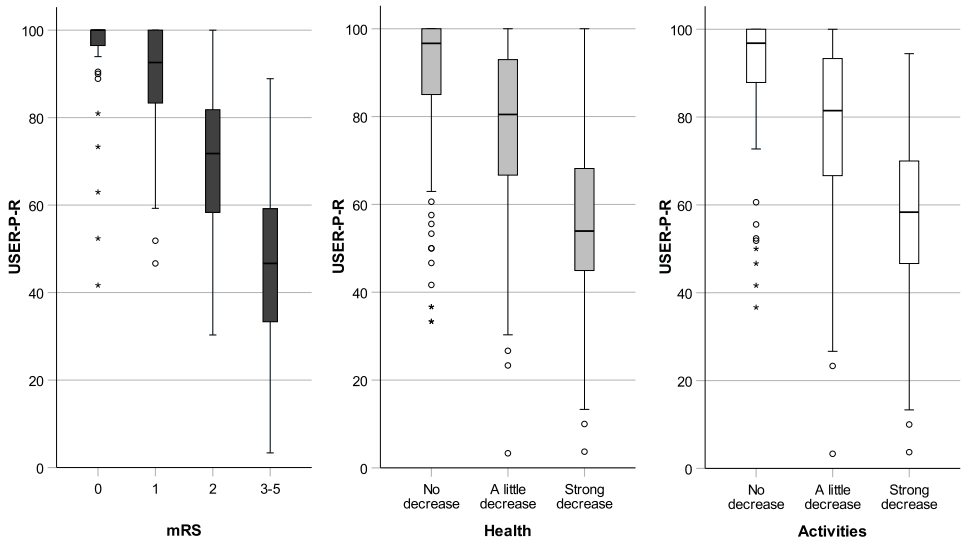

Figure 2.1: Distribution of the USER-Participation Restrictions scale across mRS scores (dark grey) and across different levels of patient-reported decrease in health (light grey) and in daily activities (white) 3 months after stroke.

Abbreviations: mRS, Modified Rankin Scale; USER-P-R, Utrecht Scale for Evaluation of Rehabilitation-Participation Restrictions scale.

Note: The bold horizontal bars in the boxes represent the median for the USER-P-R. The ends of the boxes represent the first and third quartiles. The vertical line represents the minimum and maximum scores (inside 1.5 IQR). The open dots represent outliers (outside 1.5 IQR). Higher USER-P-R scores indicate better participation outcome, higher mRS scores indicate worse disability.

The percentage of participants experiencing restrictions regarding the items of the USER-P-R increased with higher mRS levels (Figure 2.2). A few participants with no disabilities according to the mRS (mRS 0) experienced restrictions regarding USER-P-R items (range 0–14%), whereas a considerable percentage of participants with no significant disabilities (mRS 1) experienced restrictions on several USER-P-R items (range 11.9–48.5%), especially the items on work/education, housekeeping, physical exercise and outdoor activities (48.5%, 40.3%, 35.0% and 34.2%, respectively). Almost all participants with moderate to severe disabilities (mRS 3–5) experienced restrictions regarding USER-P-R items on work/education

and outdoor activities, whereas relatively few participants experienced restrictions in social activities (such as partner relationship and visits to/from family/friends).

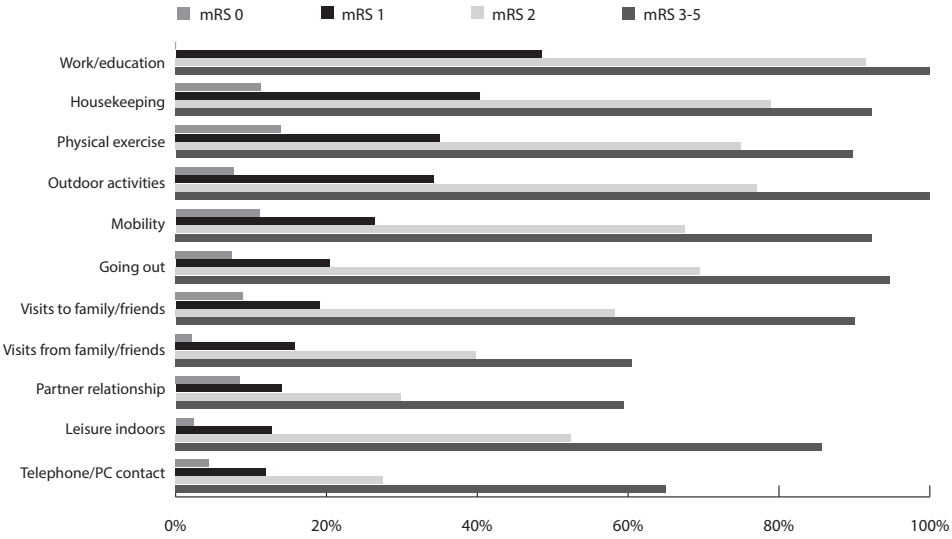

Figure 2.2: Percentage of participants experiencing restrictions regarding the items of the USER-Participation Restrictions scale across the different mRS levels.
Abbreviations: mRS, Modified Rankin Scale; USER-P-R, Utrecht Scale for Evaluation of Rehabilitation-Participation Restrictions scale.
Note: Item on work/education: only participants aged < 66 years were included, as the retirement age in the Netherlands during inclusion (2018) was 66 years.

Convergent validity

The USER-P-R showed a strong and significant negative correlation with the mRS and the EQ-5D-5L item score regarding daily activities, and a strong and significant positive correlation with the EQ-5D-5L total score, the PROMIS-10 total score and the PROMIS-10 item score regarding social participation (Table 2.3).

Discriminant ability

The USER-P-R showed strong ability to detect differences between participants with no significant disabilities versus those with slight (mRS 1 vs. 2) and those with slight versus moderate to severe disabilities (mRS 2 vs. 3–5), whereas its ability to detect differences between participants with no versus those with no significant disabilities (mRS 0 vs. 1) was moderate (Table 2.4). The USER-P-R showed a strong ability to detect differences between

participants who reported little versus strong decrease in health and in activities post-stroke, whereas its ability to detect differences between participants who did not report any decrease versus those who reported little decrease in health and activities post-stroke was moderate.

Table 2.3: Spearman correlations (rho) between the USER-Participation Restrictions scale, the modified Rankin Scale, EQ-5D-5L (including daily activities item score) and PROMIS-10 (including social participation item score)

	mRS	EQ-5D-5L total score	EQ-5D-5L item (daily activities)	PROMIS-10 total score	PROMIS-10 item (social participation)
USER-P-R	-.71*	.67*	-.73*	.66*	.55*
mRS		-.62*	.64*	-.61*	-.50*
EQ-5D-5L total score			-.72*	.75*	.54*
EQ-5D-5L item (daily activities)				-.63*	-.55*
PROMIS-10 total score					.78*

Abbreviations: EQ-5D-5L, EuroQol 5-dimensional 5-level value score; mRS, Modified Rankin Scale; PROMIS-10, Patient Reported Outcomes Measurement Information System 10-Question Short Form; USER-P-R, Utrecht Scale for Evaluation of Rehabilitation-Participation Restrictions scale.
* $p \leq 0.001$.

Table 2.4: Ability of the USER-Participation Restrictions scale to discriminate between adjacent mRS levels (mRS 0 vs. mRS 1, mRS 1 vs. mRS 2, mRS 2 vs. mRS 3–5) and different levels of patient-reported decrease in health and in activities post-stroke

		Mean Δ	SE Δ	P-value	95% CI Δ	Hedges'*g*
USER-P-R	mRS 0 vs. mRS 1	5.52	2.53	0.130	-1.01–12.05	0.46
	mRS 1 vs. mRS 2	18.99*	1.82	< 0.001*	14.29–23.69	1.31
	mRS 2 vs. mRS 3–5	25.16*	2.62	< 0.001*	18.40–31.92	1.44
	No vs. little decrease in health	11.38	2.13	< 0.001*	6.38–16.39	0.64
	Little vs. strong decrease in health	21.64	2.67	< 0.001*	15.35–27.93	1.20
	No vs. little decrease in activities	12.76	2.13	< 0.001*	7.75–17.78	0.80
	Little vs. strong decrease in activities	20.65	2.35	< 0.001*	15.13–26.17	1.22

Abbreviations: Δ, difference; CI, confidence interval; mRS, Modified Rankin Scale; SE, standard error; USER-P-R, Utrecht Scale for Evaluation of Rehabilitation-Participation Restrictions scale.
Note: Higher mRS scores indicate worse disability.
* $p < 0.05$.

DISCUSSION

We found reasonably good measurement properties of the USER-P-R when administered 3 months post-stroke in a large hospital-based cohort of community-living participants in the Netherlands. The USER-P-R had a slight ceiling effect (21.4%), but high internal consistency

(Cronbach's alpha 0.90), good convergent validity (strong correlations with the EQ-5D-5L, PROMIS-10 and mRS), moderate discriminant ability in less severely affected individuals with stroke and excellent discriminant ability in more severely affected individuals with stroke. Many individuals with stroke experienced restrictions in USER-P-R items, even persons who had no or minimal disabilities (mRS 0–1). In summary, the USER-P-R proved a useful and valid instrument to evaluate participation after 3 months in a hospital-based stroke population.

The observed ceiling effect of the USER-P-R mainly occurred in participants with no disabilities (mRS 0), 70.2% of whom had the maximum score. In the group of participants with mild to severe disabilities after stroke (mRS 1–4), 14.1% had the maximum score. A previous study among former rehabilitation outpatients (35% with stroke or traumatic brain injury) reported a comparable ceiling effect (19%) for USER-P-R.[12] The discriminant ability of the USER-P-R to detect differences among less severely affected individuals with stroke (mRS 0 vs. 1, and individuals experiencing no vs. little decrease in health/activities) was only moderate, whereas excellent discriminant ability was found for more severely affected individuals with stroke (mRS 2 vs. mRS 3–5, and individuals experiencing little vs. strong decrease in health/activities). These findings indicate that the USER-P-R is most useful for stroke patients with chronic symptoms.

About 70% of the participants with minimal disabilities according to the clinician's judgement (mRS 1) experienced restrictions regarding USER-P-R items, especially regarding the items on work (48.5%), housekeeping (40.3%), physical exercise (35.0%) and outdoor activities (34.2%). These findings show the potential of the USER-P-R to provide clinicians with valuable person-centered information on the impact of stroke on daily life, even for mildly affected stroke patients. Similar results were yielded in a comparable Dutch hospital-based stroke population (Restore4Stroke Cohort).[41] Despite the Restore4Stroke cohort (n = 136) also largely consisted of relatively mildly affected stroke patients, more than half of the stroke patients experienced restrictions in the USER-P-R items on work, housekeeping, physical exercise and outdoor activities at 2 and 6 months after stroke onset.[41] In another stroke sample recruited in Dutch rehabilitation centers after completion of a multidisciplinary individually based outpatient rehabilitation program (n = 111, median time since stroke onset = 3.4 months), persisting restrictions in USER-P-R items on physical exercise (50.0%), housekeeping (44.5%) and outdoor activities (40.9%) were most frequently reported.[20] Population differences (patient recruitment in hospitals vs. rehabilitation centers) and differences in the provided rehabilitation treatment may explain the slight differences between these studies.

Restrictions in social activities (partner relationship, visits to/from family or friends) were less frequent in our study. These results are in line with those of a recent study investigating the USER-Participation scores across different diagnostic groups, including stroke (n = 534) which concluded that participation restrictions were most often experienced in the productivity domain (work, education, housekeeping), followed by the leisure domain (physical exercise, going out, outdoor activities) and least often in the social domain (relationships with partner/family/friends).[9]

To our knowledge, correlations between the USER-P-R and the mRS, EQ-5D-5L or PROMIS-10 have not been examined previously. The weak correlation between the USER-P-R and the social participation item of the PROMIS-10, weaker than the correlation with the PROMIS-10 total score, is striking. Most participants chose the middle response category of this item ("good"), which may have reduced the correlation between the item score and the USER-P-R. This could be explained by the differences in response categories and the underlying goal of both PROMs. Maximum scores on the USER-P-R items indicate the absence of problems/difficulties in participation, whereas the maximum scores on the PROMIS-10 items indicate "excellent" HRQoL (and the middle response category already indicates "good" HRQoL outcome).

The use of PROMs for the assessment of participation after stroke, such as the USER-P-R, has many advantages, but the implementation of PROMs may face some challenges.[6] A systematic review of stroke-related randomized controlled trials found that only 21% used PROMs, and in case a PROM was used, they most commonly measured physical function and emotional status, and rarely measured participation.[42] It has been suggested that retention and response rates of PROMs in stroke aftercare could be further enhanced by reducing the size of the questionnaires.[11] The USER-Participation for patients with acquired brain injury has been recommended by experts as a measurement instrument for participation,[10] and focusing on the restrictions scale may improve the feasibility of the USER-Participation in clinical stroke care, as this scale is notably shorter (11 items), is easy to administer, and supports individually tailored goal-setting in rehabilitation after stroke. On the other hand, focusing on the restrictions scale comes at the expanse of losing potential relevant information on the frequency of participation and the satisfaction with participation after stroke.

Study limitations

The study population mainly consisted of community-living and mildly affected individuals with stroke. As a consequence, participants with mRS scores 3–5 were clustered, and no

comparisons could be made between these groups. This limits the generalizability of our results to patients with more severe stroke. However, our sample does reflect the severity of stroke in the general hospital population, as mild ischemic strokes are most common.[19] Furthermore, restrictions in participation change over time,[43] meaning that administering the USER-P-R at another point in time after stroke onset could have yielded different results. Lastly, the ability of the USER-P-R to detect change over time could not be assessed in this study.

Conclusions

The USER-P-R is a valid measurement instrument to monitor participation restrictions in routine outpatient care 3 months after stroke. A considerable number of stroke patients who are "mildly affected", according to the clinician's judgement, still experience restrictions on USER-P-R items, especially in the productivity and leisure domains. The USER-P-R appears to be most suitable for individuals with stroke who have chronic disabilities or experience decreased HRQoL since their stroke.

Clinical implications

The USER-P-R seems appropriate as a screening instrument to detect post-stroke restrictions in participation, even in patients with minor strokes. Our findings show the importance of assessing patient-reported information on restrictions in participation during follow-up after stroke, as it provides clinicians with relevant person-centered information on the impact of stroke. Regular assessment of the USER-P-R in stroke aftercare could aid timely referral to individually tailored rehabilitation interventions and prevent long-term participation restrictions.

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Chapter 3

Comparison between EQ-5D-5L and PROMIS-10 to evaluate health-related quality of life 3 months after stroke: A cross-sectional multicenter study

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Abstract

Background: Although the use of patient-reported outcome measures to assess Health-Related Quality of Life (HRQoL) has been advocated, it is still open to debate which patient-reported outcome measure should be preferred to evaluate HRQoL after stroke.

Aim: To compare the measurement properties (including concurrent validity and discriminant ability) between the 5-dimensional 5-level EuroQol (EQ-5D-5L) and the Patient-Reported Outcomes Measurement Information System 10-Question Global Health Short Form (PROMIS-10) to evaluate HRQoL 3 months after stroke.

Design: Cross-sectional study.

Setting: Neurology outpatient clinics in 6 Dutch hospitals.

Population: 360 consecutive individuals with stroke. The median age of the participants was 71 years, 143 (39.7%) were female and 335 (93.0%) had suffered an ischemic stroke.

Methods: The EQ-5D-5L, PROMIS-10, modified Rankin Scale and two items on experienced decrease in health and activities post-stroke were administered by a stroke nurse or nurse practitioner through a telephone interview 3 months after stroke. The internal consistency, distribution, floor/ceiling effects, inter-correlations and discriminant ability (using the modified Rankin Scale and experienced decrease in health and in activities post-stroke as external anchors) were calculated for both the EQ-5D-5L and PROMIS-10.

Results: Ninety-six percent of the participants were living at home and 50.9% experienced minimal or no disabilities (modified Rankin Scale 0–1) 3 months after stroke. A ceiling effect and a non-normal left skewed distribution were observed in the EQ-5D-5L. The PROMIS-10 showed higher internal consistency ($\alpha = 0.90$) compared to the EQ-5D-5L ($\alpha = 0.75$). Both the EQ-5D-5L and the PROMIS-10 were strongly correlated with the modified Rankin Scale ($r = 0.62$ and 0.60 respectively). The PROMIS-10 showed better discriminant ability in less affected individuals with stroke, whereas the EQ-5D-5L showed slightly better discriminant ability in more affected individuals with stroke.

Conclusions: Both EQ-5D-5L and PROMIS-10 prove to be useful instruments to evaluate HRQoL in patients who are living at home 3 months after stroke.

Clinical rehabilitation impact: It depends on the setting and underlying goal which patient-reported outcome measure is preferred to evaluate HRQoL 3 months after stroke. The PROMIS-10 should be preferred to detect differences in less affected stroke patients, whereas the EQ-5D-5L provides slightly more information in more affected stroke patients.

INTRODUCTION

Stroke is the second most common cause of death and the third most common cause of disability in the world.[1] The aging population and improvements in acute treatment such as intravenous thrombolysis and intra-arterial thrombectomy lead to a growing number of stroke survivors. Consequently, the number of stroke patients that have to cope with long-term sequelae of stroke is also increasing, which puts a strain on their health-related quality of life (HRQoL) and raises health care expenditures.[2] Clinical stroke audits can provide valuable information to evaluate stroke treatments, quality of stroke care and HRQoL of stroke patients.[3] However, current stroke audits are mainly focused on the acute stroke care and measurement of long-term outcome measures are scarce.[4]

A variety in quality indicators in clinical stroke audits has been observed across Europe.[4] In most countries the mortality rate during hospital stay is the only outcome measure included in the stroke audit, in some countries (including The Netherlands) accompanied with the modified Ranking Scale (mRS) measured 3 months after stroke.[5] The mRS is also the most commonly used outcome measure in clinical stroke trials.[6] It measures disability due to stroke on a single seven-point scale, incorporating body functions, activity and participation.[7] Even though the mRS is widely used, relevant shortcomings of this instrument are its lack of specificity[7] and a large interobserver variability.[8] Furthermore, the mRS measures mainly independence in the domains of mobility and self-care, and hardly takes cognitive, social or emotional functioning into account. Moreover, the mRS is a clinician-reported outcome measure. Therefore, it may not capture all the aspects of outcome that are important for the patients themselves.[9]

A recent study showed that almost half of stroke patients, who have mild limitations (median mRS score 1) as assessed by the clinician, experienced poor HRQoL as assessed by the Patient-Reported Outcomes Measurement Information System computer adaptive testing scales about physical function, satisfaction with social roles, pain and fatigue.[10] These findings emphasize the importance of a patient-reported outcome measure (PROM) to evaluate HRQoL after stroke. Moreover, the use of PROMs to evaluate HRQoL after stroke may lead to improving shared-decision making and facilitation of personalized care[11] and is in agreement with the contemporary concept of value-based health care (VBHC).[12] Compared with the growing use of PROMs in clinical practice and as performance indicator in stroke care,[9] the use of PROMs in current stroke trials is still lagging behind.[13] Moreover, to date no consensus has been reached on the preferred PROM to evaluate HRQoL post-stroke.[14] The huge heterogeneity in PROMs employed in clinical stroke trials limits the comparability of study results.[13]

The EuroQol 5-dimensional 5-level questionnaire (EQ-5D-5L) and the Patient Reported Outcomes Measurement Information System 10-Question Global Health Short Form (PROMIS-10) are among the most widely used and most promising PROMs in current stroke research.[9] The EQ-5D-5L has shown validity and reliability in stroke populations and is often used in cost-effectiveness analyses.[15] The use of the PROMIS-10 as part of the standard set of outcome measures after stroke has been recommended by an international expert panel (International Consortium for Health Outcomes Measurement [ICHOM]), since it covers the majority of the domains of HRQoL considered most important by the expert panel (representing patients, advocates, and clinical specialists in stroke outcomes, stroke registers, global health, epidemiology, and rehabilitation).[16,17] However, the clinical and research experience with the PROMIS-10 after stroke is limited and concerns have been raised about its practical implementation.[18,19] Besides, the PROMIS-10 is twice the length compared to the EQ-5D-5L (10 items versus 5 items respectively), but in contrast to the EQ-5D-5L also covers the domains of general quality of life, fatigue and social roles.[20] "No problems" indicate the maximum item score in the EQ-5D-5L, whereas individuals should score their health as "excellent" to achieve the maximum item score in the PROMIS-10.

In summary, although the use of PROMs have been advocated from a VBHC perspective,[14] it is still open to debate which PROM should be preferred after stroke. Therefore, the aim of this study was to compare the measurement properties (floor- and ceiling effects, internal consistency, concurrent validity and discriminant ability) between the EQ-5D-5L and PROMIS-10 to evaluate HRQoL 3 months after stroke.

METHODS

Study design

In this cross-sectional study data were collected in individuals with stroke 3 months after stroke onset. Inclusion took place in 6 Dutch hospitals between September 2017 and September 2018. Individuals who had suffered a stroke and were admitted to one of the stroke units of the six participating hospitals were eligible for inclusion. All individuals with stroke received a letter informing them about this study, after which informed consent was acquired. The EQ-5D-5L, PROMIS-10, mRS, self-reported decrease in health post-stroke and self-reported decrease in activities post-stroke were administered by a stroke nurse or nurse practitioner at the outpatient clinic through a telephone interview 3 months after stroke.[21] The stroke nurses and nurse practitioners were already trained to perform telephone interviews

as part of regular follow-up assessments after stroke. Before the start of the study, all stroke nurses and nurse practitioners were provided with the same instructions about the use of the extra questionnaires to screen for the consequences of stroke, including information on possibilities to elucidate certain questions to the patients. An interview took on average 30 minutes. Demographic (sex, age, marital status, residency and level of education) and stroke-related information (type and localization of stroke, severity of stroke, ADL-dependency) were obtained from medical records by the stroke nurse. The Medical Ethics Committee of the University Medical Center Utrecht declared that the study did not need formal approval under Dutch law (2017-441C). All participating hospitals approved the study.

Clinician-reported measures

Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS) at hospital admission. Scores range from 0–42 and higher scores indicate more severe stroke.[22] ADL-dependency was assessed with the Collin and Wade version of the Barthel Index (BI) four days after stroke and at discharge from the hospital.[23] Scores range from 0–20 and were dichotomized into "ADL dependent" (BI ≤ 17) and "ADL independent" (BI > 17). BI is a validated measure often used in stroke.[24]

Modified Rankin Scale

The Rankin score was introduced in 1957 to assess clinical outcomes in stroke patients and was modified to its present version in the UK-TIA study in the late 1980s.[7] Its validity and reliability has been examined thoroughly and have been confirmed.[25] The mRS is a single ordinal seven-point scale (ranging from 0 to 6) aiming to categorize level of disability after stroke.[26] The categories are "no symptoms" (mRS 0), "no significant disability, despite symptoms" (mRS 1), "slight disability" (mRS 2), "moderate disability: requires some help, able to walk" (mRS 3), "moderately severe disability: unable to walk, ADL dependent" (mRS 4), "severe disability: bedridden, requires constant nursing care" (mRS 5) and "death" (mRS 6).

Patient-reported measures

EQ-5D-5L

The EQ-5D-5L consists of 5 items, each covering a HRQoL domain, namely mobility, self-care, usual activities, pain or discomfort and anxiety or depression and each item is scored on a 5-point scale: "no problems", "slight problems", "moderate problems", "severe problems"

and "extreme problems/unable".[27] This version has proven to be valid with enhanced discriminatory power over the 3-level version (EQ-5D-3L).[28,29] The scores of the EQ-5D-5L items were converted into a total value score, using the EuroQol crosswalk index value calculator, in which a perfect health score is valued as a score of 100 and a health state worse than death is valued as a negative score, anchoring death at a score of 0.[30]

PROMIS-10

The PROMIS-10 is a HRQoL measure reporting 10 items on physical, mental and social health (e.g. "In general, how would you rate your satisfaction with your social activities and relationships?") and has been developed as a global health short-form from the comprehensive PROMIS item banks.[31] Most items are scored on a 5-point scale, ranging from "excellent" to "poor" (items 1–6 about mental/physical quality of life and social activities), "not at all" to "completely" (item 7 about fatigue), "never" to "always" (item 8 about emotional problems) and "none" to "very severe" (item 9 about fatigue). The last item ("How would you rate your pain on average?") is scored on a 10-point scale ranging from "no pain" to "the worst imaginable pain". The scores of the PROMIS-10 items were used to compute total scores ranging from 0–100 (higher scores indicate better outcome). The content of the PROMIS-10 incorporates important components of the World Health Organization's International Classification of Functioning, Disability and Health (ICF), including body functions, activity and participation.[32] The PROMIS-10 has acceptable measurement properties in the stroke population, showing moderate internal reliability and convergent validity, and excellent discriminant validity across mRS levels.[20]

Patient-reported decrease in HRQoL post-stroke

Two items were used to evaluate participants' experienced decrease in HRQoL associated with the onset of stroke. The first item asked participants to rate the decrease in their health they experienced associated with the onset of stroke. The second item asked participants to rate the decrease in their activities associated with the onset of stroke. The experienced decrease was measured on a 4-point response scale ("none", "a little", "strong" and "very strong") in both items.

Statistical analysis

All analyses were conducted with IBM SPSS version 25 (IBM, Armonk, NY). Descriptive statistics were used to describe participant characteristics and all measures. Floor and ceiling effects were considered present if > 15% of participants achieved the worst score

(floor effect) or the best score (ceiling effect). The internal consistency was examined by calculating Cronbach's alpha, which was considered acceptable at an $\alpha > 0.70$.[33]

Bivariate associations between the EQ-5D-5L, PROMIS-10 and mRS were tested using Spearman correlations. Correlation coefficients were interpreted as weak (0.10), moderate (0.30) or strong (0.50).[34] A strong correlation was interpreted as a positive finding (concurrent validity). The distribution of the EQ-5D-5L and PROMIS-10 across the mRS levels and reported decrease in health and activities since stroke were graphically displayed with boxplots. High variance within mRS levels was interpreted as a positive finding (showing potentially relevant information to evaluate HRQoL after stroke). We explored the discriminant ability of the EQ-5D-5L and PROMIS-10 with patient-reported (levels of experienced decrease in health and in activities post-stroke) and clinician-reported (mRS levels) external anchors. Effect sizes were calculated (Hedges' *g*) and interpreted as weak (0.20), moderate (0.50) or strong (0.80). Statistical significance was established in the event of an alpha-level smaller than 0.05.

RESULTS

Participant characteristics are presented in Table 3.1. A total of 360 participants were included in this study, of whom 39.7% were female. Nearly all participants lived at home 3 months post-stroke. In concordance with national incidence rates, a majority of participants suffered an ischemic stroke, most strokes were mild and most participants were ADL independent after the event. The majority of participants had no significant (mRS 1) or slight disability (mRS 2), whereas only 12% of participants suffered moderate to severe disability (mRS 3–5) 3 months after stroke (Table 3.2). In this study, the mRS scores of 3, 4 and 5 were clustered because of insufficient numbers of participants in these categories. Approximately one-third of the participants did not report any decrease in health (36.7%) or in activities (33.1%) post-stroke (Table 3.2). Because of insufficient numbers of participants reporting very strong decrease in health and activities, the responses "strong" and "very strong" were clustered in both items.

Internal consistency

The PROMIS-10 showed greater internal consistency ($\alpha = 0.90$) compared to the EQ-5D-5L ($\alpha = 0.75$), although both Cronbach's alphas were considered acceptable (Table 3.2).

Table 3.1: Patients characteristics (n = 360)

Demographic factors (3 months after stroke)	
Sex (% male)	60.3
Age in years (at time of stroke)	71.0 (17.0)[a]
Marital status (% living together)	72.2
Residency (% living at home)	96.9
Stroke-related factors	
Ischemic stroke (%)	93.0
Hemorrhagic stroke (%)	7.0
Left hemisphere (%)	46.1
Severity of stroke (NIHSS) at hospital admission (n = 242)	3.0 (3.0)[a]
No or minor stroke symptoms (% NIHSS ≤ 4)	68.2
Moderate to severe stroke symptoms (% NIHSS > 4)	31.8
ADL dependency (BI) 4 days after stroke (n = 275)	20.0 (2.0)[a]
% ADL-dependent (BI ≤ 17)	37.1
ADL dependency (BI) at discharge (n = 264)	20.0 (2.0)[a]
% ADL-dependent (BI ≤ 17)	23.5

Abbreviations: ADL, activities of daily living; BI, Barthel Index; NIHSS, National Institutes of Health Stroke Scale.
[a] Median (IQR, interquartile range).

Table 3.2: Frequencies and descriptive statistics of the EQ-5D-5L, PROMIS-10, mRS and patient-reported decrease in health and in activities 3 months after stroke

	Mean	± SD	Median	IQR	% maximum	α
EQ-5D-5L	78.0	± 19.6	80.8	69.4–91.7	21.4	0.75
PROMIS-10	54.3	± 18.5	55.0	42.5–65.0	1.9	0.90
					n	%
mRS item scores						
0: No symptoms					47	13.1
1: No significant disability, despite symptoms					136	37.8
2: Slight disability					134	37.2
3: Moderate disability: requires some help, able to walk					30	8.3
4: Moderately severe disability: unable to walk, ADL dependent					11	3.1
5: Severe disability: bedridden, requires constant nursing care					2	0.6
Patient-reported decrease in health and in activities post-stroke						
No decrease in health					132	36.7
A little decrease in health					164	45.6
Strong decrease in health					64	17.8
No decrease in activities					119	33.1
A little decrease in activities					155	43.1
Strong decrease in activities					86	23.9

Abbreviations: α, Chronbach's alpha; EQ-5D-5L, EuroQol 5-dimensional 5-level value score; IQR, interquartile range; mRS, Modified Rankin Scale; PROMIS-10, Patient Reported Outcomes Measurement Information System 10-Question Short Form.

Distribution

The EQ-5D-5L showed a non-normal left-skewed distribution with a ceiling effect (21.4% maximum score), whereas the PROMIS-10 had a normal distribution and showed no sign of floor or ceiling effects (Figure 3.1). The observed ceiling effect in the EQ-5D-5L mainly occurred in participants with no or no significant disabilities (mRS 0–1) 3 months after stroke (Figure 3.2) and in participants who did not report any decrease in health and in activities post-stroke (Figure 3.3). Participants with slight to severe disability (mRS 2–5) and participants who reported strong decrease in health and in activities showed higher variation in EQ-5D-5L scores compared to participants with no or no significant disability (mRS 0–1) and participants who did not report any decrease in health or in activities post-stroke (Figure 3.2 and 3.3). A high variation in PROMIS-10 scores was observed across all mRS levels and all levels of reported decrease in health and in activities post-stroke, even in participants with no disabilities (mRS 0) or participants who did not report any decrease in health or in activities 3 months after stroke (Figure 3.2 and 3.3).

Concurrent validity

Both the EQ-5D-5L (r = -0.62) and PROMIS-10 (r = -0.60) showed strong and significant negative correlations with the mRS. A strong and significant positive correlation (r = 0.74) was observed between the EQ-5D-5L and PROMIS-10.

Discriminant ability

The EQ-5D-5L showed strong ability to detect differences between participants with no significant versus slight (mRS 1 vs. 2) and slight versus moderate to severe disabilities (mRS 2 vs. 3–5), whereas its ability to detect differences between participants with no versus no significant disabilities (mRS 0 vs. 1) was moderate (Table 3.3). The PROMIS-10 showed strong ability to detect differences across all mRS levels, especially between participants with no versus no significant disabilities (mRS 0 vs. 1) 3 months after stroke (Table 3.3).

The EQ-5D-5L showed strong ability to detect differences between participants who reported a little versus strong decrease in health and in activities, whereas its ability to detect differences between participants who did not report any decrease versus participants who reported a little decrease in health and in activities was moderate (Table 3.3). The PROMIS-10 showed strong ability to detect differences between all levels of patient-reported decrease in health and in activities post-stroke (Table 3.3).

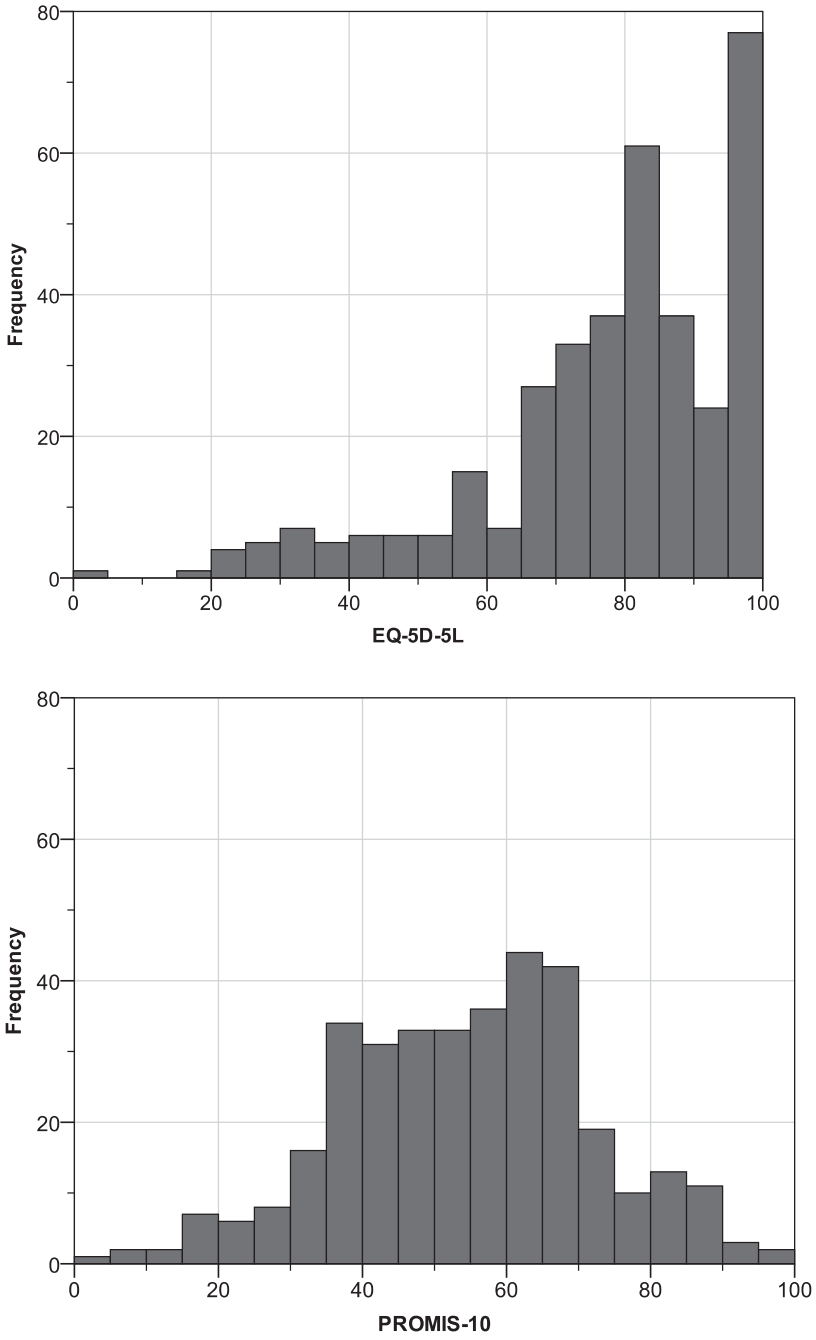

Figure 3.1: Frequency distribution of the EQ-5D-5L and PROMIS-10.
Abbreviations: EQ-5D-5L, EuroQol 5-dimensional 5-level value score; PROMIS-10, Patient Reported Outcomes Measurement Information System 10-Question Short Form.
Note: Higher EQ-5D-5L and PROMIS-10 scores indicate better function.

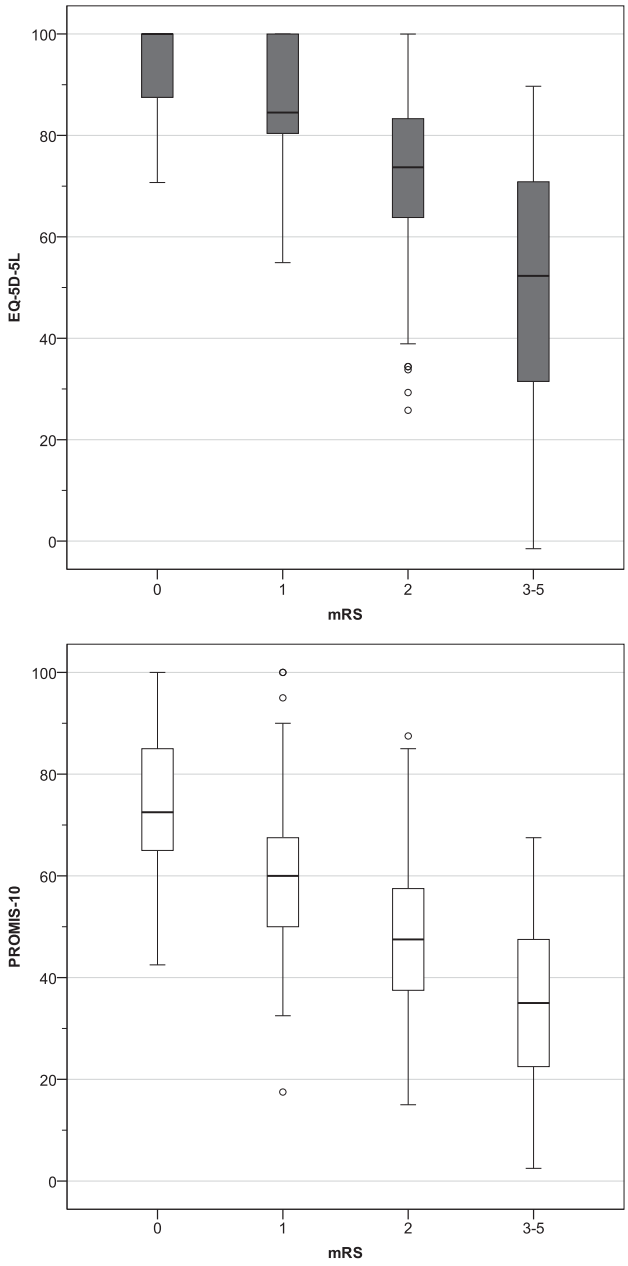

Figure 3.2: Distribution of the EQ-5D-5L and PROMIS-10 across mRS scores 3 months after stroke.
Abbreviations: EQ-5D-5L, EuroQol 5-dimensional 5-level value score; mRS, Modified Rankin Scale; PROMIS-10, Patient Reported Outcomes Measurement Information System 10-Question Short Form.
Note: the thick horizontal bar in the boxes represents the median for each mRS level. The ends of the boxes represent the first and third quartiles. The vertical line represents the minimum and maximum score (inside 1.5 IQR). The open dots represent outliers (outside 1.5 IQR). Higher mRS scores indicate worse disability, higher EQ-5D-5L and PROMIS-10 scores indicate better function.

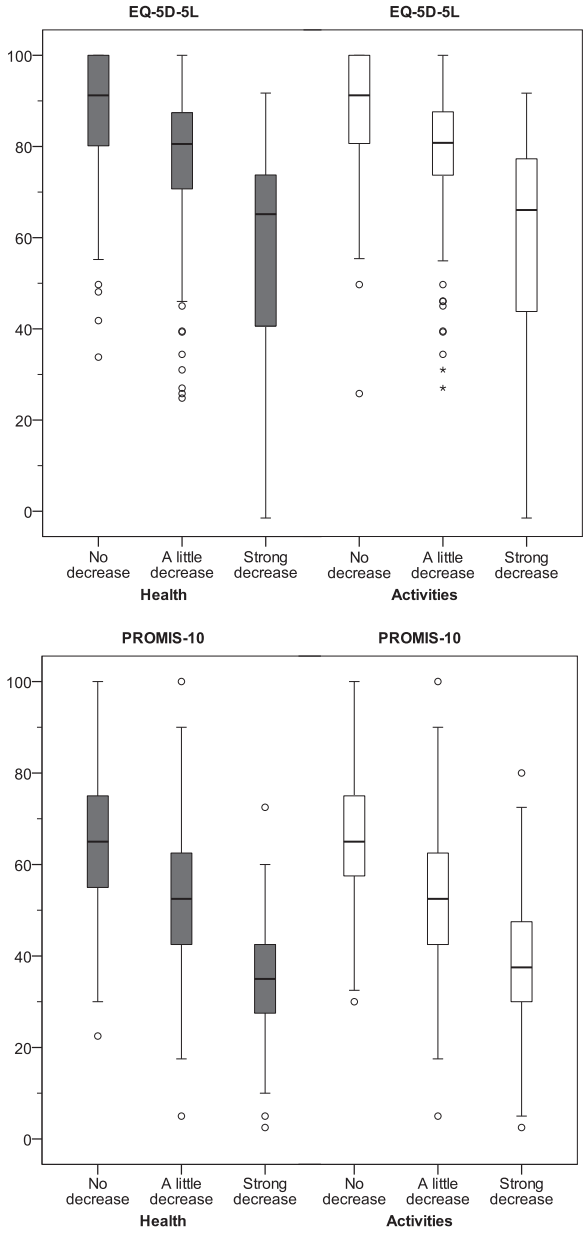

Figure 3.3: Distribution of the EQ-5D-5L and PROMIS-10 across different levels of patient-reported decrease in health (blue) and in daily activities (white).
Abbreviations: EQ-5D-5L, EuroQol 5-dimensional 5-level value score; PROMIS-10, Patient Reported Outcomes Measurement Information System 10-Question Short Form.
Note: The thick horizontal bar in the boxes represents the median for the EQ-5D-5L and PROMIS-10. The ends of the boxes represent the first and third quartiles. The vertical line represents the minimum and maximum score (inside 1.5 IQR). The open dots represent outliers (outside 1.5 IQR). Higher EQ-5D-5L and PROMIS-10 scores indicate better function.

Table 3.3: Ability of the EQ-5D-5L and PROMIS-10 to discriminate between adjacent mRS levels (mRS 0 vs. mRS 1, mRS 1 vs. mRS 2 en mRS 2 vs. mRS 3–5) and different levels of patient-reported decrease in health and in activities post-stroke

		Mean Δ	SE Δ	P-value	95% CI Δ	Hedges' *g*
EQ-5D-5L	mRS 0 vs. mRS 1	7.56	2.57	0.018*	0.94–14.19	0.71
	mRS 1 vs. mRS 2	14.45	1.85	< 0.001*	9.69–19.22	1.04
	mRS 2 vs. mRS 3–5	20.12	2.66	< 0.001*	13.26–26.98	1.07
	No vs. a little decrease in health	10.59	1.93	< 0.001*	6.05–15.12	0.71
	A little vs. strong decrease in health	20.17	2.43	< 0.001*	14.46–25.89	1.13
	No vs. a little decrease in activities	8.57	2.00	< 0.001*	3.86–13.27	0.60
	A little vs. strong decrease in activities	20.01	2.20	< 0.001*	14.82–25.20	1.14
PROMIS-10	mRS 0 vs. mRS 1	14.11	2.47	< 0.001*	7.72–20.49	0.96
	mRS 1 vs. mRS 2	12.61	1.78	< 0.001*	8.02–17.20	0.89
	mRS 2 vs. mRS 3–5	13.06	2.56	< 0.001*	6.45–19.67	0.87
	No vs. a little decrease in health	12.36	1.75	< 0.001*	8.25–16.48	0.81
	A little vs. strong decrease in health	18.89	2.20	< 0.001*	13.70–24.08	1.04
	No vs. a little decrease in activities	12.95	1.84	< 0.001*	8.62–17.29	0.85
	A little vs. strong decrease in activities	15.59	2.03	< 0.001*	10.80–20.37	1.04

Abbreviations: Δ, difference; CI, confidence interval; EQ-5D-5L, EuroQol 5-dimensional 5-level value score; mRS, Modified Rankin Scale; PROMIS-10, Patient Reported Outcomes Measurement Information System 10-Question Short Form; SE, standard error.
Higher mRS scores indicate worse disability.
* $p < 0.05$.

DISCUSSION

The aim of this study was to compare the measurement properties (floor- and ceiling effects, internal consistency, concurrent validity and discriminant ability) between the EQ-5D-5L and PROMIS-10 to evaluate HRQoL 3 months after stroke. The EQ-5D-5L appeared to have a non-normal left-skewed distribution with a ceiling effect, whereas the PROMIS-10 showed no ceiling effect and a normal distribution. The PROMIS-10 showed greater internal consistency (although both Cronbach's Alphas were considered acceptable) and both PROMs achieved adequate concurrent validity (showing strong correlations with the mRS). The PROMIS-10 showed better discriminant ability in less affected individuals with stroke, whereas the EQ-5D-5L showed slightly better discriminant ability in more affected individuals with stroke. Overall, the PROMIS-10 had slightly better measurement properties than the EQ-5D-5L.

EQ-5D-5L

The EuroQol is a feasible and commonly used PROM to evaluate HRQoL in stroke research and clinical stroke audits, and has been proven reliable, responsive and valid in the stroke population.[15,29,35] One retrospective cohort study did also find a ceiling effect (17.2% maximum scores) at the first ambulatory visit after hospital admission of 3283 individuals with stroke treated in a stroke unit in the United States,[14] whereas one prospective cohort study with 112 participants on a stroke ward in a Polish hospital did not find a ceiling effect (7.1% maximum scores) of the EQ-5D-5L at follow-up 4 months after stroke.[35] Differences in study design and follow-up duration may partially explain these diverging results. The observed ceiling effect of the EQ-5D-5L may have caused loss of relevant information in our study, as many participants with maximum EQ-5D-5L scores 3 months after stroke had minor (51.9% mRS 1) to slight disabilities (7.8% mRS 2) and often experienced deterioration in health (24.7%) and in activities (32.5%) post-stroke.

In this study, the EQ-5D-5L showed slightly stronger associations with the mRS as compared to previous studies.[14,35] Furthermore, the discriminant ability between the EQ-5D-5L across different mRS levels has not been explored in current stroke literature to our knowledge. One American prospective cohort study found similar HRQoL scores in patients with mRS 2 and mRS 3 outcomes using the EQ-5D-3L 3 months after stroke, whereas good discriminant ability was observed between all other mRS levels. However, the EQ-5D-3L has worse discriminant ability compared to the EQ-5D-5L.[28]

PROMIS-10

In contrast to the EQ-5D-5L, the PROMIS-10 showed no ceiling effect in patients who did not experience any decrease in health or activities post-stroke or scored mRS 0 (no symptoms) in our study. This could be explained by the response categories of both PROMs, as maximum scores on the PROMIS-10 items indicate "excellent" HRQoL, whereas maximum scores on the EQ-5D-5L items indicate the "no problems". A validation study of the PROMIS-10 in the stroke population showed similar internal consistency ($\alpha = 0.82–0.88$) and discriminant ability across mRS scores as our study.[20] Furthermore, only moderate correlations between PROMIS-10 items and mRS were observed, whereas a strong association was found in our study.[20]

Implementation of PROMs

Both EQ-5D-5L and PROMIS-10 provided potentially relevant additional information to evaluate HRQoL 3 months after stroke, as a high variation of EQ-5D-5L and PROMIS-10

scores among participants within each mRS score was found. This finding confirms previous literature showing the potentially valuable information PROMs could add to the mRS after stroke.[14] Although concerns have been raised about practical challenges in the implementation of PROMs in clinical practices,[19,36] the implementation of PROMs (including the EQ-5D-5L) as outcome measure in stroke patients recently proved to be feasible in a Dutch outpatient rehabilitation clinic.[18] Besides, the addition of a PROM to the clinical stroke audits could also provide potential benefits for stroke research, as patient-relevant outcome could be assessed using a continuous scale (potentially improving the power to detect change) and across different domains affected by the stroke.[37]

Future research

In this study, we chose to use the generic PROMIS-10 (as recommended by the ICHOM) and the EQ-5D-5L. Several other PROMIS scales from the comprehensive PROMIS item banks have proven to be potentially useful as outcome measure after stroke, such as the computer-adaptive scales on physical health and fatigue.[14,20,38,39] A recent systematic review in patients with aneurysmal subarachnoid hemorrhage recommended the use of a disease-specific PROM to fully capture disease-specific long-term consequences (for example cognitive deficits or communication problems).[40] Therefore, we recently validated the addition of an item on cognitive problems to the EQ-5D-5L (EQ-5D-5L+C),[41] as cognitive problems are highly prevalent after stroke and are strongly associated with decreased quality of life.[42] Comparing measurement properties between generic PROMs (such as PROMIS-10 and EQ-5D-5L+C) and disease-specific PROMs (such as the Neuro-QoL, Stroke Impact Scale and the Stroke Specific Quality Of Life scale) to evaluate HRQoL after stroke would be an interesting direction for future research.

Study limitations

The study population consisted mainly of patients with relatively mild ischemic strokes who were living at home. Consequently, mRS scores 3 to 5 were grouped because of small numbers of high mRS scores in the study population. One explanation could be that stroke nurses had more difficulties to contact patients who were living in nursery homes or inpatient rehabilitation facilities 3 months after stroke, which may have caused selection bias. This could negatively affect the generalizability of the results to severely affected stroke patient (mRS 3–5). However, current epidemiological studies show that most people have relatively mild ischemic strokes.[5] Furthermore, no information was obtained on the rehabilitation interventions that participants could have received in the first 3 months after stroke.

CONCLUSIONS

Our study confirms the importance of using PROMs to evaluate HRQoL in patients who are living at home 3 months after stroke. Both EQ-5D-5L and PROMIS-10 prove to be useful instruments to evaluate HRQoL 3 months after stroke. It depends on the setting and underlying goal which PROM is preferred. The PROMIS-10 should be preferred to detect differences in less affected stroke patients, whereas the EQ-5D-5L provides slightly more information in more affected stroke patients 3 months after stroke. One might argue that the EQ-5D-5L is suitable if detecting "problems" post-stroke is the main goal, whereas the PROMIS-10 is more appropriate if one is interested in screening on "general health" post-stroke. Practically speaking, the EQ-5D-5L is notably shorter, easier to understand and to administer, but also less comprehensive as important domains post-stroke such as fatigue, cognitive functioning and social roles are lacking. As both EQ-5D-5L and PROMIS-10 are useful PROMs in clinical practice to evaluate HRQoL during follow-up assessment after stroke, our results may provide clinicians with valuable clues to select and implement the PROM that will best suit their needs depending on the underlying goal, clinical setting and stroke population.

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Chapter 4

Validity of an enhanced EQ-5D-5L measure with an added cognitive dimension in patients with stroke

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Abstract

Objective: The 5-level EuroQol (EQ-5D-5L) is a patient-reported outcome measure frequently used in stroke research. However, it does not assess the cognitive problems many patients with stroke experience. The aim of this paper is to compare the content validity, internal consistency and discriminative ability of the EQ-5D-5L with and without an additional cognitive domain (EQ-5D-5L+C), administered 3 months post-stroke.

Design: Cross-sectional study.

Setting: Six general hospitals in the Netherlands.

Subjects: 360 individuals with stroke 3 months after the event.

Interventions: Not applicable.

Main measures: The modified Rankin Scale and EQ-5D-5L+C were administered in telephone interviews 3 months post-stroke.

Results: A total of 360 patients with stroke were included. Mean age was 68.8 years (SD = 11.7), 143 (40%) were female, 334 (93%) had had an ischemic stroke, 165 (46%) had an NIHSS score ≤4 at presentation and the Barthel Index was 17.2 (SD = 4) 4 days post-stroke. Cognitive problems were reported by 199 (55%) patients 3 months post-stroke. Internal consistencies of the EQ-5D-5L and EQ-5D-5L+C were 0.75 and 0.77, respectively. Adding a cognitive domain resulted in a decrease of the ceiling effect from 22% to 14%. Both EQ-5D-5L and EQ-5D-5L+C showed good discriminative ability, but differences between patients with different modified Rankin Scale scores and with/without reported decrease in health and daily activities were slightly larger with the EQ-5D-5L+C compared to the EQ-5D-5L.

Conclusions: The EQ-5D-5L+C, which includes a cognitive domain that is highly significant for stroke patients, showed increased content validity and good discriminative ability, without losing internal consistency.

INTRODUCTION

The use of patient-reported outcome measures (PROMs) is growing in stroke research.[1] The EuroQol (EQ-5D) is a frequently used PROM that has shown validity and reliability in stroke populations.[2] The increase in the number of response categories from 3 (EQ-5D-3L) to 5 levels (EQ-5D-5L) further improved its measurement properties.[3] However, cognitive functioning, which is frequently disturbed after stroke, is not covered by the EuroQol. In the general population, the addition of a cognitive domain to the previous EQ-5D-3L was found not to negatively impact on the reliability of the instrument, whereas its content validity increased,[4, 5] but this has never been explored for the EQ-5D-5L, nor in a stroke population.

The aim of our study was to compare the content validity, internal consistency and discriminative ability of the EQ-5D-5L with and without an additional cognitive domain (EQ-5D-5L+C), administered 3 months post-stroke.

METHODS

Consecutive patients with stroke were recruited through 6 hospitals in the Netherlands. After informed consent had been obtained, data were collected by stroke nurses by means of telephone interviews, as part of the routine follow-up 3 months post-stroke.[6] The Medical Ethics Committee of the University Medical Center Utrecht declared that the study did not need formal approval under Dutch law (2017-441C). All participating hospitals approved the study.

Stroke severity at presentation in the hospital was expressed as National Institute of Health Stroke Scale (NIHSS) scores,[7] and functional independence 4 days post stroke was expressed as Barthel index score.[8]

Three months post-stroke, overall outcome was assessed with the modified Rankin Scale and with the EQ-5D-5L+C.[9] The modified Rankin Scale ranges from 0 to 5 and higher scores indicate more disabilities. The modified Rankin Scale scores 3, 4 and 5 were merged because of low numbers of patients per category. The EQ-5D-5L assesses health status using five items: mobility, self-care, usual activities, pain or discomfort and anxiety or depression. Each item has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. A sixth item on cognitive functioning was added as described previously,[4] with the same response categories (EQ-5D-5L+C): "I have no problems with my cognitive functioning", "I have slight problems with my cognitive functioning", "I have moderate problems with my cognitive functioning", "I have severe problems with my

cognitive functioning" and "I have extreme problems with my cognitive functioning". For both versions a total score with range 0–100 (100 = perfect health) was computed.

Possible decreases in health and in daily activities associated with the onset of stroke were asked for using two single items with 4-point response scales (none, a little, strong, very strong). These scores were dichotomized into no decrease versus any decrease.

Statistical analysis

Spearman correlation coefficients were used to examine inter-correlations between items and with the modified Rankin Scale (content validity). Internal consistency was determined by calculating Cronbach's alpha (acceptable if $\alpha \geq 0.70$) and corrected item-total correlations (acceptable if ≥ 0.30).

Differences in EQ-5D-5L and EQ-5D-5L+C total scores between patients with different modified Rankin Scale levels and between those who did versus those who did not report a decrease in health or daily activities were computed and expressed in the effect size measure Hedges' *g* (discriminative ability). We explored the ability of the EQ-5D-5L and EQ-5D-5L+C to differentiate between both subjective and objective levels of post-stroke functioning, using both patient-reported (decrease vs. no decrease in health and daily activities) and clinician-reported (modified Rankin Scale) reference instruments.

RESULTS

A total of 360 patients were included. Mean age was 68.8 years (SD = 11.7), 143 (40%) were female, 334 (93%) had had an ischemic stroke, 166 (46%) had had a left hemisphere stroke, 165 (46%) had an NIHSS score ≤ 4 at presentation and the mean Barthel Index score was 17.2 (SD = 4) 4 days post-stroke.

Inter-correlations among all items are shown in Table 4.1. The cognition item showed weak to moderate associations with all other items. Cronbach's alpha values of the EQ-5D-5L and EQ-5D-5L+C were similar (0.75 and 0.77, respectively). The cognitive item showed an item-total correlation of 0.46 (range of other items 0.48–0.65).

Based on the cognition item of the EQ-5D-5L+C, more than half of the patients experienced cognitive problems: 110 (31%) slight, 71 (20%) moderate, 18 (5%) severe and 0 (0%) extreme problems. Total scores on the EQ-5D-5L and EQ-5D-5L+C were similar: 78.0 (SD = 19.6) and 81.8 (SD = 16.2), respectively. The percentage of patients with a maximum score (perfect

health) was lower with the EQ-5D-5L+C (n = 52, 14%) compared to the EQ-5D-5L (n = 77, 22%). The total EQ-5D-5L and EQ-5D-5L+C scores were strongly associated with each other (0.93) and with the modified Rankin Scale (-0.66 and -0.67, respectively). Differences between patients with different modified Rankin Scale scores and with/without reported decreases in health and daily activities were slightly larger with the EQ-5D-5L+C compared to the EQ-5D-5L (Table 4.2). Overall, both the EQ-5D-5L and the EQ-5D-5L+C showed large mean differences between these subgroups.

Table 4.1: Spearman correlations (r_s) between the EQ-5D-5L and the modified Rankin Scale, between the EQ-5D-5L+C and the modified Rankin Scale, and between all individual domains of the EQ-5D-5L+C

n = 360	mRS	Mobility	Self-care	Usual activities	Pain or discomfort	Anxiety or depression	Cognition
EQ-5D-5L total score	-0.66*	0.74*	0.56*	0.82*	0.67*	0.56*	0.43*
EQ-5D-5L+C total score	-0.67*	0.69*	0.55*	0.81*	0.65*	0.56*	0.62*
Mobility	-0.46*	-	0.48*	0.49*	0.43*	0.19*	0.20*
Self-care	-0.47*	-	-	0.46*	0.32*	0.17*	0.25*
Usual activities	-0.64*	-	-	-	0.42*	0.36*	0.42*
Pain or discomfort	-0.36*	-	-	-	-	0.25*	0.28*
Anxiety or depression	-0.31*	-	-	-	-	-	0.35*
Cognition	-0.42*	-	-	-	-	-	-

Abbreviations: mRS, modified Rankin Scale; EQ-5D-5L, EuroQol 5 dimensions; EQ-5D-5L+C, EuroQol 6 dimensions (including cognitive domain).
* $p \leq 0.001$.

Table 4.2: Differences in EQ-5D-5L and EQ-5D-5L+C scores between modified Rankin Scale levels and with/without reported decrease in health and daily activities

	EQ-5D-5L			EQ-5D-5L+C		
	Mean Δ	95% CI Δ	Hedges' *g*	Mean Δ	95% CI Δ	Hedges' *g*
mRS 0 vs. mRS 1	7.6	0.9–14.2	0.71	6.2	1.0–11.4	0.73
mRS 1 vs. mRS 2	14.5*	9.7–19.2	1.04	12.8*	9.1–16.5	1.14
mRS 2 vs. mRS 3–5	20.2*	13.3–27.0	1.07	18.2*	12.8–23.6	1.25
Decreased health	16.3*	12.4–20.1	0.90	14.0*	10.8–17.2	0.95
Decreased activities	15.7*	11.7–19.7	0.87	14.9*	11.7–18.1	1.02

Abbreviations: CI, confidence interval; mRS, modified Rankin Scale; EQ-5D-5L, EuroQol 5 dimensons; EQ-5D-5L+C, EuroQol 6 dimensions (including cognitive domain).
* $p \leq 0.001$.

DISCUSSION

More than half of the patients in this study reported cognitive problems. The addition of a cognitive domain to the EQ-5D-5L minimized the ceiling effect of this scale and improved the coverage of problems experienced by patients with stroke, while its internal consistency and discriminative ability did not substantially change. Our findings suggest that it would be beneficial to use the EQ-5D-5L+C instead of the EQ-5D-5L for stroke patients. As cognitive problems are highly prevalent after stroke and are strongly associated with decreased quality of life,[10] the addition of an item on cognitive problems in the EQ-5D-5L+C improves the coverage of key aspects of health-related quality of life after stroke. Although not tested in the current study, these results may also apply to patients with other neurological conditions and older adults, as cognitive problems are also prevalent in various neurological disorders and in the aging population.[11]

To the best of our knowledge, our study is the first to compare the EQ-5D-5L with the EQ-5D-5L+C in stroke patients. Previous work on adding a cognitive domain to the EuroQol measure has been scarce. One study explored changes in the valuation of health states after addition of a cognitive domain to the 3-level EuroQol (EQ-5D-3L) among healthy individuals.[4] The authors recommended extension of the EuroQol, since cognitive functioning is an important and independent attribute of favorable health states, and the content validity of the measure increased while its reliability remained unchanged.[4] A second study reviewed the performance of the EQ-5D-3L with and without an extra cognitive item in a population of elderly patients with cognitive impairments.[12] This study showed unchanged construct validity after addition of a cognitive domain. The authors also examined the responsiveness of the two questionnaires, i.e. the ability to detect changes over time. They concluded that adding a cognitive domain slightly decreased the responsiveness of the EuroQol, and thus that the use of the EQ-5D-3L was to be preferred.[12] However, their results may be biased due to the use of proxies to complete the added cognitive domain. The proxy-patient agreement for cognitive problems is doubtful, as the scores on the cognitive domain may be influenced by the caregivers' perceived burden.[13]

Our sample consisted mainly of patients with relatively mild strokes, as 183 patients (51%) had modified Rankin Scale scores of 0–1, but nevertheless more than half of our study population reported cognitive problems to some extent. This has also been observed in a Finnish study, in which one third of the sample (n = 152) had modified Rankin Scale scores of 0–1, but still 108 (71%) of them were impaired in at least one cognitive domain based on neuropsychological assessment.[14] These large percentages demonstrate the additional

value of the cognitive item, since these problems remain unreported if only the EQ-5D-5L is administered.[4] These cognitive problems are related to decreased quality of life after stroke and to objective cognitive impairment.[10] The accumulation of deficits in multiple cognitive domains has been suggested to contribute to the cognitive problems experienced after stroke.[15] Cognitive impairment is related to decreased quality of life,[16] more severe disabilities,[17] mortality[18] and mood problems in the long term after stroke.[19] Therefore, early detection of cognitive problems after stroke is of great importance.

In agreement with the contemporary concept of value-based health care,[20] the use of patient-reported measures such as the EQ-5D-5L to evaluate health status after stroke is increasing in clinical practice.[21] However, despite their potential, patient-reported measures remain underutilized in clinical stroke trials.[1] Moreover, the cognitive functioning domain is often lacking from the current generic patient-reported measures.[1] Stroke-specific patient-reported measures, such as the Stroke Impact Scale, do include cognitive problems and other stroke-related issues (such as communication problems), but take considerably more time to administer.[1] As cognitive problems are more prevalent than other common stroke sequalae such as aphasia,[10, 22, 23] and are considered one of the key attributes missing in the current health states valuation of the EuroQol, according to qualitative research,[24] the addition of a cognitive domain to the widely used EQ-5D-5L seems a highly relevant extension.

Several limitations of our study should be acknowledged. First, patients with more severe dysfunction were underrepresented. Although this is in line with the epidemiology of stroke, it meant that we were not able to compare scores between patients with modified Rankin Scale scores 3, 4 or 5. Second, although the EQ-5D-5L has shown good validity and reliability in the stroke population, patients with severe cognitive problems may lack the cognitive skills required to use such a self-report questionnaire, thus decreasing its measurement reliability.[25] According to population-based studies, approximately 30% of stroke patients have difficulties using self-report questionnaires due to their cognitive problems, language disorders or premorbid low health literacy.[1] We have tried to avoid these potential issues by collecting data by means of telephone interviews (so the stroke nurse could clarify questions if needed). Third, EQ-5D-5L health states can be converted into index values (using country-specific value sets), reflecting the valuation of these health states by the general population. The EQ-5D-5L+C can currently not be converted into index values, which limits its use in, for example, cost-effectiveness analysis. Fourth, a measure of cognitive functioning was lacking in this study. Therefore, external validation of the EQ-5D-5L+C in another stroke sample is needed, preferably including a comparison between the EQ-5D-5L+C and a patient-reported cognitive screening instrument such as the Checklist for Cognitive and Emotional

Consequences (CLCE-24). Future studies could also further explore the reliability (intra- and inter-observer agreement) and construct validity (dimensionality and factorial invariance) of the EQ-5D-5L+C to gain full insight into its measurement properties.[26]

Clinical message

- The EQ-5D-5L+C, which includes a cognitive domain that is highly significant to stroke patients, showed increased content validity and good discriminative ability without losing internal consistency.
- Pending further research, our findings suggest that it would be beneficial to use the EQ-5D-5L+C instead of the EQ-5D-5L to measure health-related quality of life in stroke patients.

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2

Part 2

Determinants and course of participation after stroke

Chapter 5

Long-term restrictions in participation in stroke survivors under and over 70 years of age

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Abstract

Purpose: This study aims to (1) assess differences in participation restrictions between stroke survivors aged under and over 70 years, and (2) identify predictors associated with favorable and unfavorable long-term participation in both age groups.

Methods: Prospective cohort study in which 326 patients were assessed at stroke onset, two months and one year after stroke. The Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-Participation) was used to measure participation restrictions one year after stroke. Bivariate and multivariate logistic regression analyses were performed including demographic factors, stroke-related factors, emotional functioning and comorbidity as possible predictors.

Results: Stroke survivors aged over 70 years perceived more participation restrictions in comparison to stroke survivors aged under 70 years one year after stroke. Independently significant predictors for unfavorable participation outcomes were advancing age, more severe stroke and anxiety symptoms in patients aged over 70 years, and female gender, more severe stroke, impaired cognition and depression symptoms in patients aged under 70 years. Lower age was the only independent predictor associated with favorable participation after one year in stroke survivors aged over 70 years.

Conclusions: This study emphasizes the need to pay more attention to participation restrictions in elderly stroke survivors.

INTRODUCTION

Stroke is one of the most common causes of disability. In the Netherlands the annual incidence of stroke is between 34,000 and 41,000 patients, ranging from 0.7/1,000 for people under 55 years old to 15/1,000 for people over 70 years old.[1] Therefore stroke is truly a disease of the elderly.[2] Major improvements in the acute treatment of stroke, such as thrombolysis and the implementation of stroke units, have increased post stroke survival rates.[3] Consequently, an increasing number of stroke survivors have to deal with long-term stroke sequelae, including psychosocial consequences and participation restrictions.[4]

According to the International Classification of Functioning, Disability and Health (ICF), participation can be defined as "the person's involvement in a life situation",[5] including daily activities as well as social roles.[6] Stroke survivors often experience participation restrictions in the chronic phase, despite being independent in basic activities of daily living.[7]

After stroke onset, participation improves in the first three to six months, followed by a stable phase.[8-11] Several factors have been found to contribute to participation restrictions after stroke, including cognitive deficits,[12,13] emotional deficits,[14,15] psychological factors,[16,17] functional dependency,[18] comorbidities[19] and increasing age.[14,19,20] Because of the increasing number of old stroke survivors and the association between age and participation restrictions, more research is needed to gain insight into the prediction and improvement of participation in the elderly.[21] To the best of our knowledge, predictors of long-term participation has never been determined for young and old stroke survivors separately.

Old and young stroke survivors have different participation needs, influenced by age-related changes in social status, retirement and co-morbid factors.[22] In stroke survivors at vocational age, an important rehabilitation goal is returning to work. Participation needs in the elderly are mostly not related to work but to all other domains of participation and seem to be more complex for this reason.[23] Moreover, age-related factors such as a higher incidence of comorbidity, less social support and impaired compensatory abilities make older stroke survivors particularly more likely to have difficulties in long-term participation.[24,25] Therefore, reintegration in the community after stroke remains a huge challenge for the elderly.[23,26]

Hence, more attention should be paid to older stroke survivors who are at risk for adverse participation outcome. Short-term predictors of participation in older stroke survivors have been assessed in only one study.[27] A comparison of participation restrictions and its determinants between younger and older stroke patients has not been published to date.

Therefore, this study aims to assess differences in participation restrictions between stroke survivors over 70 years and under 70 years old. Furthermore, predictors associated with favorable and unfavorable long-term participation will be identified in both age groups.

METHODS

Design

The present study is part of the multicenter prospective longitudinal Restore4Stroke Cohort study and used data collected at stroke onset, two months and one year after stroke.3 Six general hospitals in the Netherlands participated. The medical ethical committees of all participating hospitals gave approval for this study. Written informed consent was obtained from all included patients.

The first assessment took place within the first week after stroke and concerned demographical and stroke-related factors. Demographical factors were obtained from the patient or from family members. Stroke-related factors were extracted from the medical charts as assessed by the neurologist on the fourth day after stroke. At two months after stroke, comorbidity and emotional and cognitive functioning were assessed. Patients were asked to complete self-report scales on emotional functioning. Screening on comorbidity and cognitive functioning was conducted by a trained research assistant. At one year after stroke, a follow-up assessment took place during which patients were asked to complete the self-report scale of participation.

Participants

Stroke patients were enrolled in the Restore4Stroke Cohort study between March 2011 and March 2013. Stroke patients were eligible if they had a clinically confirmed diagnosis of ischemic or hemorrhagic stroke within seven days after symptom onset, and were at least 18 years old. Patients were excluded from the study if they (1) had a serious other condition that could interfere with study outcome; (2) had been dependent in basic Activities of Daily Living (ADL) before the stroke occurred (defined by a Barthel Index (BI) score of ≤ 17[28]); (3) had insufficient command of Dutch language, based on clinical judgement; or (4) had suffered cognitive decline prior to the stroke (defined by a score of ≥ 1 on the Heteroanamnesis List Cognition[29]). Patients who completed the USER-Participation at one year after stroke were included in the analysis.

Dependent variables

In this study the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-Participation) restrictions subscale was used to measure participation.[7] The restrictions subscale consists of eleven items, concerning difficulties experienced with vocational, leisure and social activities caused by the stroke. For each item four response categories are available ("not possible", "with assistance", "with difficulty" and "without difficulty"). A "not applicable" option is available for all items in case a restriction is not attributed to the stroke. The total score of the restrictions subscale ranges from 0–100, and is based on items that are applicable. A higher score indicates a higher level of participation (fewer experienced restrictions). The USER-Participation has previously shown satisfactory validity and reliability in stroke patients.[30]

Independent variables

Demographic factors

Information about gender, age, marital status and level of education was collected. The Dutch classification system of Verhage was used to assess level of education.[31] Scores range from 1–7 and were dichotomized into low (up to completed secondary education, 1–5) and high (completed university, secondary professional education or higher, 6–7).

Stroke-related factors

Information about severity of stroke, history of stroke, hemisphere, stroke type, ADL dependency, cognitive functioning, length of stay in the hospital and discharge destination was collected. Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS) four days after stroke.[32] Scores range from 0–42 and increasing scores indicate more severe strokes. ADL dependency was assessed using the BI four days after stroke. Scores range from 0–20 and were dichotomized into 'ADL dependent' (BI ≤ 17) and 'ADL independent' (BI > 17).[33] BI is a validated measure often used in stroke.[28] Cognitive functioning two months after stroke was assessed using the Montreal Cognitive Assessment (MoCA). Scores range from 0–30 and were dichotomized into 'cognitive problems' (MoCA ≤ 25) and 'no cognitive problems' (MoCA > 25). The MoCA is a brief cognitive screening tool which is also validated for stroke patients.[34] Discharge destination after hospitalization was categorized into home or inpatient rehabilitation. Inpatient rehabilitation includes geriatric rehabilitation in a nursing home and rehabilitation in a rehabilitation center.

Emotional functioning

The Hospital Anxiety and Depression Scale (HADS) was used to assess the presence of symptoms of depression or anxiety two months after stroke. This scale consists of 14 items, which are subdivided in 7 items about anxiety (HADS-A) and 7 items about depression symptoms (HADS-D). Separate scores for the presence of depression symptoms and the presence of anxiety symptoms were calculated. Each item is scored on a four-point scale (0–3) and a higher score indicates more emotional problems. The HADS-A scores range from 0–21 and were dichotomized into 'absence of symptoms of anxiety' (HADS-A < 8) and 'presence of symptoms of anxiety' (HADS-A ≥ 8). The HADS-D scores range from 0–21 and were dichotomized into 'absence of symptoms of depression' (HADS-D < 8) and 'presence of symptoms of depression' (HADS-D ≥ 8).[35] The HADS is often used in stroke patients and has shown good psychometric properties.[36]

Comorbidity

Comorbidity was assessed with the Cumulative Illness Rating Scale (CIRS) two months after stroke.[37] This scale measures physical impairment with 13 items based on 13 organ areas. Item 11 (neurological impairment) is not included in the analysis, since stroke itself is incorporated in this item.

Statistical analysis

All analyses were conducted with IBM SPSS statistics version 23. Descriptive statistics were used to describe patients' characteristics and dependent variables.

USER-Participation item score one year after stroke

The USER-Participation restrictions items were dichotomized to quantify the presence of persisting restrictions. "With difficulty", "with assistance" and "not possible" were defined as "restrictions" and "without difficulty" was defined as "no restrictions".

Chi-square statistics were calculated on the restriction items to ascertain the differences in participation restrictions between stroke survivors aged over 70 years and under 70 years.

Logistic regression analyses

To determine predictors of favorable and unfavorable participation in patients aged over 70 years and under 70 years one year after stroke, logistic regression analyses were performed. To determine favorable and unfavorable participation outcomes the USER-Participation

restrictions scores were dichotomized into high participation level (best quartile) versus the rest and low participation level (worst quartile) versus the rest, respectively. The USER-P restrictions scores in the best quartile were all 100 (maximum score) in both patients over and under 70 years old. The USER-P Restrictions scores in the worst quartile ranged from 16.7–55.6 in patients over 70 years old and from 14.3–70.0 in patients under 70 years old. Bivariate logistic regression analyses were used to identify bivariately significant determinants of favorable and unfavorable participation scores in patients over and under 70 years of age. Demographic factors, stroke-related factors, emotional functioning two months after stroke and comorbidity were entered as covariates in all bivariate analyses. Bivariately significant variables ($p < 0.10$) were included into the multivariate analyses. Possible multicollinearity was checked (VIF < 4), which did not reveal any problems. The Hosmer-Lemeshow test was used to assess the goodness of fit of the multivariate model. Odds ratios and their 95% confidence intervals were calculated. A $p < 0.05$ was considered as statistical significant.

RESULTS

A total of 395 patients were included in the Restore4Stroke Cohort study. At one year after stroke, datasets of 326 patients were available for analyses. A total of 69 patients (17.5%) dropped out during the study: 8 patients (2.0%) had died, 32 patients (8.1%) refused further participation and 29 patients (7.3%) were lost to follow-up. There were no significant differences in terms of baseline characteristics between patients and drop-outs.

Patient characteristics are presented in Table 5.1. Patients who were over 70 years old at stroke onset were significantly more likely to live alone, be more ADL dependent, more cognitively impaired, have more comorbidities and less likely to be discharged home compared to patients who were under 70 years old at stroke onset. Patients under 70 years

Table 5.1: Patient characteristics (n = 326)

	Total group (n = 326)	Age ≥ 70 yrs (n = 140)	Age < 70 yrs (n = 186)	P-value
Demographic factors				
Sex (% male)	65.0	61.4	67.7	0.237
Age in years	66.5 ± 12.4	77.9 ± 5.6	57.9 ± 8.5	< 0.001*
Marital status (% living together)	70.6	60.7	78.0	0.001*
High education level (%)[a]	26.2	26.4	25.9	0.922

Table 5.1 continues on next page.

Table 5.1: ***Continued***

		Total group (n = 326)	Age ≥ 70 yrs (n = 140)	Age < 70 yrs (n = 186)	P-value
Stroke-related factors					
Ischemic stroke (%)		92.9	91.4	94.1	0.344
Left hemisphere (%)		38.7	37.1	39.8	0.628
First stroke (%)		86.8	82.1	90.3	0.031*
Severity of stroke 4 days after stroke		2.7 ± 3.3	2.7 ± 3.1	2.7 ± 3.4	0.532
No stroke symptoms (% NIHSS 0)		24.2	24.3	24.2	0.728
Minor stroke symptoms (% NIHSS 1–4)		56.7	56.4	57.0	
Moderate stroke symptoms (% NIHSS 5–12)		16.6	17.9	15.6	
Severe stroke symptoms (% NIHSS ≥ 13)		2.5	1.4	3.2	
ADL 4 days after stroke		16.8 ± 4.9	15.8 ± 5	17.5 ± 4.6	< 0.001*
% ADL-dependent (BI ≤ 17)		33.7	45.7	24.7	< 0.001*
Cognitive functioning 2 months after stroke		23.7 ± 3.8	22.3 ± 3.8	24.7 ± 3.5	< 0.001*
% cognitively impaired (MoCA ≤ 25)		67.0	78.0	58.6	< 0.001*
Length of stay in hospital (in days)		8.3 ± 5.8	8.9 ± 6.5	7.9 ± 5.2	0.139
Discharge home after hospital stay (%)		70.2	62.9	75.8	0.011*
Emotional functioning					
Depression symptoms 2 months after stroke		4.7 ± 4	4.8 ± 4	4.6 ± 3.9	0.637
% depression symptoms (HADS-D ≥ 8)		22.4	22.7	22.2	0.917
Anxiety symptoms 2 months after stroke		4.7 ± 3.9	4.4 ± 3.9	5.0 ± 3.8	0.097
% anxiety symptoms (HADS-A ≥ 8)		20.8	15.2	25.1	0.034*
Comorbidity (CIRS)		3.9 ± 2.7	4.7 ± 2.8	3.3 ± 2.5	< 0.001*
USER-P restriction subscale					
Total score:[b]	Restriction subscale	79.2 ± 20.7	73.9 ± 22.2	83.1 ± 18.6	< 0.001*
Restriction items:[c]	Work/education	55.4 (n = 121)	60.0 (n = 15)	54.7 (n = 106)	0.700
	Housekeeping	53.7	60.8	48.6	0.036*
	Mobility	41.4	52.0	33.9	< 0.001*
	Physical exercise	55.9	62.6	51.2	0.059
	Going out	45.2	54.2	39.3	0.023*
	Outdoor activities	51.6	59.8	45.5	0.019*
	Leisure indoors	29.8	30.5	29.2	0.818
	Partner relationship	35.1 (n = 225)	42.3 (n = 78)	31.3 (n = 147)	0.099
	Visits to family/friends	39.5	49.6	31.8	< 0.001*
	Visits from family/friends	22.0	22.7	21.6	0.825
	Telephone/PC contact	20.3	22.7	18.5	0.375

NOTE. Values are percentages or mean ± SD.

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; ADL, Activities of daily living; BI, Barthel Index; HADS-D, Hospital Anxiety and Depression Scale-depression subscale; HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; MoCA, Montreal Cognitive Assessment; CIRS, Cumulative Illness Rating Scale.

[a] Completed University of Professional Education and higher.

[b] Higher scores indicate better participation outcome.

[c] Restriction items values are percentages of patients who are restricted or dissatisfied.

* P-values are significant.

old had significantly more anxiety symptoms at baseline compared to patients over 70 years old, whereas depression symptoms were equally present in both age groups.

Restrictions in participation one year after stroke

After one year, many stroke survivors still experienced restrictions in items regarding mobility, such as housekeeping (53.7%), physical exercise (55.9%) and outdoor activities (51.6%). Relatively less stroke survivors experienced restrictions in social items, such as visits from family/friends (22.0%), telephone/PC contact (20.3%), partner relationship (35.1%) and leisure indoors (29.8%).

At one year after stroke, the mean USER-Participation Restrictions score was significantly worse in patients over 70 years old and they experienced significantly more restrictions on the items housekeeping ($p = 0.036$), outdoor mobility ($p < 0.001$), going out ($p = 0.023$), outdoor activities ($p = 0.019$) and visits to family or friends ($p < 0.001$) compared to patients under 70 years old.

Patients over 70 years old

Bivariate analyses

The bivariate analyses showed that advancing age, an increased severity of stroke, the presence of anxiety symptoms and more comorbidity were associated with unfavorable participation outcomes (Table 5.2). Favorable participation outcomes were associated with lower age, ADL independency, a decreased severity of stroke, the absence of depression or anxiety symptoms and less comorbidity.

Multivariate analyses

The multivariate logistic regression analyses showed that advancing age, an increased severity of stroke and the presence of anxiety symptoms were independently associated with unfavorable participation outcomes in patients over 70 years old (Table 5.2). A reasonable fit of the multivariate model was found (Hosmer-Lemeshow test, $p = 0.644$), although the amount of explained variance was low (Nagelkerke $R^2 = 0.165$). Favorable participation outcomes were independently associated with a lower age. This multivariate model also showed a reasonable fit (Hosmer-Lemeshow test, $p = 0.283$) and the amount of explained variance was somewhat higher (Nagelkerke $R^2 = 0.255$).

Table 5.2: Bivariate and multivariate analyses: predictors for unfavorable (worst quartile) and favorable (best quartile) USER-Participation scores one year after stroke in patients ≥ 70 years old

Stroke survivors ≥ 70 years old (n = 140)		Worst quartile vs. Rest (reference): predictors for unfavorable participation outcomes								
		Bivariate analysis					Multivariate analysis (n = 132)			
Factors (measure)	Reference	n	β	SE	P-value	OR (95% CI)	β	SE	P-value	OR (95% CI)
Demographic factors										
Sex	Female	140	-0.30	0.40	0.446	0.74 (0.34–1.61)			[a]	
Age at stroke onset	-	140	0.06	0.03	0.062	1.07 (1.00–1.14)	0.08	0.04	0.044*	1.08 (1.00–1.17)
Marital status	Married	140	0.42	0.40	0.288	1.53 (0.70–3.33)			[a]	
Education	Low	140	-0.66	0.50	0.187	0.52 (0.20–1.38)			[a]	
Stroke-related factors										
Severity of stroke (NIHSS)	-	140	0.13	0.06	0.037	1.14 (1.01–1.28)	0.16	0.07	0.016*	1.17 (1.03–1.33)
Stroke history	First stroke	140	0.24	0.50	0.633	1.27 (0.48–3.36)			[a]	
Hemisphere	Left	140	0.11	0.41	0.798	1.11 (0.50–2.49)			[a]	
Stroke type	Ischemic	139	-0.52	0.80	0.515	0.59 (0.12–2.85)			[a]	
ADL 4 days after stroke	BI > 17	140	0.54	0.40	0.174	1.72 (0.79–3.74)			[a]	
Cognitive functioning	MoCA > 25	132	0.43	0.54	0.427	1.54 (0.53–4.46)			[a]	
Emotional functioning										
Depression symptoms	HADS-D < 8	132	0.72	0.46	0.119	2.05 (0.83–5.06)			[a]	
Anxiety symptoms	HADS-A < 8	132	1.00	0.51	0.051	2.73 (0.99–7.48)	1.17	0.57	0.039*	3.23 (1.06–9.82)
Comorbidity (CIRS)	-	133	0.14	0.07	0.061	1.15 (0.99–1.33)	0.14	0.08	0.075	1.16 (0.99–1.35)
Constant							-8.96	3.29		

Stroke survivors ≥ 70 years old (n = 140)		Best quartile vs. Rest (reference): predictors for favorable participation outcomes								
			Bivariate analysis				Multivariate analysis (n = 132)			
Factors (measure)	Reference	n	β	SE	P-value	OR (95% CI)	β	SE	P-value	OR (95% CI)
Demographic factors										
Sex	Female	140	0.23	0.42	0.779	1.26 (0.55–2.88)			[a]	
Age at stroke onset	-	140	-0.10	0.04	0.019	0.91 (0.83–0.98)	-0.10	0.05	0.026*	0.90 (0.83–0.99)
Marital status	Married	140	-0.27	0.42	0.518	0.76 (0.33–1.74)			[a]	
Education	Low	140	0.50	0.44	0.248	1.65 (0.70–3.88)			[a]	
Stroke-related factors										
Severity of stroke (NIHSS)	-	140	-0.23	0.11	0.026	0.79 (0.64–0.97)	-0.20	0.12	0.094	0.82 (0.64–1.04)
Stroke history	First stroke	140	0.08	0.52	0.881	1.08 (0.39–2.99)			[a]	
Hemisphere	Left	140	-0.02	0.42	0.962	0.98 (0.43–2.22)			[a]	
Stroke type	Ischemic	139	0.16	0.70	0.814	1.18 (0.30–4.65)			[a]	
ADL 4 days after stroke	BI > 17	140	-1.17	0.45	0.009	0.31 (0.13–0.75)	-0.55	0.52	0.297	0.58 (0.21–1.61)
Cognitive functioning	MoCA > 25	132	-0.05	0.49	0.925	0.96 (0.36–2.51)			[a]	
Emotional functioning										
Depression symptoms	HADS-D < 8	132	-1.18	0.65	0.070	0.31 (0.09–1.10)	-0.59	0.71	0.408	0.56 (0.14–2.23)
Anxiety symptoms	HADS-A < 8	132	-1.89	1.05	0.071	0.15 (0.02–1.18)	-1.80	1.11	0.103	0.16 (0.02–1.44)
Comorbidity (CIRS)	-	133	-0.18	0.08	0.029	0.84 (0.71–0.98)	-0.15	0.09	0.097	0.86 (0.72–1.03)
Constant							8.17	3.55		

Abbreviations: β, standardized regression coefficient; SE, Standard Error; OR, Odds Ratio; CI, Confidence interval; CIRS, Cumulative Illness Rating Scale; NIHSS, National Institutes of Health Stroke Scale; ADL, Activities of Daily Living; MoCA, Montreal Cognitive Assessment; BI, Barthel Index; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale; HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale.

* P-values are significant ($p < 0.05$).

Table 5.3: Bivariate and multivariate analyses: predictors for unfavorable (worst quartile) and favorable (best quartile) USER-Participation scores one year after stroke in patients < 70 years old

Stroke survivors < 70 years old (n = 186)		Worst quartile vs. Rest (reference): predictors for unfavorable participation outcomes								
			Bivariate analysis				Multivariate analysis (n = 169)			
Factors (measure)	Reference	n	β	SE	P-value	OR (95% CI)	β	SE	P-value	OR (95% CI)
Demographic factors										
Sex	Female	186	0.65	0.35	0.063	0.52 (0.26–1.04)	-0.93	0.43	0.030*	0.39 (0.17–0.91)
Age at stroke onset	-	186	0.00	0.02	0.943	1.00 (0.96–1.04)			[a]	
Marital status	Married	186	0.2	0.42	0.641	1.22 (0.53–2.79)			[a]	
Education	Low	185	-0.47	0.42	0.257	0.62 (0.28–1.41)			[a]	
Stroke-related factors										
Severity of stroke (NIHSS)	-	186	0.12	0.05	0.012	1.13 (1.03–1.23)	0.20	0.08	0.013*	1.22 (1.04–1.42)
Stroke history	First stroke	186	0.47	0.53	0.377	1.60 (0.56–4.54)			[a]	
Hemisphere	Left	186	-0.08	0.35	0.808	0.92 (0.47–1.81)			[a]	
Stroke type	Ischemic	186	-0.41	0.80	0.606	0.66 (0.14–3.18)			[a]	
ADL 4 days after stroke	BI > 17	186	0.94	0.37	0.010	2.57 (1.25–5.30)	0.14	0.51	0.791	1.15 (0.42–3.13)
Cognitive functioning	MoCA > 25	174	0.64	0.38	0.090	1.89 (0.91–3.95)	0.88	0.44	0.047*	2.41 (1.01–5.76)
Emotional functioning										
Depression symptoms	HADS-D < 8	171	1.41	0.40	< 0.001	4.08 (1.86–8.97)	1.43	0.44	0.001*	4.17 (1.77–9.83)
Anxiety symptoms	HADS-A < 8	171	0.53	0.40	0.183	1.70 (0.78–3.71)			[a]	
Comorbidity (CIRS)	-	178	0.08	0.07	0.215	1.09 (0.95–1.24)			[a]	
Constant							-2.11	0.48		

Stroke survivors < 70 years old (n = 186)		Best quartile vs. Rest (reference): predictors for favorable participation outcomes								
			Bivariate analysis				Multivariate analysis (n = 170)			
Factors (measure)	Reference	n	β	SE	P-value	OR (95% CI)	β	SE	P-value	OR (95% CI)
Demographic factors										
Sex	Female	186	0.90	0.36	0.013	2.46 (1.21–5.00)	0.71	0.40	0.078	2.04 (0.92–4.49)
Age at stroke onset	-	186	0.02	0.02	0.274	1.02 (0.98–1.06)			[a]	
Marital status	Married	186	-0.16	0.38	0.680	0.86 (0.41–1.80)			[a]	
Education	Low	185	-0.04	0.36	0.903	0.96 (0.48–1.92)			[a]	
Stroke-related factors										
Severity of stroke (NIHSS)	-	186	-0.06	0.05	0.222	0.94 (0.85–1.04)			[a]	
Stroke history	First stroke	186	0.21	0.51	0.674	1.24 (0.46–3.37)			[a]	
Hemisphere	Left	186	0.05	0.32	0.884	1.05 (0.56–1.94)			[a]	
Stroke type	Ischemic	186	0.49	0.63	0.430	1.64 (0.48–5.59)			[a]	
ADL 4 days after stroke	BI > 17	186	-0.82	0.40	0.040	0.44 (0.20–0.96)	-0.55	0.45	0.222	0.58 (0.24–1.39)
Cognitive functioning	MoCA > 25	174	-0.49	0.32	0.126	0.61 (0.33–1.15)			[a]	
Emotional functioning										
Depression symptoms	HADS-D < 8	171	-1.57	0.51	0.002	0.21 (0.08–0.57)	-1.04	0.58	0.070	0.35 (0.11–1.09)
Anxiety symptoms	HADS-A < 8	171	-1.54	0.47	0.001	0.22 (0.08–0.55)	-0.89	0.54	0.103	0.41 (0.14–1.19)
Comorbidity (CIRS)	-	178	-0.13	0.07	0.064	0.88 (0.77–1.01)	-0.10	0.08	0.184	0.90 (0.78–1.05)
Constant							-0.30	0.46		

Abbreviations: β, standardized regression coefficient; SE, Standard Error; OR, Odds Ratio; CI, Confidence interval; CIRS, Cumulative Illness Rating Scale; NIHSS, National Institutes of Health Stroke Scale; ADL, Activities of Daily Living; MoCA, Montreal Cognitive Assessment; BI, Barthel Index; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale; HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale.
* P-values are significant (p < 0.05).

Patients under 70 years old

Bivariate analyses

The bivariate analyses showed that female gender, an increase in severity of stroke, ADL dependency, impaired cognitive functioning and the presence of depression symptoms were associated with unfavorable participation outcomes (Table 5.3). Favorable participation outcomes were associated with male gender, ADL independency, the absence of depression and anxiety symptoms and less comorbidity.

Multivariate analyses

The multivariate logistic regression analyses showed that female gender, an increase in severity of stroke, impaired cognitive functioning, and the presence of depression symptoms were independently associated with unfavorable participation outcomes in patients under 70 years old (Table 5.3). A reasonable fit of the multivariate model was found (Hosmer-Lemeshow test, $p = 0.337$), although the amount of explained variance was low (Nagelkerke $R^2 = 0.228$). None of the variables were independently associated with favorable participation outcomes. This multivariate model also showed a reasonable fit (Hosmer-Lemeshow test, $p = 0.652$), although the amount of explained variance was low (Nagelkerke $R^2 = 0.187$).

DISCUSSION

This study shows that stroke survivors from general hospitals experience considerable restrictions after one year, regardless of discharge destination. Especially activities involving mobility, such as physical exercise and outdoor activities, were severely restricted after one year. This particularly applies to stroke survivors aged over 70 years, since they were significantly more restricted in these items compared to stroke survivors aged under 70 years. Previous literature concluded that up to 50% of stroke survivors after rehabilitation perceived participation problems in physical exercise, regardless of age.[7]

Predictors of unfavorable participation outcome

In both age groups, survivors of a more severe stroke perceived more long-term participation restrictions. This finding has previously been observed[14,18,19] and suggests that further developments in the treatment of (sub)acute stroke may be expected to lead to improvements in long-term participation restrictions.

Emotional functioning also plays an important role in the prediction of long-term participation restrictions, as anxiety symptoms in patients aged over 70 years and depression symptoms in patient aged under 70 years are independently associated with unfavorable participation outcomes. This is the first study highlighting the importance of anxiety symptoms as predictor of unfavorable long-term participation after stroke.[38] The negative influence of depression symptoms has been found in previous studies as well.[14,15,27] These results point out the importance of early screening and treatment of deficits in emotional functioning after stroke, to prevent adverse participation outcomes after one year.

Also, this study shows impaired cognitive function after stroke is a predictor of unfavorable long-term participation in stroke survivors aged under 70 years. Contradictory results have been reported about the influence of cognitive function and participation in current literature. Two studies found a negative association between impaired cognitive function and participation in stroke survivors after six months,[13,27] whereas one of these studies also observed improvement of long-term participation despite the presence of impaired cognitive function.[39] Moreover, not all domains of participation are influenced by the presence of cognitive deficits in stroke survivors aged over 65 years old.[39] This study adds to existing literature that the association between cognitive deficits and long-term participation may be age-dependent.

Advancing age in stroke survivors aged over 70 years old is associated with restrictions in participation after one year. The attribution of the normal aging process should be taken into account, as an increase in perceived restrictions has also been observed in healthy adults after the age of 80 years.[40] However, using the USER-Participation restrictions subscale, patients were asked for restrictions in participation specifically caused by the stroke. The association between age and long-term participation restrictions might be partly explained by the increasing burden of comorbidities at advancing age, since age and comorbidity are closely related. This might also explain the lack of an association between comorbidity and long-term participation restrictions in the multivariate analyses. Although current literature is inconsistent about the association between comorbidity and functional outcome in older stroke survivors,[24,41,42] one study identified comorbidity as independent predictor of long-term participation.[19]

Lastly, female gender is only negatively associated with long-term participation in stroke survivors aged under 70 years. This might be due to different activities of women at vocational age compared to man. This is a new finding in literature, suggesting female stroke survivors aged under 70 years should be watched closely.

Predictors of favorable participation outcome

Lower age is the only independent predictor associated with favorable participation after one year in stroke survivors aged over 70 years, whereas no independent positive predictors in stroke survivors aged under 70 years have been found. The positive association between lower age and participation confirms the importance of age in the prediction of long-term participation restrictions. Furthermore, despite the importance of having a spouse for determining discharge destination was highlighted by a recent study,[43] the presence or absence of a spouse was not associated with favorable or unfavorable participation one year after stroke.

Although predictors of favorable participation are scarce in this study, it is noteworthy that predictors of favorable participation are not just the opposite of predictors of unfavorable participation. For this reason, future research should keep differentiating between predictors of favorable and unfavorable participation.

Remarkably, only 17–26% of the variance could be explained in current prediction models. One explanation is the potential influence of additional factors such as environmental and psychological factors on participation. Therefore, these factors need further research to gain better insight into predictors positively and negatively influencing long-term participation which are potentially modifiable by interventions. Positive affect,[44] self-esteem[45] and hopeful thinking[16] have been found to positively influence participation.

Study strengths

The large number of participants was one of the main strengths of this longitudinal multicenter study. Also, patients were recruited in six general hospitals, well-representing the general stroke population. Furthermore, all patients were included within seven days after stroke and a wide variety of clinical and demographic factors were obtained and included in the analyses. Moreover, despite the association between age and participation is known, this study is, to the best of our knowledge, the first to compare long-term restrictions in participation between old and young stroke survivors. Besides, predictors of favorable participation have never been assessed in current literature as far as we know. Lastly, differences between both age groups were studied per participation item, providing detailed insights into participation restrictions.

Study limitations

Firstly, the large number of participants consisted mainly of patients with relatively mild strokes, possibly due to the exclusion of patients with premorbid cognitive deficits or ADL dependency. Besides patients with a severe stroke may not be able to give their informed consent in the first week after stroke. Therefore, the most vulnerable patients were probably less represented in our study population which may decrease the generalizability of the results. Secondly, although the USER-Participation is a validated tool to measure participation post stroke, this questionnaire has never been validated for the elderly. Common activities for the elderly are perhaps less represented in the questionnaire. Thirdly, this study did not take environmental and personal factors into account, while these factors could possibly have influenced long-term participation.

CLINICAL MESSAGE

The findings of the current study emphasize the need to pay more attention to stroke survivors aged over 70 years, since more restrictions in participation were perceived in comparison to younger stroke survivors one year after stroke. Therefore, general practitioners should consider to incorporate participation in the follow-up assessment of stroke survivors to detect potential restrictions in participations as early as possible. Furthermore, different predictors for long-term participation restrictions after stroke were found for stroke survivors aged over and under 70 years, suggesting a different approach to older stroke survivors regarding maintaining long-term participation after stroke is needed compared to young stroke survivors. In this context, this study highlights the importance of early recognition of anxiety symptoms in patients aged over 70 years and depression symptoms in patients aged under 70 years to prevent long-term restrictions in participation. Early screening on deficits in emotional functioning in stroke survivors can easily be achieved by using the HADS.

Lastly, a need for community based follow-up programs to promote physical activity has been observed in the current study, as restrictions with mobility and outdoor activities one year after stroke were considerable. Promoting and monitoring physical activity in the community gives not only the possibility to add years to a stroke survivor's life, but also adds quality of life to their years.

Implications for rehabilitation

- More attention in the rehabilitation process should be paid to restrictions in participation of stroke survivors aged older than 70 years, taking into account the different participation needs and predictors of older stroke survivors.
- Early screening on the presence of anxiety symptoms could potentially prevent long-term restrictions in participation in stroke survivors aged over 70 years old.
- Stroke survivors experience considerable restrictions in physical activity and mobility after one year, highlighting the need for the development of community based exercise programs for stroke survivors.

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Chapter 6

The influence of psychological factors and mood on the course of participation up to four years after stroke

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Abstract

Purpose: (1) To explore the course of participation from two months up to four years after stroke, and (2) to examine if adaptive and maladaptive psychological factors and mood measured at two months after stroke are determinants of the course of participation during this period.

Materials and methods: Prospective cohort study in which 369 individuals with stroke were assessed at stroke onset, two months, six months, one year, two years and three to four years after stroke. The Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-Participation) restrictions subscale was used to measure participation. Psychological factors were clustered into adaptive (proactive coping, self-efficacy, extraversion and optimism) and maladaptive (passive coping, neuroticism and pessimism) psychological factors. The Hospital Anxiety and Depression Scale was used to assess mood.

Results: Although improvements in participation were observed up to one year after stroke, considerable long-term restrictions in social and physical domains persisted. More mood problems and less adaptive psychological factors were independent determinants of worse participation up to four years after stroke.

Conclusions: Participation improves in the first 12 months after stroke and stabilizes afterwards. Mood problems and less adaptive psychological factors negatively influence the course of participation over time up to four years after stroke.

INTRODUCTION

Stroke is the third most common cause of disability in the world,[1] causing considerable long-term restrictions in social and community participation.[2] Participation, defined as "the person's involvement in a life situation",[3] is considered an important outcome of stroke rehabilitation as it provides clinicians valuable person-centred information on the impact of stroke on daily life.[4] Mirroring recovery of physical and cognitive functioning in the first months post-stroke, improvements in participation after stroke are observed in the first six months up to one year after stroke.[5-9] The course of participation beyond the first year after stroke remains largely unclear, as long-term prospective cohort studies regarding this subject are scarce and follow-up duration of these studies rarely exceeded one year. Nevertheless, many persons with stroke still experience restrictions in participation one year after stroke, including the domains outdoor mobility, work, housekeeping and partner relationships.[10-12] One study found participation in social activities to remain stable between one and three years after stroke,[13] but another study reported a decline in participation in daily activities between six months and two to four years after stroke.[14]

Mood problems and psychological factors are prominent among the many factors associated with participation levels in the long-term after stroke.[14-16] Mood problems, including symptoms of anxiety and depression, are common in both the subacute and chronic phase after stroke.[17] Psychological factors, including coping styles and personality traits, are notable determinants of mood problems[18] and are suggested to have even more impact on participation after stroke than physical disabilities.[2,19] Surprisingly, psychological factors are often overlooked in current stroke literature; they are, for example, not included in a recent systematic review studying biopsychosocial determinants of long-term participation after stroke.[20] Also, longitudinal studies exploring the influence of psychological factors on participation are needed to reveal causal relationships and effects of time.[21] By identifying determinants influencing the course of participation, stroke survivors at risk for restrictions in participation in the chronic phase can be selected timely and potentially modifiable determinants can be managed.

Therefore, the first aim of this study was to explore the course of participation from two months up to four years after stroke. The second aim was to test whether adaptive and maladaptive psychological factors and mood problems measured at two months after stroke are determinants of the course of participation up to four years after stroke.

METHODS

Design

The current study is an extension of the multicentre prospective longitudinal Restore4Stroke Cohort study and used data collected at stroke onset, two months, six months, one year, two years and four years after stroke.[22] Participants were recruited from six general hospitals in the Netherlands between March 2011 and March 2013. The Medical Ethics committees of all participating hospital approved this study. Written informed consent was obtained from all participants.

Participants

Patients were eligible if they had a clinically confirmed diagnosis of ischemic or hemorrhagic stroke, gave informed consent within seven days after symptom onset, and were at least 18 years old. Patients were excluded from the study if they (1) had a serious other condition that could interfere with study outcomes; (2) had been dependent in basic activities of daily living before the stroke occurred (defined by a Barthel Index score of ≤ 17[23]); (3) had insufficient command of Dutch language, based on clinical judgment; or (4) had suffered cognitive decline prior to the stroke (defined by a score of ≥ 1 on the Heteroanamnesis List Cognition[24]). Participants who completed the participation measure at least once after stroke were included in the analysis.

Procedure

After informed consent was obtained, stroke-related factors (type of stroke, hemisphere and stroke severity) assessed by the neurologist on day four after stroke were retrieved from the medical files. Demographic factors were obtained from the participant or from family members. At two months after stroke, screening on cognitive functioning, psychological factors and mood was conducted by a trained research assistant. Also, participants were asked to complete a self-report participation questionnaire at two and six months, and one, two and three to four years after stroke.

Dependent variables

The Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-Participation) restrictions subscale was used to measure participation at two and six months, and one, two and three to four years after stroke.[11] The restrictions subscale consists of eleven items,

concerning difficulties experienced with vocational, leisure and social activities caused by the stroke (e.g. housekeeping, outdoor activities and partner relationship). Response categories are: "not possible," "with assistance," "with difficulty," and "without difficulty". A "not applicable" option is available for all items in case an activity is not performed for other reasons or a restriction is not attributed to the stroke. The total score of the restrictions subscale ranges from 0–100 and is based on items that are applicable. A higher score indicates a more favourable level of participation (fewer experienced restrictions). The USER-Participation has previously shown satisfactory validity and reliability[25] and excellent responsiveness in stroke patients.[26,27]

Independent variables

Demographic factors

Information about gender, age, marital status and level of education was collected. Level of education was dichotomized into low (up to completed secondary education) and high (completed higher secondary professional education or university).

Stroke-related factors

Information about severity of stroke, history of stroke, hemisphere, stroke type, ADL dependency, cognitive functioning, length of stay in the hospital and discharge destination was collected. Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS) four days after stroke.[28] Scores range from 0–42 and higher scores indicate more severe stroke. ADL dependency was assessed using the BI four days after stroke. Scores range from 0–20 and higher scores indicate fewer ADL dependencies.[23] Cognitive functioning two months after stroke was assessed using the Montreal Cognitive Assessment (MoCA).[29] Scores range from 0–30 and higher scores indicate better cognitive functioning. Discharge destination after hospitalization was categorized into home or inpatient rehabilitation.

Mood

The severity of mood problems two months after stroke was assessed by the Hospital Anxiety and Depression Scale (HADS), which has good psychometric properties and is commonly used for stroke population.[30] Scores range from 0–42, a higher score indicating more mood problems.

Psychological factors

All psychological factors were measured with valid and reliable scales at two months after stroke.[22,31-35]

Optimism and pessimism were assessed with the Life Orientation Test-Revised.[31] This questionnaire consists of six items, three items each measuring optimism and pessimism, and are scored on a 5-point scale.

Neuroticism and extraversion were assessed with the Neuroticism and Extraversion scales of the Eysenck Personality Questionnaire Revised Short Scale.[32] Both scales consist of 12 items with dichotomous (yes/no) response option.

Passive coping was assessed with the passive reaction pattern subscale of the Utrecht Coping List.[33] This subscale consists of seven items scored on a 4-point scale, and is found to be reliable and valid to assess passive coping.[33] Proactive coping competencies were assessed with the Utrecht Proactive Coping Competence List.[34] This list consists of 21 items scored on a 4-point scale.

Self-efficacy was assessed with the General Self-Efficacy Scale.[35] This scale consists of 10 items scored on a 4-point scale.

Statistical analysis

All analyses were conducted with IBM SPSS statistics version 24 (IBM, Armonk, NY). Descriptive statistics were used to describe participant characteristics and dependent variables.

Psychological scales

We clustered adaptive and maladaptive psychological factors, based on theoretical arguments and findings of exploratory factor analyses as described in an earlier study.[36] Passive coping, neuroticism and pessimism are maladaptive psychological factors associated with decreased quality of life after stroke, whereas proactive coping, self-efficacy, extraversion and optimism are adaptive psychological factors associated with increased quality of life after stroke.[21,37-40]

First, scores on all measures were standardized to obtain a common metric (mean = 0 and SD = 1). After that, the adaptive psychological factor score (A-PF) was computed as the average of the standardized scores on extraversion, optimism, proactive coping and self-efficacy. Similarly, the maladaptive psychological factor score (M-PF) was computed as the average of the standardized scores on neuroticism, pessimism and passive coping.

Item scores USER-Participation

The USER-Participation restrictions items were dichotomized to quantify the presence of persisting restrictions. "With difficulty," "with assistance," and "not possible" were defined as "restrictions" and "without difficulty" was defined as "no restrictions". The differences in participation scores between different timepoints were analysed in participants who completed the follow up till three to four years after stroke. To ascertain overall differences over time across all test occasions in total participation scores and in participation item scores, the Friedman's test and Cochrane's Q test were calculated respectively. To ascertain differences between two consecutive test occasions in total participation scores and participation item scores, the Wilcoxon signed-rank test and McNemar's test were calculated respectively.

Mixed model

The course of participation over time after stroke was analysed using a linear mixed model. All available data could be used as participants who completed the follow-up assessment at least once were available for the mixed model analysis. This statistical method contains fixed effects (differences from the overall mean) and random effects (variance component, allowing the average response to vary between clusters), and can be used to explore the course of participation using repeated measurements over time. In this way, we were able to explore the influence of the maladaptive and adaptive psychological scales and mood problems on the course of participation over time, taking into account the effects of known predictors such as demographic and stroke-related factors.

First, the course of participation over time was modelled with time as continuous variable, using the exact dates of measurements for every single participant. Since this course over time is non-linear, both linear and quadratic functions of time were added in sequence.[41] Time was entered as random factor, with random intercepts across persons. The USER-Participation restrictions subscale was entered as continuous variable. Secondly, potential predictors were added as fixed factors to the linear mixed model, using a hierarchical approach: known predictors were entered into the model first. The predictors were divided into 'demographic' (age, gender, education), 'stroke-related' (NIHSS, MoCA, discharge destination), 'psychological factors' (A-PF, M-PF) and 'mood' (HADS). Age, NIHSS, MoCA, HADS, A-PF and M-PF were entered as continuous variables. Gender, education and discharge destination (inpatient rehabilitation vs. home) were entered as dichotomous variables. Maximum likelihood estimation was used to assess model fit (-2loglikelihood). Bivariate associations between mood, M-PF and A-PF were tested using Spearman correlations.

In the first model (model 1), stroke-related and demographic variables were fitted. In the second model, the stroke related factors and demographic factors combined with either mood (model 2a), M-PF (model 2b) or A-PF (model 2c) were fitted. Lastly, a model was fitted with all variables together (model 3). Predictors were separately tested for possible interactions with time (linear and quadratic terms). A p-value < 0.05 was considered as statistically significant.

RESULTS

A total of 395 participants were included in the Restore4Stroke study. The number of participants who completed the participation measure differed at each time point: 343 participants at two months, 344 participants at six months, 326 participants at one year, 319 participants at two years and 136 participants at three to four years after stroke. A total of 369 participants completed the participation measure at least once and were available for the mixed model analysis. Twenty-six participants (6.6%) had missing participation data at all time points as they had dropped out during the first two months of this study: two participants had died, 16 refused further participation, one was lost to follow-up and seven participants dropped out because of an insufficient general physical condition.

Participant characteristics are presented in Table 6.1. Except for age and at stroke onset and ADL dependency at two months after stroke, there were no significant differences in baseline characteristics between participants and dropouts at three to four years after stroke.

Course of participation

The course of participation (total and item scores) over time of participants who completed the follow up till three to four years after stroke (n = 136) are presented in Table 6.2 and Figure 6.1. A total of 233 participants (59%) had dropped out of the study population (n = 395) during follow-up: 33 participants had died, 120 refused further participation, 71 were lost to follow-up and 35 participants dropped out because of an insufficient general physical condition.

Overall participation improved over time up to four years after stroke ($p < 0.001$). Improvements took place between two and six months ($p < 0.001$) and six months and a year ($p = 0.012$) after stroke. Almost all item scores improved between two months and four years after stroke, except for partner relationship, visits from family/friends and telephone/pc contact. Restrictions in going out ($p = 0.029$), outdoor activities ($p = 0.024$) and leisure indoors ($p = 0.015$) improved between two and six months after stroke. Restrictions in

Table 6.1: Participant characteristics

Study participants		Total (n = 369)	At 4 years (n = 136)	Dropouts (n = 233)	P-value[b]
Demographic factors					
Sex (% male)		64.5	68.4	62.2	0.415
Age in years		66.7 ± 12.4	64.0 ± 10.9	68.3 ± 12.9	0.020*
Marital status (% living together)		69.4	74.3	66.5	0.284
High education level (%)[a]		27.0	27.2	26.8	0.959
Stroke-related factors					
Ischemic stroke (%)		93.0	91.9	93.6	0.690
Left hemisphere (%)		40.2	34.8	43.3	0.257
First stroke (%)		87.5	85.3	88.8	0.168
Severity of stroke four days after stroke (NIHSS)		2.7 ± 3.2	2.7 ± 3.0	2.7 ± 3.3	0.738
No stroke symptoms (% NIHSS 0)		24.4	23.5	24.9	
Minor stroke symptoms (% NIHSS 1–4)		56.1	56.6	55.8	
Moderate stroke symptoms (% NIHSS 5–12)		17.3	18.4	16.7	
Severe stroke symptoms (% NIHSS ≥ 13)		2.2	1.5	2.6	
ADL 2 months after stroke (BI)		20 ± 2.1	20 ± 1.3	20 ± 2.4	0.022*
% ADL-dependent (BI ≤ 17)		9.4	4.6	12.2	0.019*
Cognitive functioning 2 months after stroke (MoCA)		23.6 ± 4.0	24.3 ± 3.6	23.1 ± 4.2	0.119
% cognitively impaired (MoCA ≤ 25)		67.6	60.0	72.2	0.076
Length of stay in hospital (in days)		8.5 ± 6.2	8.0 ± 5.5	8.8 ± 6.6	0.289
Discharge home after hospital stay (%)		71.0	75.0	68.7	0.374
Mood					
Mood 2 months after stroke (HADS)		9.4 ± 7.3	9.7 ± 6.5	9.2 ± 7.7	0.366
% impaired (HADS ≥ 11)		37.4	44.3	33.2	0.170
Psychological functioning					
Extraversion (EPQ-RSS-E)	n = 345	7.1 ± 3.2	7.1 ± 3.4	7.1 ± 3.1	0.989
Neuroticism (EPQ-RSS-N)	n = 345	3.6 ± 3.1	3.6 ± 3.3	3.7 ± 3.0	0.679
Optimism (LOT-R)	n = 346	8.2 ± 2.1	8.1 ± 2.0	8.2 ± 2.2	0.788
Pessimism (LOT-R)	n = 345	4.4 ± 2.8	4.2 ± 2.6	4.5 ± 2.9	0.521
Self-efficacy (GSES)	n = 345	31.6 ± 6.4	32.0 ± 5.6	31.3 ± 6.8	0.782
Proactive coping (UPCC)	n = 345	64.8 ± 11.9	66.1 ± 10.7	64.0 ± 12.5	0.385
Passive coping (UCL-P)	n = 346	10.5 ± 2.8	10.7 ± 2.6	10.4 ± 3.0	0.266

Values are percentages or mean ± SD.
ADL, activities of daily living; BI, Barthel Index; EPQ-RSS-N and EPQ-RSS-E, Eysenck Personality Questionnaire Revised Short Scale Neuroticism and Extraversion; GSES, General Self-Efficacy Scale; LOT-R, Life Orientation Test-Revised; UCL-P, Utrecht Coping List; UPCC, Utrecht Proactive Coping Competence List.
[a] Completed University of Professional Education and higher.
[b] Comparison between population 'at four years' and 'dropouts'.
* P-values are significant ($p < 0.05$).

Table 6.2: Course of participation after stroke of participants who completed the follow up till four years after stroke (n = 136)

USER-P restriction scale[a]	2 months[c]	6 months[c]	1 year[c]	2 years[c]	4 years[c]	P-value[c]
Mean (SD)	74.1 (± 21.3)	80.9 (± 18.3)[#]	82.9 (± 19.0)[#]	82.1 (± 21.2)	83.0 (± 20.1)	< 0.001*
Median	75.8	85.7	87.5	91.3	91.8	
IQR	57.6–93.9	69.7–96.7	70.8–100	66.8–100	70.9–100	
Restriction scale items			Persisting restrictions in items USER-P (%)[b]			
Work/education	78.3	66.7	47.3[#]	46.6	35.7	< 0.001*
Housekeeping	60.8	52.0	48.4	44.8	42.5	0.002*
Mobility	59.5	44.9[#]	34.4[#]	34.1	30.0	< 0.001*
Physical exercise	62.2	54.2	53.2	46.7	51.6	0.020*
Going out	59.6	47.1[#]	36.0	41.8	38.3	< 0.001*
Outdoor activities	60.2	48.6[#]	46.0	48.3	44.6	0.002*
Leisure indoors	39.0	27.5[#]	24.8	20.8	20.5	< 0.001*
Partner relationship	22.6	31.3	33.3	31.5	32.2	0.397
Visits to family/friends	49.6	40.3	29.5	33.3	30.5	< 0.001*
Visits from family/friends	24.4	27.3	18.9	21.1	17.8	0.118
Telephone/PC contact	16.7	19.4	21.5	16.9	20.3	0.723

Abbreviations: IQR, interquartile range.

[a] USER-P restriction scale: higher score indicates good level of participation (less restrictions).

[b] USER-P restriction items values are percentages of participants who are restricted.

[c] Different p-values were calculated to ascertain significant differences between all time points (cited with *) and between two consecutive time points (cited with [#]).

[#] P-values are significant ($p < 0.05$), comparing the cited time point with the previous time point.

* P-values are significant ($p < 0.05$), comparing all time points.

work/education improved between six months and one year (p = 0.039) and restrictions in mobility improved between two months and one year (p = 0.004). At three to four years after stroke, a considerable percentage of participants experienced restrictions in participation, such as physical exercise (51.6%), outdoor activities (44.6%) and housekeeping (42.5%).

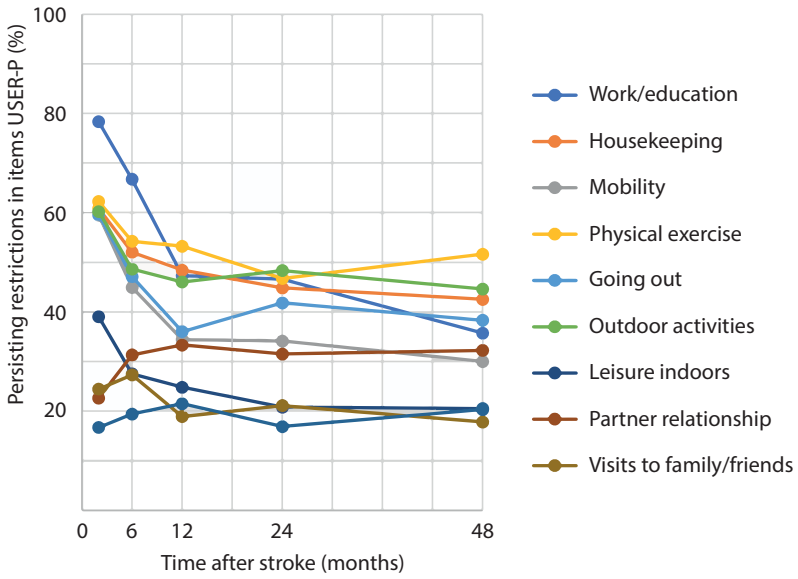

Figure 6.1: The course of the proportion of participants (who completed the follow up till four years after stroke, n = 136) experiencing restrictions in participation items over time.

Mixed model analyses

No significant interaction effects between time and other variables were found. The results of the linear mixed model analyses are presented in Table 6.3.

Model 1

Model 1 (including stroke-related and demographic variables) showed that female gender, a more severe stroke, impaired cognitive functioning and discharge to inpatient rehabilitation were associated with worse participation.

Model 2

Model 2 showed that, adjusted for demographic and stroke related factors, more mood problems (model 2a), more M-PF (model 2b) and less A-PF (model 2c) were all associated with worse participation.

Table 6.3: Linear mixed model analyses showing the predictions of participation restrictions (USER-P restrictions subscale) over time

	Model 1: basic model		Model 2a: HADS		Model 2b: M-PF		Model 2c: A-PF		Model 3: final model	
	Coef. β	95% CI	Coef. β	95% CI	Coef. β	95% CI	Coef. β	95% CI	Coef. β	95% CI
Intercept	63.03**	45.56–80.50	84.60**	68.09–101.11	100.51**	80.50–120.53	35.79**	17.96–53.61	66.44**	43.67–89.21
Time	0.44**	0.28–0.60	0.45**	0.29–0.61	0.43**	0.27–0.59	0.44**	0.28–0.60	0.44**	0.28–0.61
Time*Time	-0.01**	-.01–0	-0.01**	-0.01–0	-0.01**	-0.01–0	-0.01**	-0.01–0	-0.01**	-0.01–0
Age	-0.13	-0.28–0.02	-0.21*	-0.34–-0.07	-0.16*	-0.30–-0.02	-0.12	-0.26–0.02	-0.18*	-0.32–-0.05
Gender	6.80**	3.23–10.37	5.25**	2.08–8.43	5.15*	1.73–8.57	6.00**	2.63–9.36	5.08*	1.94–8.22
Education	0.40	-3.21–4.02	-0.13	-3.31–3.05	1.04	-2.38–4.47	1.49	-1.91–4.88	0.53	-2.62–3.69
Stroke severity (NIHSS)	-1.12**	-1.77–-0.47	-1.34**	-1.91–-0.77	-0.99*	-1.61–-0.38	-0.96*	-1.57–-0.34	-1.18**	-1.75–-0.61
Cognitive functioning (MoCA)	0.89**	0.41–1.36	0.67*	0.24–1.09	0.58*	0.12–1.03	0.77**	0.32–1.21	0.68*	0.26–1.11
Discharge destination	-9.58**	-13.97–-5.20	-8.05**	-11.93–-4.17	-10.27**	-14.42–-6.12	-10.32**	-14.46–-6.17	-9.15**	-13.02–-5.29
Emotional functioning (HADS)			-1.08**	-1.29–-0.86					-0.95**	-1.24–-0.66
Maladaptive psychological scale					-0.56**	-0.72–-0.39			0.02	-0.19–0.24
Adaptive psychological scale							0.58**	0.42–0.75	0.27*	0.09–0.44
-2 Restricted Log Likelihood Ratio	11720.76		11513.00		11575.97		11567.72		11380.49	

Abbreviations: β, standardized regression coefficient; CI, confidence interval.
* $p < 0.05$.
** $p < 0.001$.

Model 3

Model 3 (including stroke related factors, demographic factors, mood, A-PF and M-PF) showed that more mood problems and less A-PF were associated with worse participation. In contrast to model 2b, M-PF was not significantly associated with participation when taking emotional functioning and A-PF into account. Based on the comparison of the -2Restricted Log Likelihood Ratios, model 3 showed the best fit of all models. Spearman correlations between mood and M-PF (r = 0.66, 95% CI = 0.59–0.72, p < 0.001), mood and A-PF (r = 0.48, 95% CI = 0.39–0.56, p < 0.001) and M-PF and A-PF (r = 0.51, 95% CI = 0.42–0.59, p < 0.001) were strong.

DISCUSSION

This study shows that the course of participation improves up to one year after stroke and stabilizes afterwards. Considerable restrictions in participation were observed after one year, predominantly in dynamic activities such as physical exercise, outdoor activities and housekeeping. Furthermore, less adaptive psychological factors and mood problems assessed at two months after stroke were associated with worse participation up to four years after stroke. Early detection of mood problems after stroke can be achieved using the HADS. The development of a brief screening tool is needed to enable early detection of adaptive psychological factors after stroke. Timely treatment of mood problems and the development of interventions promoting adaptive psychological factors during rehabilitation could potentially prevent restrictions in long-term participation after stroke.

In alignment with other studies, the improvements in participation over time largely took place in the first six months and stabilized after twelve months.[13,14,42] Possibly, persons with stroke are able to adjust their lives according to their new situation as soon as their functional recovery is stabilizing, explaining the similarity in course of functional recovery and participation.[43] Although no improvements in participation have been observed in persons with stroke after one to four years in this study, qualitative research shows the course of participation in chronic stroke is a dynamic and individual process influenced by several interacting personal and contextual factors.[44,45] As improvements in participation cease after one year, nearly half of persons with stroke face restrictions in social and physical domains four years after stroke, predominantly in dynamic activities requiring both mobility and cognitive skills. This has also been observed in previous studies, including a rehabilitation population and a cross-sectional study at four years after stroke.[11,46]

Previous literature also described associations between various adaptive psychological factors and participation, even in multivariate analyses when taking into account the presence of depressive symptoms.[47-49] In a cross-sectional study, hopeful thinking, self-esteem and the absence of depressive symptoms were identified as most important predictors of participation 12 months after stroke.[47] In a prospective cohort study, acceptance of stroke and the presence of depressive symptoms were among the main contributors of participation in social roles up to six months after stroke.[48] In another prospective cohort study, positive affect was identified as independent predictor of social participation three months after discharge from the rehabilitation centre.[49] As these studies lacked a long-term follow up, this is the first study proving adaptive psychological factors being notable determinants of the course of participation up to four years after stroke.

The importance of adaptive psychological factors is also shown in recent qualitative research, as stroke survivors state that the ability to accept stroke-related problems and adapt accordingly are key to successful participation after stroke.[50-52] Interestingly, adaptive psychological factors are not fixed over time, as they seem to deteriorate during the first two years after stroke.[36] This emphasizes the importance of the development of interventions to enhance adaptive psychological factors during early stages of rehabilitation, for example interventions promoting self-efficacy, proactive coping and being optimistic.[53,54]

The association between maladaptive psychological factors and participation vanished in the final model. The strong correlation between maladaptive factors and mood problems could be a possible explanation. Maladaptive psychological factors such as passive coping have been determined as independent predictors of the presence of mood problems in earlier studies.[18,55-57] Therefore, it seems plausible that mood problems mediated the effect of maladaptive factors on the course of participation in the final model of this study.

The relation between psychological factors and participation has also been studied in other neurological diseases, although most studies mainly focused on maladaptive psychological factors.[58-60] Cross-sectional studies identified helplessness in persons with amyotrophic lateral sclerosis and lower self-efficacy scores in persons with spinal cord injury as psychological factors related to restrictions in participation.[58,59] A longitudinal study of persons with traumatic brain injury identified passive coping, neuroticism and mood problems as determinants of restrictions in participation.[60]

Study strengths

This is the first study using adaptive and maladaptive psychological clusters to study determinants of participation after stroke. The use of mixed model analyses, which allowed us to include all available data, the large sample size and long-term follow-up increased the power of the study. The study population represents the stroke population well, as inclusion took place in hospitals within seven days of stroke onset. This study builds on previous publications using the Restore4Stroke cohort to study demographic and stroke-related factors as determinants of participation.[12,41,42] The current study adds a prolonged follow up duration up to four years after stroke and insight into the relation between participation and psychological factors.

Study limitations

Firstly, the study population largely consisted of relatively mild stroke patients with mostly ischemic strokes. Although this is in line with the epidemiology of stroke, it could negatively affect the generalizability of the results to more severely affected stroke patients and those with other types of strokes. Secondly, more than half of the study population dropped out during follow-up. However, apart from age and ADL dependency, no significant differences at baseline were found between the participants still in the study at four years and the dropouts. Thirdly, despite the USER-P restriction subscale specifically asks for restrictions caused by the stroke, it could have been challenging for participants to distinguish restrictions in participation caused by the stroke and those due to, for example, normal aging or comorbidities. This may have caused an overestimation of restrictions in participation over time caused by the stroke.[61]

CONCLUSIONS

Among persons with stroke participation restrictions are considerable up to four years after stroke, especially in dynamic activities requiring both mobility and cognitive skills. Improvements in participation are only observed up to one year after stroke. Hence, the addition of a follow-up assessment one year after stroke can be beneficial as restrictions in participation are likely to be permanent from then onwards. Both mood problems and less adaptive psychological factors are independently associated with worse participation up to four years after stroke. Therefore, follow-up assessments after stroke should not only focus on cognitive and motor impairment, but also encompass screening on mood problems and adaptive psychological factors.

Implications for rehabilitation

- Follow-up assessments after stroke should not only focus on cognitive and motor impairment, but also encompass screening on mood problems and adaptive psychological factors.
- Implementation of a routine follow-up assessment one year after stroke can be beneficial as restrictions in participation are unlikely to diminish spontaneously from then onwards.

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Chapter 7

Which approach to measure cognitive functioning should be preferred when exploring the association between cognitive functioning and participation after stroke?

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Abstract

A variety of approaches are currently used to explore the relationship between cognitive functioning and participation after stroke. We aimed to gain insight into the preferred approach to measure cognitive functioning when exploring the association between cognitive functioning and participation in the long term after stroke. In this inception cohort study 128 individuals with stroke, of whom 40 (31.2%) were females and mean age was 63.7 years (SD 11.0), participated and were assessed at a single time point three to four years after the event. Participation was measured using the Restrictions subscale of the Utrecht Scale for Evaluation of Rehabilitation-Participation. Subjective cognitive complaints were assessed using the Cognition subscale of the Checklist for Cognitive and Emotional Consequences (CLCE-24-C). Objective cognitive performance was measured using the Montreal Cognitive Assessment (MoCA) and a neuropsychological test battery (NTB) testing multiple cognitive domains. Participation showed a strong correlation (r = 0.51) with the CLCE-24-C and moderate correlations with the domains of visuospatial perception (r = 0.37) and mental speed (r = 0.36). Backward linear regression analyses showed that participation restrictions were best explained by the combination of the CLCE-24-C and a test for visuospatial perception (R^2 = 0.31). Our findings suggest the use of a combination of subjective cognitive complaints and objective cognitive performance to explore the relationship between cognitive functioning and participation after stroke.

INTRODUCTION

Stroke is one of the main causes of disability in the world.[1] Due to the aging population and increased survival, more and more individuals with stroke have to deal with long-term restrictions in social and community participation.[2] According to the International Classification of Functioning, Disability and Health (ICF), participation has been defined as "the person's involvement in a life situation" and is regarded an important goal in stroke rehabilitation.[3] Depending on stroke characteristics, demographic factors and diagnostic criteria, the prevalence of cognitive deficits after stroke varies from 20–80%.[4] Since cognitive functioning is an important determinant of participation in individuals with stroke, evaluation of cognitive functioning during follow-up assessments after stroke is essential to select potential rehabilitation interventions to improve participation.[5-7] In the current stroke literature, various types of cognitive assessments are used to study the relationship between cognitive functioning and participation, measuring either objective or subjective cognitive functioning. It is largely unknown, however, which approach is preferable to study the association between cognitive functioning and restrictions in participation after stroke.

Objective cognitive performance can be assessed using cognitive screening instruments or standardized neuropsychological tests. Cognitive screening instruments, such as the Montreal Cognitive Assessment (MoCA), are often used in daily practice and can serve as a brief screening tool to detect global cognitive deficits.[8] MoCA scores have been associated with levels of activities after aneurysmal subarachnoid hemorrhage[9] and with return to work and participation in individuals aged under 70 years one year after stroke.[10,11] A neuropsychological test battery (NTB) is the "gold standard" to assess domain-specific cognitive deficits after stroke and can serve both diagnostic and prognostic purposes.[12] Verbal expression,[13] visuospatial perception[14] and memory[15] have been identified as cognitive domains negatively affecting participation after stroke. Additionally, attention and executive functioning were also found to predict levels of activities up to one year after stroke.[16] The rationale behind the importance of these specific cognitive domains has not yet been fully elucidated.[17] A recent systematic review exploring the relationship between objective cognitive performance and long-term participation after stroke concluded that this relationship partially depends on the type of cognitive assessment undertaken.[16] In general, NTBs have shown more consistent associations with participation after stroke than cognitive screening instruments.[16] This may be explained by the limited sensitivity of the MoCA to assess essential cognitive domains, such as executive functioning.[18]

However, the ecological validity of NTBs is weak,[19] and it is the subjective cognitive complaints in everyday life that matter most from the patients' perspective.[20] Subjective cognitive complaints can be measured using a self-report questionnaire, are highly prevalent after stroke and tend to increase over time.[21] Subjective cognitive complaints are related to both objective cognitive performance and long-term restrictions in participation after stroke, but do not necessarily coexist with deficits in objective cognitive performance.[22,23] Although approximately half of the individuals with stroke who experience subjective cognitive complaints show evidence of deficits in objective cognitive performance,[24] the relationship between subjective cognitive complaints and objective cognitive performance is inconsistent.[22] The accumulation of deficits in multiple cognitive domains has been suggested to contribute to subjective cognitive complaints after stroke.[23]

In conclusion, cognitive functioning after stroke can be measured using screening instruments or an NTB to measure objective cognitive performance, or a self-report instrument to measure subjective cognitive complaints. The relationship between cognitive functioning and participation is inconsistent due to the variety of approaches used to measure cognitive functioning in the current stroke literature.[25] Therefore, the aim of this study was to gain insight into the preferred approach to measure cognitive functioning when exploring the association between cognitive functioning and participation in the long term after stroke. Both objective cognitive performance (global cognitive screening and an NTB) and subjective cognitive complaints were used to measure cognitive functioning. As we were solely interested in the bivariate relationship between cognitive functioning and participation, we did not take the effect of other determinants of participation after stroke into account. Our hypothesis is that a combination of objective cognitive performance and subjective cognitive complaints will provide the highest association with participation and would therefore be preferable when studying the relationship between cognitive functioning and participation after stroke.

METHODS

Design

The present study is a follow-up assessment (three to four years post-stroke) of the multicenter prospective longitudinal Restore4Stroke cohort study, in which individuals with stroke were followed for two years, including five measurements.[26]

Participants

Participants were consecutively recruited from stroke units in six participating hospitals in the Netherlands between March 2011 and March 2013. For the present study, participants were asked to participate in an additional assessment at three to four years post stroke. Individuals with stroke were eligible for Restore4stroke if they [1] had a clinically confirmed diagnosis of ischemic or hemorrhagic stroke; [2] gave informed consent within seven days after symptom onset; and [3] were at least 18 years old. Participants were excluded from the study if they [1] had a serious other condition that could interfere with study outcomes; [2] had been dependent in basic activities of daily living before the stroke occurred (defined by a Barthel Index score of ≤ 17[27]); [3] had insufficient command of Dutch to complete the questionnaires and neuropsychological tests, based on clinical judgment; or [4] had suffered cognitive decline prior to the stroke (defined by a score of ≥ 1 on the Heteroanamnesis List Cognition[28]). Participants who completed the Restriction subscale of the USER-Participation at three to four years after stroke were included in the analysis of the current study. Informed consent was obtained from all participants.

Procedure

Three to four years after stroke, a neuropsychological assessment, including a global cognitive screening, was conducted by a trained research assistant (graduated neuropsychologist), either in the nearest participating hospital or at the participants' home (if participants were not able to travel). Participants were also asked to complete a self-report questionnaire including measures of participation and subjective cognitive complaints. These measurements were conducted between July 2015 and October 2016. The Restore4Stroke cohort study and the additional follow-up measurements reported here were approved by the Medical Ethics Committees of all participating hospitals.

Dependent variables

The Restrictions subscale of the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-Participation) was used to measure participation.[29] The Restrictions subscale (USER-P-R) consists of 11 items, concerning difficulties experienced with vocational, leisure and social activities due to the stroke. For each item four response categories are available ("not possible," "with assistance," "with difficulty," and "without difficulty"). A "not applicable" option is available for all items in case an activity is not performed for other reasons or a restriction is not attributed to the stroke. The total score of the Restrictions subscale ranges from 0–100 and is based on items that are applicable. A higher score indicates a more favourable level of

participation (fewer restrictions experienced). The USER-Participation has previously shown satisfactory validity and reliability[30] and excellent responsiveness in individuals with stroke.[31,32]

Independent variables

Demographic factors

Information about gender, age, marital status and level of education was collected. Education levels were dichotomized into low (up to completed secondary vocational education) and high (completed higher secondary professional education or university).[33]

Stroke-related factors

The hemisphere involved, the type of stroke (ischemic or hemorrhagic), history of stroke, length of stay in hospital and discharge destination were obtained from medical charts. The severity of stroke was assessed with the National Institutes of Health Stroke Scale four days after stroke.[34] Activities of daily living were assessed by the stroke nurses with the Barthel Index four days after stroke.[35]

Neuropsychological test battery

The Visual Object and Space Perception test (VOSP)[36] assesses visuospatial perception abilities. The test consists of four subtests for object perception and four subtests for space perception, which can be used separately. The number of correct responses per subtest is scored, and if this number exceeds the minimal threshold, one point is given. The total score is calculated by adding up all points (which leads to a maximum score of 8).

The Boston Naming Test (BNT)[37] is a test of verbal expression. The short version was used, in which the participant is asked to name 29 items ranging in familiarity.

The Rivermead Behavioural Memory Test (RBMT)[38] measures different aspects of memory. In one of the subscales the participant is read a story and asked to recall, both immediately (RBMT-I) and after a delay (RBMT-D), as many elements of the story as possible. The number of correctly recalled elements is scored.

The Symbol Digit Modalities Test (SDMT)[39] primarily assesses complex scanning and visual tracking. The test is mostly used to measure speed of information processing or mental speed. It consists of a sheet of paper with, at the top, a sequence of nine symbols and nine corresponding numbers (key). Within a 90-second time limit the participant is required, consulting the key as necessary, to insert the numbers associated with the symbols.

The Trail Making Test (TMT)[40] is a test for visual attention, executive functioning and task switching/cognitive flexibility. This test requires speed of information processing, visual search strategies and visuo-motor behavior. The test has various parts (part A and part B), in which the participant is asked to connect numbers, letters or a combination of numbers and letters in the correct order. The time needed to complete part A and B is scored.

MoCA

The MoCA is a brief cognitive screening tool, which has been validated for individuals with stroke.[8] Scores range from 0–30 and higher scores indicate better cognitive functioning. Participants with < 12 years of education were assigned one additional point on their MoCA score.[8] Cognitive impairment can be defined as MoCA < 26, as this cut-off yields the best balance between sensitivity and specificity in detecting cognitive impairment.[8]

Subjective cognitive complaints

The presence of subjective cognitive complaints was assessed using the Cognition subscale of the Checklist for Cognitive and Emotional Consequences (CLCE-24-C), which consists of 13 items (e.g., problems with "doing two things at once" or "remembering new information").[41] The items involve multiple cognitive domains (including executive functioning, attention, memory, speed of processing and visuospatial perception) and are indicative of the cognitive complaints the patient experiences. The interviewer scores a "0" for the absence of complaints, a "1" for possible complaints and a "2" for the presence of complaints. Total scores range from 0–26 and higher scores indicate more cognitive complaints. The CLCE-24 is a feasible and valid instrument to use in individuals with stroke.[42]

Statistical analysis

All analyses were conducted with SPSS statistics version 24 (IBM, Armonk, NY). Descriptive statistics were used to describe participant characteristics and dependent variables. Baseline characteristics of participants lost to attrition and study participants were compared using independent T-tests (continuous variables) and Chi-square tests (categorical variables).

Raw scores of the RBMT-I, RBMT-D, SDMT and TMT were converted to t-scores using age-specific (and, when available, education- and gender-specific) normative data. The TMT t-score is based on the raw scores of TMT part B, adjusted for the raw scores on TMT part A. Scores on the BNT were converted to percentiles using age- and education-specific normative data. Scores on the VOSP were adjusted for age.[36]

Bivariate associations of the NTB (BNT, RBMT-I, RBMT-D, SDMT, TMT and VOSP), MoCA and CLCE-24-C with the USER-P-R were tested using Spearman correlations. As proposed by Cohen, correlation coefficients of the order of 0.10 were interpreted as "weak", those of 0.30 as "moderate" and those of 0.50 or higher as "strong".[43] Bonferroni correction was used to account for multiple comparisons, and $p < 0.001$ was considered statistically significant.

Multiple linear regression analysis was used to explore the association between different combinations of cognitive measures and participation three to four years after stroke. The USER-P-R was entered as a dependent variable in all models. The models were built using a hierarchical approach. The NTB, currently regarded as a "gold standard" to assess cognitive functioning, was entered in model 1. As we were interested in the association between participation and a combination of objective cognitive performance (MoCA and NTB) and subjective cognitive complaints (CLCE-24-C), we entered the MoCA and CLCE-24-C in model 2 and the NTB and CLCE-24-C in model 3. In order to explore which combination of approaches is preferable when exploring the relationship between cognitive functioning and participation, backward selection was used to fit the best model of cognitive measures (out of the NTB, MoCA and CLCE-24-C) in model 4. Possible multicollinearity was checked (VIF < 4), which did not reveal any problems. A value of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 395 participants were included in the Restore4Stroke study within the first week after stroke onset, and 160 of them (40.5%) were tested three to four years after stroke. The Restrictions subscale of the USER-P was completed by 128 participants (80.0%) at three to four years after stroke, and they were included in the analysis. Of the 235 resigned participants, 33 had died, 120 refused further participation, 47 were lost to follow-up and 35 were lost to attrition because of an insufficient general physical condition.

Participant characteristics are presented in Table 7.1. The study participants were significantly younger at stroke onset and were less cognitively impaired than the participants lost to attrition. The participation and cognitive test scores at three to four years after stroke are presented in Table 7.2. The CLCE-24-C showed adequate internal consistency (Cronbach's $\alpha = 0.79$). The majority of participants (89.0%) reported subjective cognitive complaints for at least one item of the CLCE-24-C. According to the MoCA, almost half (45.3%) of participants were cognitively impaired at three to four years after stroke. Cognitive domains

most often affected according to the NTB were immediate and delayed recall (49.1% and 25.2% respectively), higher visual perception (20.0%) and mental speed (15.3%).

Table 7.1: Participant characteristics (n = 395)

	Study participants (n = 128)	Dropouts (n = 267)	P-value[b]
Demographic factors			
Sex (% male)	68.8	62.9	0.256
Age in years (at time of stroke)	63.7 ± 11.0	68.1 ± 13.1	0.001*
Marital status (% living together)	73.4	66.3	0.152
High education level (%)[a]	28.1	25.8	0.624
Stroke-related factors			
Ischemic stroke (%)	92.1	94.0	0.275
Stroke location			
Left hemisphere (%)	33.9	43.1	0.165
Right hemisphere (%)	44.9	41.2	
Vertebrobasilar stroke (%)	21.3	15.7	
First stroke (%)	85.2	89.5	0.211
Discharge home after hospital stay (%)	75.8	67.8	0.104
Severity of stroke	2.7 ± 3.1	2.8 ± 3.3	0.647
No stroke symptoms (% NIHSS 0)	24.2	23.6	0.612
Minor stroke symptoms (% NIHSS 1–4)	57.0	55.4	
Moderate stroke symptoms (% NIHSS 5–12)	17.2	18.4	
Severe stroke symptoms (% NIHSS ≥ 13)	1.6	2.6	
ADL 4 days after stroke	17.1 ± 4.6	16.7 ± 4.9	0.382
% ADL-dependent (BI ≤ 17)	31.3	34.5	0.527
Cognitive functioning 2 months after stroke			
Cognitive functioning (MoCA)	24.5 ± 3.6	23.0 ± 4.1	0.001*
% cognitively impaired (MoCA ≤ 25)	58.2	72.4	0.007*

Note: Values are percentages or mean ± SD.
ADL, activities of daily living; BI, Barthel Index; MoCA, Montreal Cognitive Assessment; NIHSS, National Institutes of Health Stroke Scale.
[a] Completed University of Professional Education and higher.
[b] Comparison between 'study participants' and 'dropouts'.
* $p < 0.05$.

Bivariate analyses

CLCE-24-C scores were strongly correlated with participation scores three to four years after stroke ($r = 0.51$), as shown in Table 7.3. MoCA ($r = 0.24$) and NTB scores correlated weakly with participation, except for the SDMT ($r = 0.36$) and VOSP scores ($r = 0.37$) which showed a moderate correlation with participation. CLCE-24-C scores showed weak negative correlations with the MoCA and NTB. Weak (BNT, TMT and VOSP) or moderate (RBMT-I, RBMT-D and SDMT) positive correlations were observed between the MoCA and

Table 7.2: Scores on participation and cognitive tests (MoCA, CLCE-24-C and NTB) (n = 128) at four years after stroke

			n	Mean (± SD)	Range	% impaired
USER-P-R			128	83.55 (± 19.72)	13–100	
SCC:	CLCE-24-C		127	7.28 (± 5.53)	0–23	89.0[b]
OCP:	MoCA		124	24.96 (± 3.18)	15–30	45.3[c]
	NTB:	BNT[a]	118	45.71 (± 32.61)	5–100	2.5[d]
		RBMT-I[a]	112	36.14 (± 8.91)	20–68	49.1[d]
		RBMT-D[a]	111	40.67 (± 9.13)	23–80	25.2[d]
		SDMT[a]	111	46.67 (± 10.92)	17–71	15.3[d]
		TMT[a]	106	51.01 (± 9.81)	29–86	4.7[d]
		VOSP	75	6.72 (± 0.75)	3–8	20.0[e]

Abbreviations: BNT, Boston Naming Test; CLCE-24-C, Checklist for Cognitive and Emotional Consequences – cognitive subscale; MoCA, Montreal Cognitive Assessment; NTB, Neuropsychological Test Battery; OCP, objective cognitive performance; RBMT-D, Rivermead Behavioral Memory Test – Delayed recall; RBMT-I, Rivermead Behavioral Memory Test – Immediate recall; SCC, subjective cognitive complaints; SD, standard deviation; SDMT, Symbol Digits Modalities Test; TMT, Trail Making Test; USER-P-R, Utrecht Scale for Evaluation of Rehabilitation – Participation Restrictions subscale; VOSP, Visual Object and Space Perception Test.
[a] *t*-scores, using age-matched (and, when available, education and gender) normative data.
[b] Impairment defined as reported subjective cognitive complaints in at least one item of the CLCE-24-C.
[c] Impairment defined as MoCA scores < 26.
[d] Impairment defined as scores < 1.5 SD below the mean.
[e] Impairment defined as VOSP scores < 7.

the NTB. Except for the very strong correlation between RBMT-I and RBMT-D ($r = 0.83$), inter-correlations between NTB test scores were weak to moderate. The CLCE-24-C ($R^2 = 0.19$), VOSP ($R^2 = 0.18$), SDMT ($R^2 = 0.15$) and MoCA ($R^2 = 0.06$) explained the largest amount of variance in participation scores three to four years after stroke.

Multivariate linear regression

Results of the multivariate regression analyses are shown in Table 7.4. In model 1 (including NTB) higher scores on the SDMT and VOSP were associated with fewer restrictions in participation three to four years after stroke. In model 2 (including MoCA and CLCE-24-C), only having fewer cognitive complaints was associated with fewer restrictions in participation three to four years after stroke. In both model 3 (combining NTB and CLCE-24-C) and model 4 (using backward selection), fewer cognitive complaints and a higher score on the VOSP were associated with fewer restrictions in participation three to four years after stroke. Combining the CLCE-24-C and the VOSP in model 4 ($R^2 = 0.31$) explained a larger amount of variance in participation scores three to four years after stroke than the NTB in model 1 ($R^2 = 0.20$), combining the CLCE-24-C and the MoCA in model 2 ($R^2 = 0.20$) or the CLCE-24-C and the NTB in model 3 ($R^2 = 0.29$).

Table 7.3: Bivariate analyses: correlations between the neuropsychological tests, MoCA, CLCE-24-C and participation (n = 128) at three to four years after stroke

			CLCE-24-C	MoCA	BNT	RBMT-I	RBMT-D	SDMT	TMT	VOSP
USER-P-R			-0.51*	0.24*	-0.04	0.14	0.11	0.36*	0.20	0.37*
SCC:	CLCE-24-C			-0.27*	-0.08	-0.25*	-0.22	-0.32*	-0.26*	-0.27
OCP:	MoCA				0.07	0.35*	0.39*	0.37*	0.24	0.26
	NTB:	BNT				0.22*	0.21	0.16	0.15	0.06
		RBMT-I					0.83*	0.29*	0.13	0.10
		RBMT-D						0.30*	0.14	0.15
		SDMT							0.40*	0.32*
		TMT								0.29

Abbreviations: BNT, Boston Naming Test; CLCE-24-C, Checklist for Cognitive and Emotional Consequences – cognitive subscale; MoCA, Montreal Cognitive Assessment; NTB, Neuropsychological Test Battery; RBMT-D, Rivermead Behavioral Memory Test – Delayed recall; RBMT-I, Rivermead Behavioral Memory Test – Immediate recall; SDMT, Symbol Digits Modalities Test; TMT, Trail Making Test; USER-P-R, Utrecht Scale for Evaluation of Rehabilitation – Participation Restrictions subscale; VOSP, Visual Object and Space Perception Test.

* $p < 0.001$.

Table 7.4: Multivariate analysis: determinants of USER-P-R three to four years after stroke

			Model 1 (n = 75)			Model 2 (n = 124)			Model 3 (n = 75)			Model 4 (n = 75)		
			NTB			MoCA and CLCE-24-C			NTB and CLCE-24-C			Backward model		
			B	(95% CI)	β	B	(95% CI)	β	B	(95% CI)	β	B	(95% CI)	β
		Constant	-0.12	(-42.74–42.49)		74.56	(46.71–102.41)		25.11	(-18.41–68.64)		28.39	(-8.75–65.54)	
SCC:	CLCE-24-C					-1.46	(-2.06–-0.86)	-0.41*	-1.18	(-1.96–-0.40)	-0.33*	-1.35	(-2.07–-0.64)	-0.38*
OCP:	MoCA					0.79	(-0.26–1.83)	0.13				[a]		
	NTB:	BNT	-0.06	(-0.20–0.07)	-0.10				-0.05	(-0.18–0.08)	-0.09	[a]		
		RBMT-I	0.31	(-0.70–1.32)	0.14				0.11	(-0.85–1.07)	0.05	[a]		
		RBMT-D	-0.13	(-1.11–0.84)	-0.06				-0.05	(-0.97–0.88)	-0.02	[a]		
		SDMT	0.47	(0.01–0.92)	0.26*				0.32	(-0.12–0.76)	0.18	[a]		
		TMT	0.05	(-0.42–0.52)	0.03				-0.03	(-0.47–0.42)	-0.01	[a]		
		VOSP	8.39	(2.18–14.60)	0.32*				7.99	(2.12–13.85)	0.30*	9.67	(4.37–14.97)	0.37*
		R^2	0.20			0.20			0.29			0.31		

Abbreviations: 95% CI, 95% confidence interval; B, unstandardized regression coefficient; β, standardized regression coefficient; BNT, Boston Naming Test; CLCE-24-C, Checklist for Cognitive and Emotional Consequences – cognitive subscale; MoCA, Montreal Cognitive Assessment; NTB, Neuropsychological Test Battery; OCP, objective cognitive performance; RBMT-D, Rivermead Behavioral Memory Test – Delayed recall; RBMT-I, RBMT – Immediate recall; SCC, subjective cognitive complaints; SDMT, Symbol Digits Modalities Test; TMT, Trail Making Test; USER-P-R, Utrecht Scale for Evaluation of Rehabilitation – Participation Restrictions subscale; VOSP, Visual Object and Space Perception Test.

[a] Variable removed in final backward analysis.

* $p < 0.05$.

DISCUSSION

The aim of this study was to gain insight into the preferred approach to measure cognitive functioning when exploring the association between cognitive functioning and participation in the long term after stroke. Although significant relationships were found between all cognitive measures and participation after stroke, the subjective CLCE-24-C score showed the strongest bivariate association with participation after stroke (19% explained variance). Among the NTB tests, the domains of visuospatial perception (VOSP) and mental speed (SDMT) were moderately associated with participation after stroke. Global cognitive screening (MoCA) showed a weak association with participation after stroke. The combination of the CLCE-24-C and VOSP explained the highest proportion (31%) of the variance in participation scores. Therefore, a combination of subjective and objective measures (preferably including the cognitive domains of visuospatial perception and mental speed) is to be recommended when exploring the association between cognitive functioning and participation after stroke.

Subjective cognitive complaints

The high prevalence of subjective cognitive complaints three to four years after stroke found in this study (89.0%) is in accordance with previous studies.[22] The strong association between subjective cognitive complaints and participation after stroke is a relatively new finding. One cross-sectional study concerned individuals who had been discharged home and were assessed at least 6 months post-stroke. It showed a weak association between subjective cognitive complaints and difficulties of community reintegration (r = -0.23).[44] In another study, subjective cognitive complaints were among the main predictors of participation restrictions in individuals six months after an aneurysmal subarachnoid hemorrhage.[45] A possible explanation could be the similarity between the CLCE-24-C and USER-P. Both instruments are self-reported questionnaires asking about complaints/restrictions experienced in everyday life, whereas NTB and MoCA may lack ecological validity and may less accurately reflect daily life functioning.[19]

Our study showed a weak correlation between subjective cognitive complaints and objective cognitive performance. Although some studies found associations between cognitive screening instruments (including the MoCA in one study[46]) and subjective cognitive complaints,[42,47,48] other studies did not find a relationship between subjective cognitive complaints and NTB tests.[49-51] This inconsistency may be explained by the limited ecological validity of the NTB tests used in some studies[23] and by the huge variation of NTB tests across

studies. Also, it has been suggested that the accumulation of cognitive deficits in various cognitive domains contributes to subjective cognitive complaints after stroke, explaining the lack of correlation between individual NTB tests and subjective cognitive complaints.[23] However, the MoCA, a global cognitive screening instrument covering multiple domains, also weakly correlated with subjective cognitive complaints in our study (r = 0.27).

Objective cognitive performance

The cognitive domains of visuospatial perception (VOSP) and mental speed (SDMT) showed the strongest correlation with participation after stroke (r = 0.37 and 0.36 respectively), and were also associated to participation in the multivariate models (SDMT only in model 1, VOSP in all models). Previous studies identified the same cognitive domains as determinants of quality of life up to one year after stroke.[17] It has been suggested that visuospatial perception is a more fundamental aspect of cognitive functioning, upon which other cognitive domains depend, and that this is a prerequisite for daily life functioning.[17] Impairments in executive functioning and mental speed may affect the ability to plan, monitor and evaluate more complex daily tasks, having a negative impact on daily life functioning.[16]

In the final multivariate model (model 4 using backward selection) the combination of the visuospatial perception (VOSP) domain and subjective cognitive complaints (CLCE-24-C) provided the strongest association with participation. Previous studies also found an association between visuospatial perception and participation up to 6–12 months after stroke.[14,15,52] According to a recent systematic review looking into the relationship between cognitive functioning and participation after stroke, cognitive screening instruments such as the MoCA show less consistent associations with participation than NTBs.[16] Our results confirm the suggestion that specific cognitive domains are more strongly associated with participation than global cognitive functioning,[53] as the MoCA showed a weak correlation and no association with participation after stroke in the multivariate models.

Limitations

Due to the relatively long period that elapsed between the follow-up assessments, a considerable number of participants were lost to follow-up. It could be that only the most motivated participants were willing to participate in an additional assessment. This may have led to selection bias, as the study sample was significantly younger at stroke onset and was less cognitively impaired compared to the resigned participants. This could therefore negatively affect the generalizability of the results to older individuals with stroke and those

with severe cognitive impairments. However, current epidemiological studies show that most people have relatively mild strokes. Furthermore, missing NTB data (especially the VOSP) considerably reduced the sample size (n = 75) in the multivariate models (models 1, 3 and 4). However, apart from cognitive functioning (participants with missing NTB data being more cognitively impaired based on the MoCA), no significant differences in any of the baseline characteristics were observed between the multivariate model sample (n = 75) and the participants at stroke onset (n = 395) or at 3–4 years after stroke (n = 128). Lastly, although we aimed to cover the most important cognitive domains after stroke, not all aspects of cognitive functioning are represented in the NTB (e.g. planning, visual memory and social cognition are lacking).

CONCLUSIONS

This study has shown the impact of subjective cognitive complaints on everyday life in the long term after stroke, as subjective cognitive complaints were strongly related to restrictions in participation three to four years after stroke. A combination of objective cognitive performance (preferably including the domains of visuospatial perception and mental speed) and subjective cognitive complaints showed the strongest association with participation, and is therefore to be recommended when exploring cognitive functioning as a determinant of participation after stroke. External validation in another stroke sample is needed to confirm whether these results also apply to older individuals with stroke and those with severe cognitive impairments due to the limited generalizability to these patient categories in our study population. Last but not least, since participation is an important goal in rehabilitation, it is important to consider subjective cognitive complaints in stroke aftercare.

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Chapter 8

The longitudinal association between movement behavior patterns and the course of participation up to one year after stroke

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Abstract

Background: Movement behavior (the composition of time spend sedentary and time spend in light, moderate or vigorous physical activity) is a modifiable factor in stroke rehabilitation, but its association with the course of participation after stroke is currently unknown.

Objective: (1) To investigate the differences in the course of participation up to one year after stroke between distinct movement behavior patterns identified directly after discharge to the home setting, and (2) to investigate the longitudinal association between the development of movement behavior patterns over time and participation after stroke.

Methods: 200 individuals with a first-ever stroke were assessed directly after discharge to the home setting, at six months and at one year. The Participation domain of the Stroke Impact Scale 3.0 was used to measure participation. Movement behavior was objectified using accelerometry for 14 days. Participants were categorized into three distinct movement behavior patterns: sedentary exercisers, sedentary movers and sedentary prolongers. Generalized estimating equations (GEE) were performed.

Results: Participation improved up to six months after discharge and stabilized afterwards across all movement behavior patterns. People who were classified as sedentary prolonger directly after discharge were associated with a worse course of participation up to one year after stroke. The development of sedentary prolongers over time was also associated with worse participation compared to sedentary exercisers.

Conclusions: The course of participation after stroke differs across distinct movement behavior patterns after discharge to the home setting. Highly sedentary and inactive people with stroke are at risk for restrictions in participation over time.

INTRODUCTION

Stroke is the second leading cause of death and the third leading cause of disability worldwide.[1] Stroke prevalence has increased over the last decades, most likely because of longer survival and reduced mortality of people experiencing stroke[2] due to improved stroke care and risk factor management.[3,4] This results in more people living with the long term consequences of stroke, such as physical, emotional, and cognitive problems, that contribute to restrictions in participation and quality of life.[5-7] Participation defined as "the person's involvement in a life situation"[8] is among the most impacted domains of health-related quality of life after stroke,[9] and is considered the cornerstone of successful rehabilitation after stroke.[10] Improvements in participation mainly occur in the first six months after stroke and recovery is often incomplete, remaining lower compared to the general population.[11,12] Consequently, many people experience considerable and ongoing restrictions in participation after stroke,[13] including the domains outdoor mobility, work and physical exercise.[14]

Physical activity has been shown to be one of the key components in stroke rehabilitation, as interventions that enhance physical activity were associated with improvement in participation after stroke.[15,16] Three small cross-sectional studies (n = 19–31) in community-living chronic stroke patients (ranging from six months till ten years after stroke onset) reported moderate correlations between the participation domain of the Stroke Impact Scale (SIS) and the Six-Meter Walk Test,[17] steps per day (using pedometry)[18] and physical activity (using accelerometry).[19] However, stroke patients are not only less physically active in all phases after stroke, but also spend more time sedentary than healthy individuals,[20] especially in prolonged periods of time.[21-23]

Movement behavior is defined as the composition of time spend sedentary and time spend in light, moderate or vigorous physical activity.[24] Research has shown that time spent in moderate to vigorous physical activity (MVPA), light physical activity (LPA) and sedentary behavior all interact to impact physical functioning in people after stroke.[23] These are partly independent behaviors, and it is suggested that research should focus on movement behavior patterns instead of separate aspects of movement behavior.[23] Currently, physical activity is the most studied aspect of movement behavior, and longitudinal studies investigating the relationship between physical activity and participation are lacking.[5] To our knowledge, the association between participation and other types of movement behavior, such as sedentary behavior, has rarely been studied.[25]

Recently, three distinct movement behavior patterns in people after stroke were identified: (1) the so called 'sedentary exercisers', characterized by interrupted sedentary and active

movement patterns, (2) 'sedentary movers', characterized by interrupted sedentary and inactive movement patterns, and (3) 'sedentary prolongers', who were characterized by a prolonged and highly sedentary and inactive movement pattern.[23] These movement behavior patterns turned out to be predictive of the course of physical functioning up to two years after stroke, as sedentary prolongers showed worse physical functioning over time compared to the sedentary movers and sedentary exercisers.[24] Furthermore, more individuals develop a more unfavourable movement behavior pattern over time.[26] Namely, after initial improvement in the first six months after discharge to the home setting, movement behavior often deteriorated and the proportion of sedentary prolongers (the most unfavorable movement behavior pattern) increased.[26]

Whether these distinct movement behavior patterns are also predictive of the course of participation after stroke is currently unknown. Gaining a better understanding of the relationship between movement behavior and participation may yield possibilities for the development of tailored interventions targeting movement behavioral change. Therefore, this study aims (1) to explore the differences in the course of participation up to one year after stroke between distinct movement behavior patterns identified directly after discharge to the home setting, and (2) to investigate the longitudinal association between the development of movement behavior patterns over time and participation after stroke.

METHODS

Participants and study design

This prospective cohort study is part of the RISE-study.[23] Participants were recruited from four stroke-units in the Netherlands. Participants were deemed eligible to participate when: presenting with a clinically confirmed first-ever stroke, expected to return home (with or without inpatient rehabilitation before returning home), activities of daily living independent before stroke (Barthel index > 18),[27] > 18 years old, able to maintain a conversation (score > 4 on the Utrecht Communication assessment),[28] and at least able to walk with supervision when they returned home (Score ≥ 3 in the Functional Ambulation Categories).[29] People with subarachnoid hemorrhage were excluded. Written informed consent was obtained at the stroke unit. The study was approved by the Medical Ethics Research Committee of the University Medical Center Utrecht (study number 14/76).

Demographic, stroke, and care characteristics were obtained from medical health records. Within three weeks after discharge from inpatient care, six months after discharge from

inpatient care and one year after discharge from inpatient care, participants were visited at home by trained researchers to obtain measurements. Before the participant was visited at home, a postal questionnaire was sent to get information on emotional symptoms. During the visits at home, data on physical functioning and a self-report participation questionnaire were obtained. After each visit, participants wore an accelerometer to objectify movement behavior for 14 days.

Dependent variable

Participation was measured using the Participation domain of the Stroke Impact Scale 3.0 (SIS Participation).[30,31] The SIS is a self-administered questionnaire that estimates how stroke affects health and quality of life. It comprises 59 questions divided into eight domains, including strength, hand function, mobility, activities of daily living (ADL), emotion, communication, memory and thinking, and participation. The SIS Participation has eight questions that ask the participant to range his or her limitations in the past four weeks in (1) work, volunteer or other activities; (2) social activities; (3) quiet recreation; (4) active recreation; (5) role as a family member or friend; (6) participation in spiritual or religious activities; (7) ability to control life as he or she wished; and (8) ability to help others. Each question is rated on a five-point scale to indicate how often the participant has experienced restrictions in certain activities. The possible scores range from 1–5, where 1 is never, and 5 is always. The SIS 3.0 is valid and sensitive to changes in stroke-related recovery,[30,31] and evaluation of the use of separate domain scores has also shown excellent validity.[32]

For a particular participant, if ≥ 50% of the questions had missing responses, the SIS Participation was assigned as missing. Otherwise, scores for the SIS Participation were computed using the following equation: SIS Participation = (mean-1/5-1) * 100, where the mean is the mean of the non-missing item scores within the domain. Using this algorithm, the SIS Participation has a range from 0–100.[31]

Independent variables

Movement behavior

Movement behavior was measured by an accelerometer (Activ8, a three-axial accelerometer) worn on the thigh for two consecutive weeks during waking hours. The Activ8 is validated in community living ambulatory people with stroke.[33] Ten different movement behaviors were calculated from data supplied by the accelerometer, including mean time spent sedentary, the mean time spent in uninterrupted periods of sitting and lying down (bouts), measured

in periods of ≥ 5 minutes per day, ≥ 30 minutes a day or ≥ 60 minutes per day. Also, time spent in LPA and time spent in MVPA were measured.

In total, three distinct movement behavior patterns were identified: sedentary exercisers, sedentary movers and sedentary prolongers.[23] Sedentary exercisers were characterized by interrupted sedentary and active movement patterns, sedentary movers were characterized by interrupted sedentary and inactive movement patterns, and sedentary prolongers were characterized by a prolonged and highly sedentary and inactive movement pattern. The sedentary exercisers group was sedentary for 9.0 hours per day and had a mean MVPA time of 1.4 hours a day, while the sedentary prolongers were sedentary for on average 10.7 hours per day and spent a mean time of 0.4 hours per day on MVPA (Table 8.1).[24]

Demographic characteristics

Demographic characteristics included age, sex, educational level, comorbidities and living situation. Educational level was asked using the Dutch classification system and dichotomized into low (score 1–5, up to completed secondary education) and high (score 6–7, completed secondary professional education, university or higher).[34] Comorbidity was assessed using the Cumulative Illness Rating Scale (Range 0–52, a higher score indicates more comorbidities).[35] The living situation was divided into living with a partner and living without a partner.

Stroke characteristics

Stroke characteristics obtained from medical records included type, location, the severity of stroke symptoms, and discharge destination. The severity of symptoms was measured within four days after stroke with the National Institutes of Health Stroke Scale (NIHSS, range 0–42) and was divided into (1) no stroke symptoms (0 points), (2) minor stroke symptoms (1–4 points); and (3) moderate to severe stroke symptoms (≥ 5 points).[36] Discharge destination after hospitalization was categorized into home or inpatient rehabilitation.

Physical functioning

Physical functioning at discharge from inpatient care was measured with the physical domain of the Stroke Impact Scale 3.0 (SIS Physical) and the Five Meter Walk Test (5MWT). The SIS Physical consists of ten questions regarding ADL, eight regarding mobility, and five regarding hand function.[31] Scores range from 0–100, and lower scores indicate lower levels of physical functioning. Walking speed was measured with the 5MWT.[37] Participants were asked to perform this test three times. The mean test time was calculated. A higher score on the 5MWT reflects a lower walking speed.

Psychological and cognitive factors

Cognitive functioning after stroke was assessed with the Montreal Cognitive Assessment (MoCA). Scores range from 0–30 (< 26 indicates impaired cognitive function), and higher scores indicate better cognitive functioning.[38] The Hospital Anxiety and Depression Scale (HADS) was used to assess the presence of symptoms of anxiety or depression. The HADS consists of 14 items, divided into seven items about anxiety (HADS-A) and seven items about depression (HADS-D). Both the HADS-A and HADS-D scores range from 0–21; scores ≥ 8 indicate the presence of symptoms of anxiety and depression respectively.[39] Self-efficacy was evaluated with the Self-Efficacy for Symptom Management Scale (SEsx) which consists of 13 items. Scores range from 13–130, and scores < 115 indicate low/moderate self-efficacy.[40]

Statistical analysis

All analyses were conducted with IBM SPSS statistics version 26 (IBM Corp., Armonk, NY). To describe the patients' characteristics and independent variables, descriptive statistics were used. Missing data were considered missing at random because data were more often missing for female participants. For that reason, multiple imputation using Multivariate Imputation by Chained Equation was used.[41] Multiple imputation was performed by fitting models to predict missing outcomes based on all other observed variables. Five imputed data sets were created and combined with a pooled set using Rubin's rules.[42]

Generalized estimating equations (GEE) were performed to explore the relationship between movement behavior patterns and participation over time. An exchangeable correlation structure was used to correct for within-subject correlations.[43] SIS Participation (measured at discharge, at six months and at one year) was entered as a dependent variable and time as a categorical within-subject variable.

By adding age, sex, stroke severity (NIHSS), discharge destination, cognitive functioning (MoCA), anxiety symptoms (HADS-A), depressive symptoms (HADS-D) and self-efficacy (SEsx) to the model, potential confounding variables were identified. A variable was considered to be a confounder if the coefficient of the movement behavior patterns changed more than 10% after adding the variable to the model. If not, the variable was left out of the analyses. Results are expressed as regression coefficients (β) with 95% confidence intervals (CI). A positive score implies an improvement in SIS Participation scores compared to the reference category with β units, containing both within-subject as between-subject effects. P-values of < 0.05 were considered statistically significant. To answer both research questions, two GEE models were performed.

In the first model, the course of participation over time for each movement behavior pattern at baseline was explored. Therefore, movement behavior patterns at baseline (measured directly after discharge to the home setting) were entered as independent factor. As a non-linear recovery pattern of participation over time was expected,[5] time was added to the model as a categorical variable, modelling each time interval separately. Interaction terms between time and movement behavior patterns at discharge were added to the model to explore the course of participation over time for each movement behavior pattern at discharge.

In the second model, the longitudinal association between the development of movement behavior patterns over time and participation was explored. Therefore, the development of movement behavior patterns over time (measured at discharge, six months and one year) were entered as independent factor, and differences between the movement behavior patterns were calculated.

RESULTS

In total, 262 people from the stroke-unit agreed to participate in the study. A total of 200 people were included in the study at discharge from inpatient care, of whom 184 (92%) participated after six months and 175 (88%) after one year (flowchart and reasons for refusal are presented in Figure 8.1).[24]

The participants' characteristics at baseline are presented in Table 8.1.[24] The mean age at stroke onset was 67.8 years, 64.0% was male and 91.5% had an ischemic stroke. The majority of the participants experienced no or minor stroke symptoms (68.5%) and were discharged home after hospitalization (73.5%). A total of 44 people (22%) were classified as sedentary exercisers, 90 people (45%) were classified as sedentary movers, and 66 people (33%) were classified as sedentary prolongers directly after discharge to the home setting (Figure 8.2). Sedentary exercisers were younger, had less comorbidities, better physical functioning and higher walking speed compared to the sedentary movers and sedentary prolongers. Sedentary exercisers had higher levels of self-efficacy compared to the sedentary prolongers. The composition of the movement behavior patterns remained relatively stable over time (Figure 8.2).

The course of participation over time across the movement behavior patterns

All movement behavior patterns showed significant improvement in the first six months after discharge to the home setting (Table 8.2), adjusted for the confounding effects of age,

sex, stroke severity (NIHSS), anxiety symptoms (HADS-A) and discharge destination. Between six months and one year, a non-significant decline in participation was observed in all movement behavior groups, most distinctive in the sedentary prolongers (Figure 8.2). Overall, only the sedentary movers showed significant improvement over time in the first year after discharge to the home setting.

Table 8.1: Baseline characteristics

	Total group (n = 200)	Sedentary exercisers (n = 44)	Sedentary movers (n = 90)	Sedentary prolongers (n = 66)
Demographic characteristics				
Age, years	67.8 ± 11.2	62.6 ± 11.2	69.2 ± 11.6[a]	69.3 ± 10.8[c]
Sex, male	64.0	79.5	56.7[a]	63.6
High education level	29.8	43.2	23.3	28.8
Comorbidities (CIRS)	3.2 ± 2.8	2.1 ± 2.5	3.5 ± 2.8[a]	3.4 ± 2.8[c]
Living together with partner	76.3	72.7	72.2	83.3
Stroke characteristics				
Ischemic stroke	91.5	93.2	90.0	92.4
Side of stroke, left	53.5	56.8	48.8	57.6
Stroke severity (NIHSS)	4.0 ± 4.0	3.8 ± 3.9	3.6 ± 3.5	4.7 ± 4.7
No symptoms (NIHSS 0)	13.0	13.6	14.4	10.6
Minor symptoms (NIHSS 1–4)	55.5	54.5	57.8	53.0
Moderate/severe symptoms (NIHSS ≥ 5)	31.5	31.8	27.7	36.4
Discharge destination, home	73.5	79.5	75.6	66.7
Physical functioning & movement behavior				
SIS Physical	83.9 ± 17.3	94.3 ± 6.8	82.9 ± 16.8[a]	78.4 ± 19.9[c]
Walking speed (5MWT in seconds)	6.0 ± 3.7	4.5 ± 0.7	6.1 ± 3.3[a]	7.2 ± 4.8[c]
Sedentary time (hours)	9.3 ± 1.8	9.0 ± 1.6	8.4 ± 1.5	10.6 ± 1.4[b,c]
LPA (hours)	3.8 ± 1.5	3.8 ± 1.2	4.6 ± 1.5[a]	2.8 ± 0.8[b,c]
MVPA (hours)	0.6 ± 0.5	1.3 ± 0.4	0.4 ± 0.3[a]	0.4 ± 0.3[c]
Psychological and cognitive factors				
Impaired cognition (MoCA ≤ 25)	59.0	61.4	58.9	57.6
Symptoms of depression (HADS-D ≥ 8)	26.5	22.7	30.0	24.2
Symptoms of anxiety (HADS-A ≥ 8)	27.0	34.1	28.9	19.7
Self-efficacy (SEsx)	92.9 ± 22.0	98.3 ± 20.6	92.9 ± 23.1	89.4 ± 21.0[c]

Values are percentages or mean ± SD.
Abbreviations: 5MWT, Five Minute Walk Test; CIRS, Cumulative Illness Rating Scale; HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale; LPA, light physical activity; MoCA, Montreal Cognitive Assessment; MVPA, moderate-vigorous physical activity; NIHSS, National Institutes of Health Stroke Scale; SEsx, Self-Efficacy for Symptom Management Scale.
[a] Statistically significant differences ($p < 0.05$) between sedentary exercisers and sedentary movers.
[b] Statistically significant differences ($p < 0.05$) between sedentary movers and sedentary prolongers.
[c] Statistically significant differences ($p < 0.05$) between sedentary exercisers and sedentary prolongers.

Sedentary exercisers had better participation outcomes compared to the sedentary movers and sedentary prolongers at discharge (p = 0.006 and p = 0.003, respectively) and at six months (p = 0.036 and p = 0.003, respectively), but at one year, the differences between sedentary exercisers and sedentary movers were no longer statistically significant. Sedentary prolongers had the most unfavorable course of participation up to one year after stroke (Figure 8.3), as they had the worst participation scores at all time points.

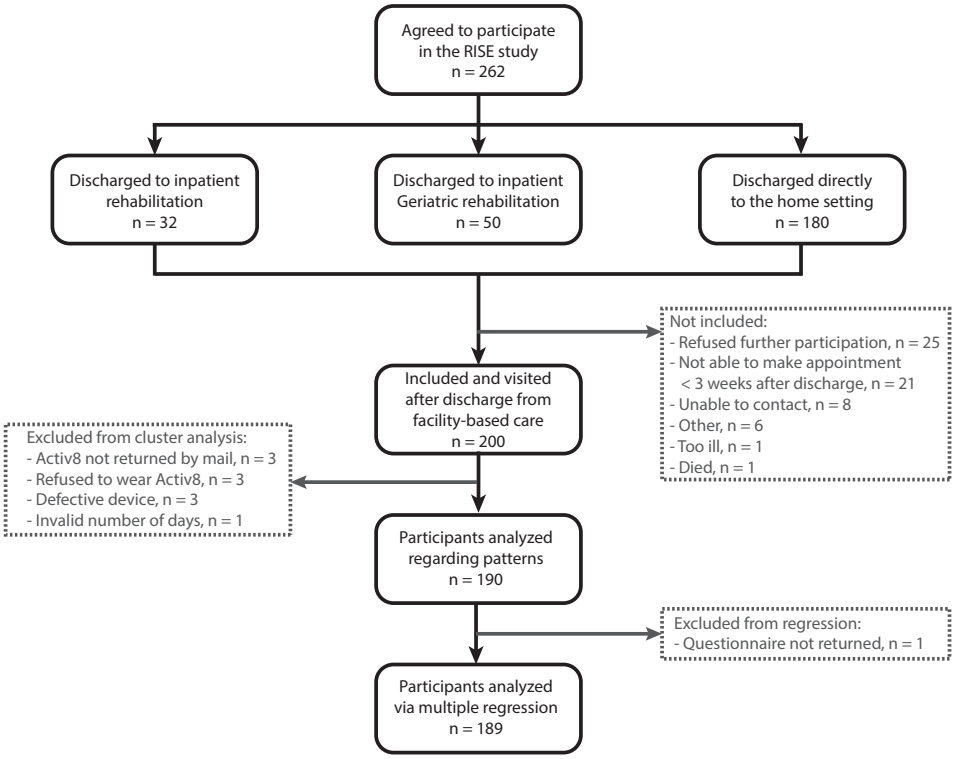

Figure 8.1: RISE study flowchart.[23]

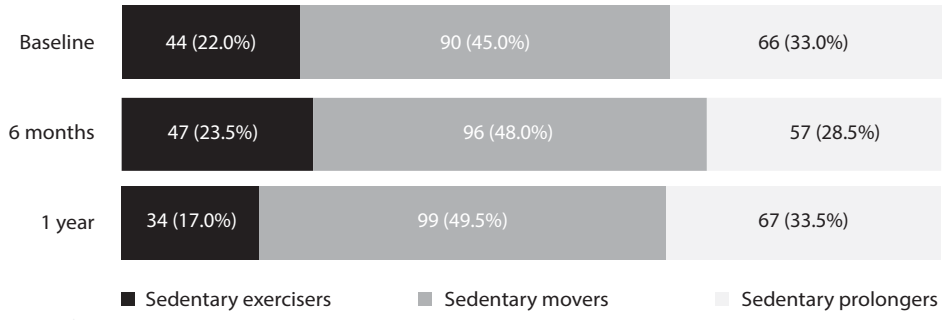

Figure 8.2: Distribution movement behavior pattern groups at baseline, 6 months and 1 year (n = 200).

Table 8.2: Changes in SIS Participation during the first year after discharge across different movement behavior patterns identified directly after discharge to the home setting

Time interval after stroke	Sedentary exercisers		Sedentary movers		Sedentary prolongers	
	β (95% CI)	SE	β (95% CI)	SE	β (95% CI)	SE
Discharge–6 months	5.54 (1.20–9.89)*	2.22	8.65 (5.09–12.21)*	1.82	6.81 (2.96–10.66)*	1.96
6 months–1 year	-1.36 (-4.87–2.16)	1.80	-0.42 (-2.78–1.95)	1.21	-2.53 (-5.40–0.34)	1.47
Discharge–1 year	4.19 (-0.87–9.24)	2.58	8.23 (4.38–12.07)*	1.96	4.28 (-0.24–8.80)	2.31

Abbreviations: β, regression coefficient for the effect of time; CI, confidence interval; SE, standard error; SIS Participation, Stroke impact scale 3.0 Participation domain.
Outcomes are adjusted for the confounding effects of stroke severity (NIHSS), age, sex, symptoms of anxiety (HADS-A) and discharge destination after hospitalization.
Note: a positive regression coefficient (β) implies an improvement in SIS Participation in the cited time interval with β units.
* $p < 0.05$.

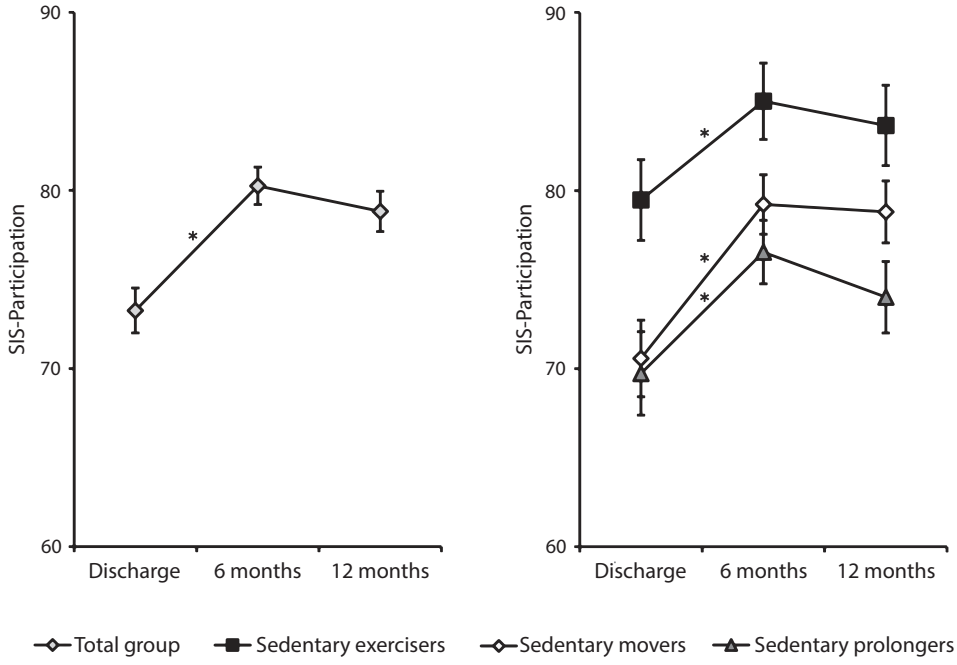

Figure 8.3: The modelled course of participation during the first year after discharge to the home setting in people with a first-ever stroke per movement behavior pattern at baseline.
Abbreviations: SIS Participation, Stroke Impact Scale 3.0 Participation domain.
Outcomes are adjusted for the confounding effects of stroke severity (NIHSS), age, sex, symptoms of anxiety (HADS-A) and discharge destination after hospitalization.
Note: higher SIS Participation scores indicate better participation outcome. The error bars represent the standard error (SE).
* $p < 0.05$, comparing mean SIS Participation scores between consecutive time points.

The longitudinal association between movement behavior patterns and participation

Sedentary prolongers were associated with worse participation compared to sedentary exercisers, adjusted for the confounding effects of age, sex, stroke severity (NIHSS), anxiety symptoms (HADS-A) and discharge destination (Table 8.3). No association was found between sedentary exercisers and sedentary movers, and between sedentary exercisers and sedentary movers.

Table 8.3: The longitudinal association between the course of SIS Participation and the development of movement behavior patterns over time

	Course of SIS Participation over time	
Movement behavior patterns	β (95% CI)	SE
Sedentary exerciser[a] vs. sedentary mover[b]	2.65 (-0.69–6.00)	1.71
Sedentary exerciser[a] vs. sedentary prolonger[b]	4.30 (0.39–8.20)*	1.99
Sedentary mover[a] vs. sedentary prolonger[b]	1.64 (-1.72–5.01)	1.72

Abbreviations: β, regression coefficient for the effect of time; CI, confidence interval; SE, standard error; SIS Participation, Stroke impact scale 3.0 Participation domain.
Outcomes are adjusted for the confounding effects of stroke severity (NIHSS), age, sex, symptoms of anxiety (HADS-A) and discharge destination after hospitalization.
Note: a positive regression coefficient (β) implies an improvement in SIS Participation on average over time in the cited category ([a]) compared to the reference category ([b]) with β units (including both within-persons as between-persons effects).
* $p < 0.05$.

DISCUSSION

In this prospective cohort study, we showed that the course of participation over time differed based on distinct movement behavior patterns identified directly after discharge to the home setting. Sedentary prolongers, being inactive and highly sedentary, experienced the most restrictions in participation over time. Furthermore, a longitudinal association between the participation and the development of movement behavior patterns over time was observed after stroke, showing worse participation in sedentary prolongers compared to sedentary exercisers. These results show that supporting people with stroke to adapt and maintain a healthy movement behavior after discharge to the home setting could prevent potential long-term restrictions in participation.

The course of participation over time across the movement behavior patterns

Our results showed that participation improved in the first six months after stroke and stabilized from six months onwards, which is in accordance with previous literature on

the course of participation over time.[5] Similar recovery patterns of participation were observed across the different movement behavior patterns, but baseline and long-term levels of participation differed. At discharge to the home setting, both sedentary prolongers and sedentary movers were already experiencing worse participation outcome compared to sedentary exercisers. However, the sedentary movers were able to catch up with the sedentary exercisers at one year after discharge, whereas the sedentary prolongers were never able to close this gap and still experienced considerably worse participation one year after discharge compared to the sedentary exercisers. A comparison between the recovery patterns of physical functioning (using the SIS Physical) across movement behavior patterns yielded somewhat similar results: after initial improvement in physical functioning in the first six months, sedentary prolongers were at risk for decline in physical functioning from six months onwards.[24]

Although no minimal clinically important difference has been defined for the SIS Participation in current literature, the difference between sedentary exercisers and sedentary prolongers at one year (10 points) seems clinically meaningful.[44] Among all SIS domains, the SIS Participation has been identified as the SIS domain showing the most clinically meaningful changes between three months and one year after stroke in a similar Swedish stroke cohort, as many people experienced either improvement or deterioration in participation within this time period.[45] More improvement in SIS Participation over time was observed in our study, resulting in slightly higher SIS Participation scores at one year after stroke in our study compared to the Swedish cohort (78.8 versus 70.3).[45]

The longitudinal association between movement behavior patterns and participation

To the best of our knowledge, this is the first study exploring the longitudinal association between the development of movement behavior patterns over time and participation after stroke. Similarly to our study, a Canadian study exploring the longitudinal effect of a home-based sedentary behavior change intervention in 34 people with stroke after discharge from inpatient rehabilitation, found improvement in SIS Participation in the first 16 weeks after discharge to the home setting.[46] Also, a Chinese prospective cohort study in first-ever ischemic stroke patients reported about the longitudinal relation between quality of life (measured with the 12-item Short-Form Health Survey) and exercise frequency and exercise time up to two years after stroke onset.[47] They concluded that irregular exercisers had an unfavorable course of quality of life over time compared to regular exercisers after stroke. Although exercise frequency and exercise time were only measured using self-report questionnaires and no other types of movement behavior (such as sedentary behavior or LPA)

were taken into account, these results are in line with the unfavorable course of participation in sedentary prolongers as stated in our study.

Furthermore, our results revealed worse participation in sedentary prolongers versus sedentary exercisers over time. A recent study found that people's movement behavior pattern often deteriorated over time (as for example 9.0% of the sedentary prolongers at one year were actually classified as sedentary exercisers at baseline).[26] Therefore, early identification of sedentary prolongers and prolonged follow-up to prevent a relapsing sedentary and inactive lifestyle are essential. On the other hand, no differences in the course of participation between the development of other movement behavior patterns over time were found in our study. Premorbid movement behavior patterns, the growing contribution of other factors associated with long-term participation and movement behavior over time, such as personal and environmental factors, and the stabilization of participation outcome after six months, may be possible explanations.[48,49]

Future research

As this study identified movement behavior as important determinant of participation after stroke, we also recommend future studies to consider movement behavior as a whole (combining LPA, MVPA and sedentary behavior), instead of focusing on just one aspect of movement behavior. Currently, exercise interventions in stroke rehabilitation are mainly focused on raising MVPA levels, while attention for other essential components of movement behavior such as sedentary behavior and LPA is often lacking.[50] Preliminary results of interventions incorporating sedentary behavior and LPA already yielded promising results in older adults and people with stroke.[46,51] Interventions including tailored counseling towards behavioral change were found to be effective to pursue sustainable long-term change in movement behavior.[52] Therefore, these interventions may also have the potential to promote the course of participation after stroke.

Strengths & limitations

The longitudinal design, the large sample size and the stratification based on the individual's movement behavior patterns are among the main strengths of this study. Furthermore, extensive measurements on the individual's movement behavior took place using accelerometry for 14 days, enabling accurate insights into habitual movement behavior of the participants over time. Last but not least, our results were highly robust due to the statistical technique used for the longitudinal data analysis (GEE), which took into account that the

repeated observations within one subject are not independent and allowed adjustment for confounding effects in the analyses.

Although participants were directly recruited from the stroke-units to enable an accurate representation of the general stroke population, the study population largely consisted of relatively mild stroke patients with mostly ischemic strokes. This could negatively affect the generalizability of the results to more severely affected stroke patients and those with hemorrhagic strokes. Furthermore, causality between movement behavior and participation could not be proven with our study design, as an association does not imply causation. Therefore, whether or not participation could be modified by improving movement behavior is not entirely certain.

CONCLUSIONS

In conclusion, this study shows that the course of participation in people with a first-ever stroke up to one year after discharge to the home setting differed based on three distinct movement behavior patterns, i.e. sedentary exercisers, sedentary movers and sedentary prolongers. Early identification of highly sedentary and inactive people with stroke after discharge to the home setting is important, as sedentary prolongers are associated with an unfavorable course of participation compared to sedentary exercisers over time. To unravel the potential of movement behavior as modifiable factor to improve participation after stroke, more research about the effectiveness of tailored interventions targeting movement behavioral change on long-term participation is needed.

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Chapter 9

Participation in daily life activities at two months after stroke predicts long-term health-related quality of life

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Abstract

Background: After stroke, many patients experience problems with participation in daily activities. Improving participation is the main goal in stroke rehabilitation. However, the longitudinal relationship between participation and health-related quality of life (HRQoL) remains unclear.

Objectives: This study aimed to examine (1) the predictive value of participation at two months on long-term HRQoL and (2) the longitudinal relationship between participation and HRQoL.

Methods: In this multicenter, prospective cohort study, patients were assessed at two and 12 months after stroke. Participation was measured with the Restriction subscale of the Utrecht Scale for Evaluation of Rehabilitation – Participation. HRQoL was assessed with the three-level version of the EuroQoL five dimensions questionnaire index score.

Results: This study included 291 patients. Mean age was 66.6 ± 12.4 years, 64.3% were male and mean National Institutes of Health Stroke Scale (NIHSS) was 2.5 ± 2.9. Multivariable linear regression, adjusted for demographic characteristics, stroke characteristics, physical and cognitive impairment, showed that a higher level of participation at two months correlated with a higher HRQoL at one year (B = 0.004; 95% CI = 0.002–0.005). Patients whose participation improved had a greater increase in HRQoL, compared to patients without improvement (0.080 ± 0.21 versus -0.054 ± 0.21; $p < 0.001$).

Conclusions: The level of participation at two months post-stroke predicts HRQoL at one year. Improvement in participation during the first year after stroke is associated with improvement in HRQoL. We recommend including the assessment of participation in daily activities at follow-up visits.

INTRODUCTION

The global burden of stroke is high: studies have estimated a prevalence of more than 80 million stroke survivors worldwide in 2016.[1] A substantial proportion of patients with stroke suffer from impairments, such as physical disability, cognitive problems and emotional complaints.[1-3]

Participation is defined as a person's "involvement in a life situation", including daily activities and social roles.[4] After stroke, large numbers of patients experience restrictions of participation, for example in household activities, social activities and return to work.[5, 6] While the level of participation tends to improve over time, restrictions might persist in the long term: many patients report participation restrictions at five years after stroke.[7-9] Participation restrictions are associated with symptoms of depression, cognitive problems, immobility and activity limitations.[10] In addition, a lower level of participation restrictions is associated with environmental factors such as the amount of social support, being in a relationship or not, and access to appropriate health and social services.[11]

In clinical practice, participation restrictions after stroke are illustrative of the consequences of stroke on a patient's daily functioning. Improving a patient's level of participation is the main goal of stroke rehabilitation.[12] Therefore, the assessment of participation restrictions facilitates referral for rehabilitation treatment based on patient-centered needs.[12-14]

The relevance of assessing participation in stroke care could be even greater if participation early after stroke predicts long-term health-related quality of life (HRQoL), and if an improvement in participation correlates with an improvement in HRQoL. Multiple studies have examined the cross-sectional association between participation and HRQoL at various time points.[15] Most of these studies demonstrated that participation and HRQoL are related, but not all findings were consistent, as the magnitude of the correlations ranged from "no association" to a "strong association".[15,16] While most studies examined the association in a cross-sectional manner, only one previous study showed that early participation is independently associated with longitudinal HRQoL and concluded that participation is a modifiable predictor of HRQoL.[17] There have been no studies to examine if an improvement in the level of participation leads to an improvement in HRQoL.

The aims of this study were to examine (1) the predictive value of participation restrictions two months after stroke for HRQoL one year after stroke and (2) the longitudinal relationship between participation and HRQoL after stroke. Our hypotheses were that (1) the presence of participation restrictions at two months post-stroke would predict a lower HRQoL one

year post-stroke and (2) that participants who showed improvement in participation in the first year after stroke would show greater improvements in HRQoL compared to those who did not show improvement in participation.

METHODS

Design and procedure

The current study is part of a multicenter, prospective, longitudinal cohort study called the Restore4stroke Cohort. This cohort study has been conducted in six general hospitals in the Netherlands and included 395 patients between March 2011 and March 2013.[18] The study complies with the Declaration of Helsinki and was approved by the Committee on Research involving Human Subjects of the St. Antonius Hospital in Nieuwegein in the Netherlands (R10.41A, February 2011) and by the medical ethics committees of all participating hospitals. Written informed consent was obtained from all participating patients.

In the Restore4stroke Cohort, patients were assessed at five follow-up moments from stroke onset up to 24 months after stroke. Data obtained within the first week after stroke (T1), two months after stroke (T2) and one year after stroke (T3) were used for the current paper. If patients met the eligibility criteria and provided written informed consent, research nurses extracted demographic and medical information from the medical charts at T1. Data at T2 were obtained by a trained research assistant. The data at T3 were collected by means of questionnaires that were completed by the patients on paper or online. The protocol of the Restore4stroke Cohort has been described in more detail elsewhere.[18] The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants

Patients were considered eligible when a clinical diagnosis of stroke (either ischemic or hemorrhagic) had been established in the past seven days, as confirmed by a neurologist. The following exclusion criteria were applied: (1) comorbidity interfering with the study outcomes, (2) dependence in activities of daily living before the stroke, as defined by a Barthel Index (BI) score of 17 or lower, (3) insufficient command of the Dutch language, based on clinical judgement, and (4) cognitive decline before stroke as defined by a score of one or higher on the Heteroanamnesis List Cognition.[19]

Patients from the Restore4stroke Cohort were included in the current study if the following measurements had been completed at T2 and T3: the Restriction subscale of the Utrecht Scale for Evaluation of Rehabilitation – Participation (USER-P-R) and the three-level version of the EuroQoL five dimensions questionnaire (EQ-5D-3L).

Measures

Demographics and stroke characteristics

At T1, the following demographic characteristics were recorded: sex, age, marital status and level of education. Recorded stroke characteristics included type of stroke and stroke severity. Stroke severity was measured with the National Institutes of Health Stroke Scale (NIHSS). The NIHSS ranges from 0–42 and a higher score indicates greater severity.[20] The BI was used to measure functional independence in activities of daily living. The BI ranges from 0–20; a higher score reflects greater independence in activities of daily living.[21]

At T2, cognitive functioning after stroke was assessed with the Montreal Cognitive Assessment (MoCA). The MoCA includes ten items with a total score ranging from 0–30, and a higher score indicates better cognitive functioning.[22] Besides, comorbidities were assessed at T2 with the sum score of the Cumulative Illness Rating Scale (CIRS). The CIRS ranges from 0–52 and a higher score reflects more and/or more severe comorbidities.[23]

Participation

At T2 and T3, participation was measured with the USER-P-R instrument. The USER-P-R instrument was chosen because it is validated to measure the concept of participation in patients rehabilitating after stroke and demonstrated to have a good responsiveness compared to other instruments.[24,25] The USER-P-R examines if a total of 11 subdomains of participation (e.g. "work", "household activities" or "relationship") can be performed "independently without difficulty", "with difficulty", "with assistance" or "cannot be performed". The USER-P-R compares the current situation with the situation before the stroke for each subdomain. The sum of the items is converted to a 0–100 scale, with a higher score being indicative of fewer restrictions, so a higher level of participation.[24-26]

Health-related quality of life (HRQoL)

At T2 and T3, HRQoL was measured with the EQ-5D-3L. The EQ-5D-3L consists of five items, viz. "mobility", "self-care", "usual activities", "pain or discomfort" and "anxiety or depression". Each item has three levels: "no problems", "some problems" and "extreme

problems". An index score of the EQ-5D-3L was obtained using the index score calculator. The index score ranges from -0.329 to 1.000 in Dutch normative populations.[27] A lower index score reflects more problems, so a lower HRQoL.[27, 28]

Statistical analysis

All patients from the Restore4stroke Cohort who were excluded from the analyses of this paper were compared with the included patients with regard to demographics, stroke characteristics, comorbidities and data on the MoCA, USER-P-R and EQ-5D-3L index score at T2.

Demographic and stroke characteristics were analyzed using descriptive statistics. Marital status was recorded as being married or not being married. Educational level was dichotomized into "low" (≤ 5) versus "high" (≥ 6; i.e. having completed higher professional education or university), based on the Dutch classification system developed by Verhage.[29] Stroke type was divided into ischemic and hemorrhagic stroke. Length of hospital admission due to stroke was recorded in days. USER-P-R sum scores at T2 and T3, and EQ-5D-3L index scores at T2 and T3 were analyzed using descriptive statistics.

The association between the predictor of interest, i.e. the USER-P-R at T2, and the dependent variable, the EQ-5D-3L index score at T3, was examined using bivariate linear regression. Bivariate linear regression was also performed for the following covariates: sex, age at stroke, marital status, educational level, type of stroke, NIHSS, BI, length of hospital stay and MoCA score. If the predictor of interest was significantly associated with the dependent variable, a multivariable model was constructed, which was adjusted for the aforementioned covariates. The assumptions of linearity, homoscedasticity, multicollinearity, and normally distributed errors were checked.

Next, the change in the EQ-5D-3L index scores at T2 and T3 was computed by subtracting scores at T2 from the scores at T3, resulting in a delta (Δ) EQ-5D-3L index score. A Δ USER-P-R score was computed accordingly. A Pearson correlation coefficient was calculated to explore the relationship between Δ EQ-5D-3L index scores and Δ USER-P-R scores. Furthermore, the cohort was divided into two groups: patients with an improvement in USER-P-R scores, i.e. an improvement in participation, and patients without improvement in USER-P-R scores, i.e. a decline or no change in participation between T2 and T3. Patients with a maximum USER-P-R score (100) at T2 were excluded from this analysis, because their score could not improve any further. Since the Δ EQ-5D-3L index sores were not normally distributed, the differences between patients with improvement in participation

versus no improvement in participation were analyzed for statistical significance using a Mann-Whitney U test.

A p-value of 0.05 was used to determine statistical significance. IBM SPSS version 25.0 was used for analyses.

RESULTS

A total of 395 patients were included in the original Restore4stroke Cohort study. Of these, 104 patients (26.3%) were excluded from the current study based on missing data at T2 or T3. Patients dropped out because of the following reasons: 11 patients (2.8%) had died, 28 patients (7.1%) refused further participation, 7 patients (1.8%) were lost to follow-up and 58 patients (14.7%) did not complete the USER-P-R and/or EQ-5D-3L at T2 or T3. This resulted in 291 patients (73.7%) being included in the current analyses. Baseline data for included and excluded patients are presented in Table 9.1. The mean age of the included patients was 66.6 ± 12.4 years, and 64.3% were male.

Table 9.2 shows the results of the bivariate and multivariable linear regression. Bivariate linear regression demonstrated that a higher USER-P-R score at T2 was associated with a

Table 9.1: Baseline characteristics

	Included patients (n = 291)	Excluded patients (n = 104)	P-value
Sex (% male)	64.3	66.3	0.722
Age in years (mean ± SD)	66.6 ± 12.4	70.0 ± 13.2	0.766
Marital status (% married)	69.8	65.4	0.460
High education level (%)	27.1	24.7	0.688
Ischemic stroke (%)	92.4	95.2	0.578
First stroke (%)	86.3	93.3	0.251
NIHSS (mean ± SD)	2.5 ± 2.9	3.6 ± 3.7	0.005*
BI (mean ± SD)	17.2 ± 4.4	15.8 ± 5.6	0.047*
Length of hospital stay in days (mean ± SD)	8.1 ± 5.4	10.4 ± 13.2	0.002*
MoCA at 2 months (mean ± SD)	23.7 ± 3.7	22.6 ± 5.1[†]	0.213
USER-P-R at 2 months (mean ± SD)	72.2 ± 22.6	77.7 ± 20.3[‡]	0.125
EQ-5D-3L index score at 2 months (mean ± SD)	0.74 ± 0.22	0.72 ± 0.25[§]	0.810

BI indicates Barthel Index; EQ-5D-3L, three-level version of the EuroQoL Five Dimensions; MoCA, Montreal Cognitive Assessment; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; USER-P-R, the Restriction subscale of the Utrecht Scale for Evaluation of Rehabilitation – Participation.
[†] n = 58; [‡] n = 52; [§] n = 52.
* $p < 0.05$.

Table 9.2: Linear regression: effects of participation at two months on HRQoL at one year after stroke

		HRQoL measured by EQ-5D-3L at one year post-stroke							
		Bivariate analyses				Multivariable analysis†			
	Reference	B (95% CI)	SE	β	P-value	B (95% CI)	SE	β	P-value
Sex	Male	-0.049 (-0.101–0.004)	0.027	-0.107	0.068	-0.031 (-0.082–0.019)	0.025	-0.069	0.218
Age in years		0.003 (-0.005–0.000)	0.001	-0.143	0.015*	-0.001 (-0.003–0.001)	0.001	-0.077	0.188
Marital status	Not married	0.016 (-0.039–0.071)	0.028	0.033	0.576	-0.065 (-0.119–-0.011)	0.027	-0.137	0.018*
Education level	Low education	0.028 (-0.029–0.085)	0.029	0.057	0.330	-0.007 (-0.058–0.045)	0.026	-0.013	0.8015
Type of stroke	Ischemic	0.049 (-0.040–0.139)	0.045	0.064	0.278	0.064 (-0.014–0.142)	0.040	0.082	0.109
NIHSS		-0.016 (-0.024–-0.008)	0.004	-0.222	< 0.001*	0.001 (-0.008–0.010)	0.005	0.016	0.799
BI		0.019 (0.014–0.024)	0.0003	0.386	< 0.001*	0.012 (0.005–0.019)	0.003	0.246	0.001*
Length of hospital stay		-0.007 (-0.012–-0.003)	0.002	-0.182	0.002*	0.000 (-0.004–0.005)	0.002	0.005	0.936
MoCA		0.009 (0.002–0.016)	0.003	0.152	0.010*	0.002 (-0.005–0.009)	0.003	0.032	0.580
USER-P-R		0.004 (0.003–0.005)	0.001	0.462	< 0.001*	0.004 (0.002–0.005)	0.001	0.373	< 0.001*

B indicates unstandardized beta; β indicates standardized beta; BI, Barthel Index; CI, Confidence Interval; EQ-5D-3L, three-level version of the EuroQoL Five Dimensions; MoCA, Montreal Cognitive Assessment; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; SE, standard error; USER-P-R, Restriction subscale of the Utrecht Scale for Evaluation of Rehabilitation – Participation.

† Adjusted for sex, age at stroke, marital status, educational level, type of stroke, National Institutes of Health Stroke Scale (NIHSS), Barthel Index (BI), length of hospital stay in days and Montreal Cognitive Assessment (MoCA).

* $p < 0.05$.

significantly higher EQ-5D-3L index score at T3 (unstandardized beta (B) = 0.004; 95% confidence interval (95% CI) = 0.003–0.005). With regard to the covariates, lower age, lower NIHSS, higher BI and higher MoCA were associated with significantly higher EQ-5D-3L index scores in the bivariate linear regression. Multivariable linear regression demonstrated that a higher USER-P-R score at T2 remained significantly associated with a higher EQ-5D-3L index score at T3 (B = 0.004; 95% CI = 0.002–0.005), after adjustment for sex, age, marital status, educational level, type of stroke, NIHSS, BI, length of hospital stay and MoCA score. With regard to the covariates, marital status and the BI remained associated with a better EQ-5D-3L index score at T3 in the multivariable linear regression analysis. Other covariates were not associated with EQ-5D-3L at T3 in the multivariable model.

Next, the study sample was divided into patients showing improvement in participation between T2 and T3 (n = 174; 59.8%) and those not showing improvement in participation (n = 63; 21.6%). Patients with a maximum USER-P-R score at T2 were excluded from the subsequent analysis (n = 54; 18.6%). Table 9.3 displays the mean and delta scores of the USER-P-R and EQ-5D-3L index scores for the two groups. At T2, the EQ-5D-3L index scores were comparable for both groups. Patients showing improvement in participation between T2 and T3 had a significantly higher EQ-5D-3L index score at T3 (0.77 ± 0.20 versus 0.66 ± 0.25; p = 0.001) and a significantly higher Δ EQ-5D-3L index score (0.080 ± 0.21 versus -0.054 ± 0.16; p < 0.001) compared to patients without improvement in participation. The Δ EQ-5D-3L index score was significantly correlated with the Δ USER-P-R score (r = 0.379; p < 0.001).

Table 9.3: Changes over time in USER-P-R and EQ-5D-3L index scores

	No improvement in USER-P-R (n = 63)†	Improvement in USER-P-R (n = 174)†	P-value
USER-P-R at 2 months	74.6 ± 16.1	62.7 ± 20.7	< 0.001*
USER-P-R at 12 months	63.1 ± 18.3	82.3 ± 17.6	< 0.001*
Δ USER-P-R‡	-11.5 ± 9.6	19.5 ± 14.1	< 0.001*
EQ-5D-3L index score at 2 months	0.71 ± 0.22	0.69 ± 0.21	0.559
EQ-5D-3L index score at 12 months	0.66 ± 0.25	0.77 ± 0.20	0.001*
Δ EQ-5D-3L index score ‡	-0.054 ± 0.16	0.080 ± 0.21	< 0.001*

EQ-5D-3L indicates three-level version of the EuroQoL Five Dimensions; USER-P-R, the Restriction subscale of the Utrecht Scale for Evaluation of Rehabilitation – Participation.
† Patients with a maximum score (100) on the USER-P-R at two months were excluded.
‡ Difference in USER-P-R or EQ-5D-3L scores between two months and 12 months.
* p < 0.05.

DISCUSSION

This study demonstrated that a higher level of participation at two months after stroke predicted a higher HRQoL at one year. Besides, we showed that if participation improved during the first year after stroke, HRQoL increased as well.

Our findings are in line with previous studies that have shown that a higher level of participation after stroke is associated with a higher HRQoL.[15-17] While the vast majority of previous studies examined this relationship in a cross-sectional manner, one longitudinal cohort study (n = 134) found that a higher level of participation was associated with a higher HRQoL after stroke.[17] Our study reaffirms this longitudinal relationship in a larger cohort, and adds to this knowledge that an increase in participation is associated with an increase in HRQoL and that no (further) improvement in HRQoL occurred without such an improvement of participation.

Participation can be defined as a person's "involvement in a life situation"; participation is what a person does in real life, with or without a health condition, and is influenced by personal and environmental factors.[30] HRQoL can be defined as "those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment".[31] Logically speaking, both characteristics are likely to be negatively impacted by stroke and its possible physical, cognitive, emotional, and social consequences. Therefore, it is not surprising to find a relationship between participation and HRQoL. However, as little research has been conducted examining participation as a determinant of HRQoL after stroke, our study provides additional insights into this relationship. Moreover, since the instruments that measure the level of participation and HRQoL are used differently, it is relevant to determined their longitudinal relationship. Currently, HRQoL assessment is widely used and has grown to be an important patient-reported outcome measure in medical research.[32] Since the assessment of participation is used to evaluate outcomes as well, it also plays a pivotal role in clinical decision-making in stroke care. The assessment of participation, as a diagnostic instrument, facilitates the assessment of a patient's needs in terms of rehabilitation treatment. Besides, the goal of rehabilitation after stroke is not only to stimulate functional recovery but also, or even more so, to improve the level of participation.[12] Since the assessment of participation has an essential role in clinical stroke rehabilitation, it is important to know that participation, and its improvement, predicts a widely accepted outcome parameter such as HRQoL.

According to the International Classification of Functioning, Disability and Health model, a health condition (e.g. stroke) can lead to disability at the following three levels: (1)

impairments (e.g. paralysis or cognitive impairment), (2) activity limitations (e.g. having trouble walking) and (3) participation restrictions (e.g. not being able to return to work).[4] Our study showed that activity limitations (measured with the BI) and patient-reported participation restrictions (measured with the USER-P-R) are significantly associated with a lower HRQoL in multivariable analysis. Remarkably, measurements of impairment (with the NIHSS and MoCA) were related to HRQoL in bivariate analysis, but not in multivariable analysis. Previous systematic reviews, in other fields of neurology, showed comparable results among patients with spinal cord injury and Parkinson's disease.[33, 34] This suggests that it is not the severity of the disease nor the physical or cognitive impairment itself, but the impact of impairment on a person's daily functioning, that determines HRQoL.

Our findings underline guideline recommendations to screen all patients with stroke not only for possible impairments, but also for the broader effects of stroke at the level of participation.[35] This recommendation is even more relevant as aggregated evidence shows that approximately half of all patients with stroke report unmet needs with regard to activities and participation.[36] Since rehabilitation interventions seem to improve participation in patients with stroke, the options for rehabilitation services can be discussed if a restriction of participation is found.[8, 13, 37] Moreover, specifying the participation restrictions experienced by a patient in terms of concrete subdomains, such as sports or return to work, helps with patient-centered goal-setting and supports shared decision making for a follow-up plan.[14] Therefore, when patients with stroke are assessed after the acute phase, for example at outpatient clinics after discharge, we recommend evaluating participation comprehensively with validated instruments, such as the USER-P-R. If participation restrictions are found, rehabilitation interventions should be considered and discussed.

The following strengths of our study can be mentioned. First, this was a multicenter, prospective cohort study. Second, a large number of patients completed the long-term follow-up measurements, which made it possible to adjust for multiple variables in a linear regression analysis. Third, as patients were included in hospitals within seven days after stroke, the current cohort describes a general stroke population with varying discharge destinations.

Limitations of the study are the relatively large number of patients with minor stroke and the relatively low number of patients with a hemorrhagic stroke. Moreover, patients excluded from the current analyses had more severe strokes than the included patients. Consequently, the external validity is restricted for patients with severe strokes and patients with hemorrhagic strokes. Also, patients with comorbidity interfering with the study outcomes were excluded in order to minimize the effects of comorbidities on the study outcomes.

This led to a selection bias of previously healthy patients with presumably higher levels of participation and QoL. It is unknown whether this selection substantially influenced the relationship between participation and QoL. Furthermore, a substantial number of patients were excluded from the current analysis based on missing data. Although a comparison between included and excluded patients did not reveal statistically significant differences with regard to the main outcomes, this could have led to bias. Lastly, a previous review showed that the minimal clinically important difference (MCID) for the EQ-5D-3L index score ranged widely, from 0.03 to 0.52, and also showed that the MCID had not been examined in a stroke population. The five-level variant of the EQ-5D index score has been examined in one study among 65 stroke patients, in which the MCID was 0.10.[38] However, whether or not the statistically significant improvement in HRQoL in the current paper is clinically relevant for stroke patients cannot be determined with certainty.[39]

CONCLUSIONS

This multicenter, prospective, cohort study showed that a higher level of participation at two months after stroke independently predicts a higher HRQoL at one year after stroke. In addition, an improvement in participation in the first year after stroke is associated with an improvement in HRQoL. Therefore, we recommend incorporating the assessment and treatment of a patient's restrictions of participation in daily activities at follow-up visits.

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Discussion

Chapter 10

MAIN FINDINGS

Part 1: Measuring participation

The first part of the Thesis focusses on the validation of and comparison between commonly used patient-reported outcome measures in the participation and HRQoL domains after stroke. Measurement properties of the USER-P-R, EQ-5D-5L and PROMIS-10 are discussed, and recommendations are given on the preferred PROM to evaluate participation and HRQoL after stroke depending on the setting and underlying goal. Overall, the results show the additional value of PROMs to evaluate participation and HRQoL post-stroke, providing clinicians with relevant person-centered information on the impact of stroke.

In **Chapter 2**, we examined the internal consistency, convergent validity and discriminant validity of the USER-P-R in community-living individuals three months after stroke. In this cross-sectional multicenter validation study, reasonably good measurement properties of the USER-P-R were found. The USER-P-R appeared to be most suitable for individuals with stroke who have chronic disabilities or experience decreased HRQoL since their stroke. Although the USER-P-R had a slight ceiling effect, a considerable number of stroke patients who were "mildly affected" according to the clinician's judgement, appeared to experience restrictions on USER-P-R items (especially in the productivity and leisure domains). Altogether, the USER-P-R is a valid measurement instrument to monitor participation restrictions in routine outpatient care three months after stroke.

Subsequently, the measurement properties of two promising and commonly used measures to evaluate HRQoL after stroke (the EQ-5D-5L and PROMIS-10) were compared in **Chapter 3**. Both questionnaires proved to be useful instruments to evaluate HRQoL three months after stroke, but the PROMIS-10 provided slightly better overall measurement properties. The PROMIS-10 showed better discriminant ability in less affected individuals with stroke, whereas the EQ-5D-5L showed slightly better discriminant ability in more affected individuals with stroke. This may be partially explained by differences in the type of questions between EQ-5D-5L and PROMIS-10 items. One might argue that the EQ-5D-5L is suitable if detecting "problems" post-stroke is the main goal, whereas the PROMIS-10 is more appropriate if one is interested in screening on "general health" post-stroke.

In **Chapter 4**, we proposed to upgrade the EQ-5D-5L with a cognitive domain, and compared the validity between the EQ-5D-5L with and without an additional cognitive domain (EQ-5D-5L+C) administered three months after stroke. The EQ-5D-5L+C, which included a cognitive domain that is highly significant to stroke patients, showed increased

content validity and good discriminative ability without losing internal consistency. Our findings suggest that it would be beneficial to use the EQ-5D-5L+C to measure HRQoL in stroke patients.

Part 2: Determinants of participation

The second part of this Thesis provides valuable insights into the long term course of participation after stroke and explores the influence of several potential factors on participation, including age-specific predictors, mood, psychological factors, cognitive functioning and movement behavior.

In **Chapter 5**, we compared differences in participation outcomes between individuals with stroke aged under and over 70 years and identified predictors associated with favorable and unfavorable long term participation in both age groups. Individuals with stroke aged over 70 years perceived more restrictions in participation compared to younger individuals one year after stroke, emphasizing the need to pay more attention to individuals with stroke aged over 70 years in stroke aftercare. Also, different predictors for restrictions in participation after one year were found for both age groups, suggesting a different approach to older individuals with stroke regarding maintaining long term participation after stroke compared to young individuals with stroke. In this context, this study highlights the importance of early recognition of anxiety symptoms in individuals aged over 70 years and depression symptoms in individuals aged under 70 years to prevent long-term restrictions in participation after stroke.

The course of participation up to four years after stroke and the influence of psychological factors on this course of participation were explored in **Chapter 6**. The course of participation improved up to one year after stroke and stabilized afterwards. Considerable restrictions in participation were observed after one year, predominantly in dynamic activities such as physical exercise, outdoor activities and housekeeping. Absence of adaptive psychological factors (pro-active coping, self-efficacy, extraversion and optimism) and mood problems were associated with worse participation up to four years after stroke. Therefore, timely treatment of mood problems and the development of interventions promoting adaptive psychological factors during rehabilitation could potentially prevent restrictions in long term participation after stroke.

In **Chapter 7** we tried to gain insight into the preferred approach to measure cognitive functioning when exploring the association between cognitive functioning and participation in the long term after stroke. The results highlighted the impact of subjective cognitive

complaints on everyday life in the long term after stroke, as subjective cognitive complaints were strongly related to restrictions in participation three to four years after stroke. A combination of objective cognitive performance (preferably including the domains of visuospatial perception and mental speed) and subjective cognitive complaints showed the strongest association with participation, and is therefore to be recommended when exploring cognitive functioning as a determinant of participation after stroke. Also, it is important to consider subjective cognitive complaints in stroke aftercare.

Movement behavior is defined as the composition of time spend sedentary and time spend in light, moderate or vigorous physical activity, and is a promising and potential modifiable factor in stroke rehabilitation. In **Chapter 8**, we showed that the course of participation up to one year after discharge to the home setting differed based on distinct movement behavior patterns, i.e. sedentary exercisers, sedentary movers and sedentary prolongers. Sedentary prolongers, being inactive and highly sedentary, experienced the most restrictions in participation over time. As sedentary prolongers are associated with an unfavorable course of participation compared to sedentary exercisers over time, early identification of highly sedentary and inactive people with stroke after discharge to the home setting is important.

The longitudinal relationship between participation and HRQoL up to one year after stroke was examined in **Chapter 9**. We showed that the level of participation at two months post-stroke predicts HRQoL at one year. Furthermore, improvement in participation during the first year after stroke was associated with improvement in HRQoL. The longitudinal association between participation and HRQoL shows the potential of participation outcome measures after stroke. As participation measures also serve as useful clinical tool, promoting patient-centered goal-setting and supporting shared decision making for a follow-up plan, we recommended incorporating the assessment and treatment of a patient's restrictions in participation at follow-up visits after stroke.

DISCUSSION OF THE MAIN FINDINGS

The discussion of the main findings will be centered around the following themes: (1) outcome measures after stroke, (2) cognitive functioning, (3) psychological factors, and (4) personalized stroke care.

OUTCOME MEASURES AFTER STROKE

Our findings confirm the importance of PROMs to evaluate participation and HRQoL after stroke, as many people with stroke experienced restrictions in participation and impaired HRQoL (**Chapter 2** and **Chapter 3**). Nevertheless, PROMs measuring participation or HRQoL are scarcely used to assess stroke outcome in current stroke literature,[1] as the mRS remains by far the most commonly used outcome measure in clinical stroke trials.[2] In these studies, "favorable outcome" is often defined by neurologists as mRS 0–2 (no disabilities to slight disabilities),[3] whereas our findings show that about 70% of the individuals with minimal disabilities after stroke according to the clinician's judgement (mRS 1) experienced restrictions in participation three months after stroke (**Chapter 2**), especially regarding work (48.5%), housekeeping (40.3%), physical exercise (35.0%) and outdoor activities (34.2%). As clinicians would probably not define "favorable outcome" in the same way if they would take into account the impact of stroke on everyday life, the current distinction between "favorable" and "unfavorable" outcome based on mRS scores seems inappropriate. Moving from current black-and-white thinking to a more nuanced and patient-centered mindset is needed to define outcomes that matter to the patients themselves.

Since the number of individuals with "favorable outcome" (mRS 0–2) according to the clinician's judgement is expected to increase even further due to the recent advances in the management of acute stroke (as discussed in the introduction),[3] capturing changes in participation and HRQoL from the perspective of these "mildly affected" individuals becomes even more important. Besides, the capability of the mRS to capture clinically important treatment effects within this large "favorable outcome" group is doubtful.[4] Therefore, the use of PROMs to evaluate HRQoL or participation also may improve the power to detect patient-relevant changes in clinical stroke trials.

Quality indicators

Insights into the impact of stroke on everyday life of individuals with stroke are pivotal to enable quality improvement across the continuum of stroke care.[5] The results presented in this Thesis show the potential of PROMs on the participation or HRQoL domain to serve as quality indicator in clinical stroke audits, providing valuable person-centered information on the burden of stroke in mildly affected individuals (**Chapter 2–4**). Measuring patient-reported stroke outcomes could aid clinical decision making after stroke, allows clinicians and stroke services to monitor their practice and provides tools for quality improvement of stroke care pathways on a national and international level.[6]

In the European Stroke Action Plan (composed by the European Stroke Organisation in 2018), "collecting patient-reported outcomes and longer term outcomes (e.g. six months and one year), covering both hospital and community care" has been set as an important target for 2030.[6] However, in most countries the mortality rate during hospital stay is currently the only outcome measure included in the stroke audit,[7] in some countries (including The Netherlands) accompanied with the clinician-reported mRS measured three months after stroke.[8] Despite international attempts (such as the International Consortium for Health Outcomes Measurement [ICHOM])[9] to define a core set of stroke outcomes that matter most to stroke patients, recent efforts to develop a common set of stroke quality indicators across Europe still lacked PROMs.[10]

Among the studied PROMs in this Thesis, the USER-P-R may have the highest potential to function as quality indicator after stroke, as the USER-P-R has the most optimal tradeoff between psychometric properties and clinical value to our opinion. The USER-P-R is a valid and brief screening to detect restrictions in participation during post-stroke follow up assessments, adds relevant information to the mRS (**Chapter 2**) and also showed to be predictive of HRQoL one year after stroke (**Chapter 9**). Moreover, since the USER-P-R also provides relevant information for clinical purposes, for example supporting individually tailored goal-setting during rehabilitation after stroke, the probability of successful implementation of the USER-P-R into routine clinical practice may be greater compared to generic HRQoL measures (such as the PROMIS-10 and EQ-5D-5L).

Implementation into clinical practice

The implementation of PROMs to measure participation or HRQoL after stroke may be hampered by several factors. First, filling out a questionnaire requires a certain level of cognitive function, communication skills and health literacy, which may be impaired in individuals with stroke.[11] According to population-based studies after stroke, approximately one-fourth of individuals with stroke requires assistance in accurately reporting PROM data.[12] Further validation of alternative methods and adaptation of PROMs for these patient categories are important to tackle these practical issues, for example by offering assistance in questionnaire completion or using proxy respondents.[13]

Second, clinicians often perceive several barriers to administer PROMs in daily practice, due to the administrative burden of PROMs and implementation hiccups (negatively impacted by top-down processes and the misfit of PROMs with current clinical practice).[14] Therefore, clinicians and individuals with stroke should be involved in the production and implementation

process to increase the practical and clinical applicability of PROMs after stroke.[15] Online administration, integration into existing stroke care pathways, integration into the electronic health records across the regional stroke networks, and automatically generated output that facilitates clinical purposes could promote the use of PROMs in routine clinical practice.[16]

Third, the feasibility of collecting PROM data after stroke could be further improved by reducing the questionnaire size. In this regard, the development of PROMs to measure participation or HRQoL based on computer adaptive testing (for example using the comprehensive PROMIS databank) is promising as the obtained information can be maximized with a smaller number of questions.[17]

COGNITIVE FUNCTIONING

Cognitive impairments and subjective cognitive complaints are common after stroke, affecting approximately two-thirds to three-quarters of individuals with stroke.[18,19] Concerningly, subjective cognitive complaints are also highly prevalent in mildly affected stroke patients (**Chapter 4**), despite good clinical recovery and physical functioning,[20] and are presumed one of the key contributing factors to long term restrictions in participation.[21] Especially younger people (aged under 70 years) with cognitive impairments (based on the MoCA) after stroke are at risk for long term restrictions in participation (**Chapter 5**), possibly due to the engagement in more complex and cognitively demanding activities (such as returning to work and social roles) in this age group, and thus need to be watched closely after stroke.

Since cognitive impairments are highly prevalent and often cause "invisible" restrictions in participation after stroke, cognitive screening is an important aspect of post-stroke assessments.[22] In current clinical practice, the MoCA is used as a brief screening instrument to identify cognitive impairment after stroke.[23] However, the subjective cognitive complaints in everyday life matter most from the patients' perspective.[24] To adopt a more person-centered and holistic view on cognitive functioning after stroke, the ecological validity of current neuropsychological tests and cognitive screening instruments needs to be improved (for example by the development of virtual reality applications[25]) and the impact of cognitive complaints on everyday life should be taken into account. Screening on subjective cognitive complaints (which could be achieved by using the CLCE-24) during post-stroke assessments is recommended for this purpose, as subjective cognitive complaints had the greatest impact on participation after stroke across several cognitive measures and provided valuable person-centered information (**Chapter 7**).

Although accumulation of deficits in multiple cognitive domains has been suggested to contribute to subjective cognitive complaints after stroke,[26] subjective cognitive complaints and deficits in objective cognitive performance do not necessarily coexist.[18] Mood problems (symptoms of anxiety and depression) and psychological factors were found to be important factors influencing subjective cognitive complaints.[27,28] Similar factors were identified as determinants of participation after stroke in this Thesis (**Chapter 6**), as cognitive impairment, mood problems and the lack of adaptive psychological factors (proactive coping, self-efficacy, extraversion and optimism) were associated with an unfavorable course of participation over time. These findings highlight that both cognitive functioning and participation after stroke are multidimensional concepts in need of a biopsychosocial approach to identify targets for rehabilitation interventions.

PSYCHOLOGICAL FACTORS

Surprisingly, psychological factors (i.e. personality traits and coping styles) are often overlooked in current stroke literature,[29] despite emerging evidence on its importance after stroke.[30] Adaptive psychological factors (such as proactive coping, self-efficacy, extraversion and optimism) and mood problems (symptoms of anxiety and depression) are important determinants of the course of participation after stroke (**Chapter 6**). In contrast to our findings, previous literature also identified maladaptive psychological factors (such as passive coping, neuroticism and pessimism) as important determinants of HRQoL after stroke.[30] Although a strong association between the presence of maladaptive psychological factors and restrictions in participation was found with the bivariate analysis of our study, this association was not found with the multivariate analysis. It seems plausible that mood problems mediated the relationship between maladaptive psychological factors and participation, as maladaptive psychological factors are often concomitant with depressive symptoms.[31]

Concerningly, scores on the measures of psychological factors seem to worsen after stroke, as the adaptive psychological factors often deteriorate whereas the prevalence of mood problems increases over time.[32] Therefore, adaptive psychological factors and mood problems are interesting targets for rehabilitation interventions to potentially prevent long term restrictions in participation. Although it is not entirely clear to what extent psychological factors are modifiable by interventions, emerging evidence shows beneficial effects from interventions targeting adapting psychological factors.[33] For example, multimodal exercise interventions were found to improve adjustment and coping among people with stroke,[33] confirming its potential to achieve both physical and behavioral changes (**Chapter 8**). Also,

qualitative research yielded positive experiences with Acceptance and Commitment Therapy (ACT) in people with stroke, supporting successful adjustment and the development of new coping strategies.[34] Further evaluation of the effectiveness of emerging psychological interventions for managing cognitive impairment and enhancing participation after stroke are needed to unravel its potential in stroke rehabilitation.[33,35]

Furthermore, early recognition of absent adaptive psychological factors and the presence of mood problems at follow-up assessments after stroke is important to timely identify those individuals with stroke at risk for long term restrictions in participation. Early detection of mood problems after stroke can be achieved using the HADS, but a brief screening tool to assess the presence of adaptive psychological factors after stroke is not yet available to our knowledge. Pending further validation in the stroke population, the Connor-Davidson Resilience Scale (CD-RISC-10) might potentially be an appropriate questionnaire for this purpose, as it consists of 10 items and focuses on adaptive personality traits that "enable one to thrive in the face of adversities".[36] Including psychological factors when taking a medical history (by asking questions like: "how would you describe your personality?" or "how do you cope with setbacks?") could already be helpful to get a first impression of personality traits and coping styles. The ICF serves as a useful tool for this purpose as well, as this framework could support clinicians to adopt a more person-centered approach (focusing on the impact of stroke according to the individual rather than on the stroke itself) and encompasses personal and environmental factors. This may also help to identify and disentangle the complex and often intertwined effects of psychological factors, mood and cognitive problems on participation, and select the most suitable rehabilitation intervention based on each patient's individual needs.

PERSONALIZED STROKE CARE

In general, the results presented in this Thesis advocate a person-centered approach to improve participation after stroke, which is in agreement with recent developments in health care such as the rise of the contemporary concept of value-based health care[37] and the positive health model.[38] The American Geriatrics Society Expert Panel stated that person-centered care means that "individuals' values and preferences are elicited and, once expressed, guide all aspects of their health care, supporting their realistic health and life goals".[39] The ongoing shift from a biomedical approach (solely focusing on biological factors "within the body") towards a biopsychosocial approach (also taking into account psychological, social and environmental factors) in health care, kicked off in 1977 by George

Engel, is among the essential components contributing to person-centered care.[40] However, despite the biopsychosocial approach is widely used in current stroke rehabilitation practice, implementation of person-centered care along the continuum of stroke care appears to be challenging and requires major changes in stroke management.[41,42] As small changes can potentially lead to big progress, we would like to discuss first steps to pursue personalized stroke care during post-stroke follow-up assessments in the following paragraphs.

"It is never too late for rehabilitation"

In the Netherlands, post-stroke follow-up assessments are often limited to the first three months after stroke onset,[43] following the course of spontaneous neurological recovery. Traditionally, the period of spontaneous neurological recovery (level of body functions) is often wrongly referred to as the "window of opportunity" (roughly the first three to six months after stroke).[44] As a consequence, most follow-up assessments and rehabilitation interventions are restricted to this relatively small time window and are mainly focused on improvements in body functions and activities, despite overwhelming evidence on the effectiveness of interventions aimed at enhancing long term participation after stroke utilizing an adaptive or compensatory approach.[45] This outdated but deep-rooted belief causes the risk for a self-fulfilling prophecy, since the lack of rehabilitation interventions targeting long term restrictions in participation (outside the "window of opportunity") may also be an explanation for the stabilization of participation in people with stroke after six months (**Chapter 6**).

Concerningly, the majority of people with stroke experienced considerable long term restrictions in participation (**Chapter 2**, **Chapter 5** and **Chapter 6**). Qualitative research showed that recovery of participation after stroke is a highly heterogenous and dynamic process of re-engagement in valued activities, within the context of influencing personal and environmental factors (Figure 10.1).[46,47] As the needs of people with stroke vary over time, the need for rehabilitation services may change during different stages of recovery and adaptation.48 Fortunately, international consensus on the timing of rehabilitation services has recently been reached, as the European Stroke Action Plan 2018–2030 states that "it is never too late for rehabilitation".[6]

To close the gap between the long term needs of people with stroke and current stroke practices, we emphasize the importance of improving access to long term stroke care and to increase collaboration across the regional stroke networks to be able to provide the right rehabilitation services at the right time. Furthermore, routine post-stroke assessments should not solely

focus on secondary prevention and motor impairment, but also encompass screening on participation and accompanying risk factors for long term restrictions in participation (such as emotional, psychological and cognitive problems). Extended follow-up periods after stroke outside the classical "window of opportunity" should be considered for people at risk for long term restrictions in participation. In the Netherlands, the general practitioner often is the only physician who assesses people with stroke outside this "window of opportunity", but their assessments are currently mainly focused on cardiovascular risk management.

Figure 10.1: The dynamic process of participation after stroke, adapted from Norlander et al. (2021).[46]

The ICF Pyramid

The ICF framework can serve as a useful tool for clinicians to describe the impact of stroke on the individual in an orderly manner, and to gain insight into the role of biopsychosocial factors influencing participation after stroke (Figure 10.2). However, the ICF has a few limitations for this purpose (Figure 10.3): (1) Participation does not appear to be a central theme, as "activities" are placed in the heart of the model, (2) as all components are connected by bidirectional arrows and a hierarchical structure is lacking, little guidance is provided on the practicality of potential determinants of participation, (3) the ICF seems disease-centered rather than person-centered, since the model is centered around the "health condition" rather than the individual and (4) the ICF does not reflect the growing importance of personal and environmental factors as determinants of participation. Therefore, we propose an adapted version of the ICF, the so-called "ICF Pyramid", to increase its applicability as a tool to assess potential determinants of participation during post-stroke assessments and to pursue personalized stroke care.

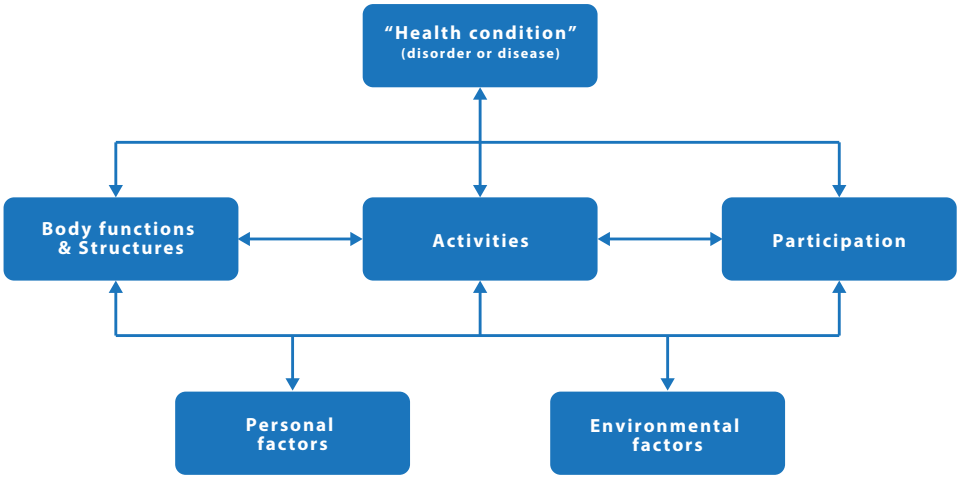

Figure 10.2: The International Classification of Functioning, Disability and Health (ICF), World Health Organization, 2001.

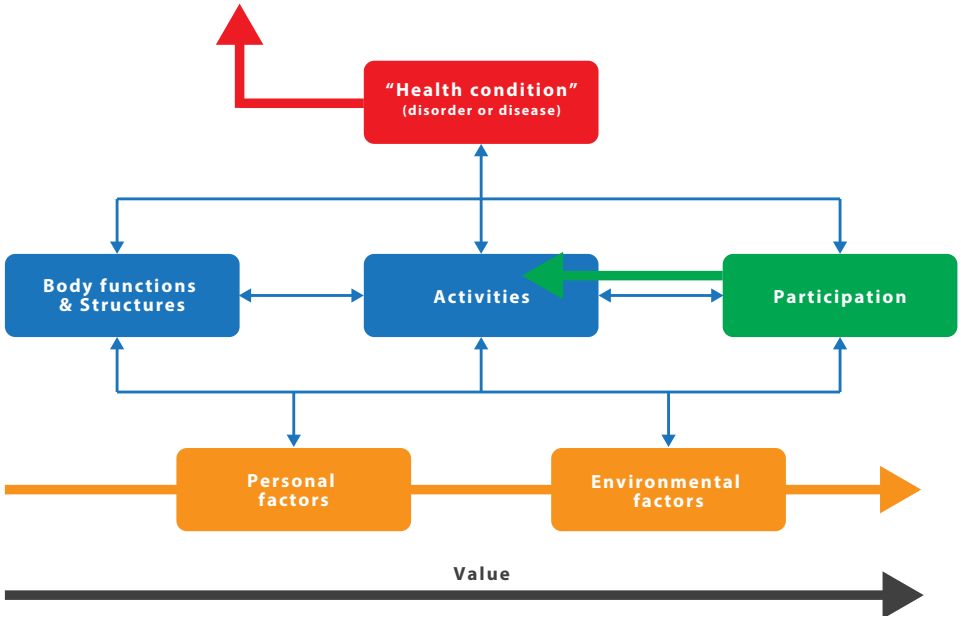

Figure 10.3: Limitations of the current ICF framework.
(1) Participation does not appear to be a central theme (green), (2) a hierarchical structure is lacking (black), (3) the ICF seems disease centered as the "health condition" is placed on top of the model (red), (4) the ICF does not reflect the growing importance of personal and environmental factors as determinants of participation (orange).

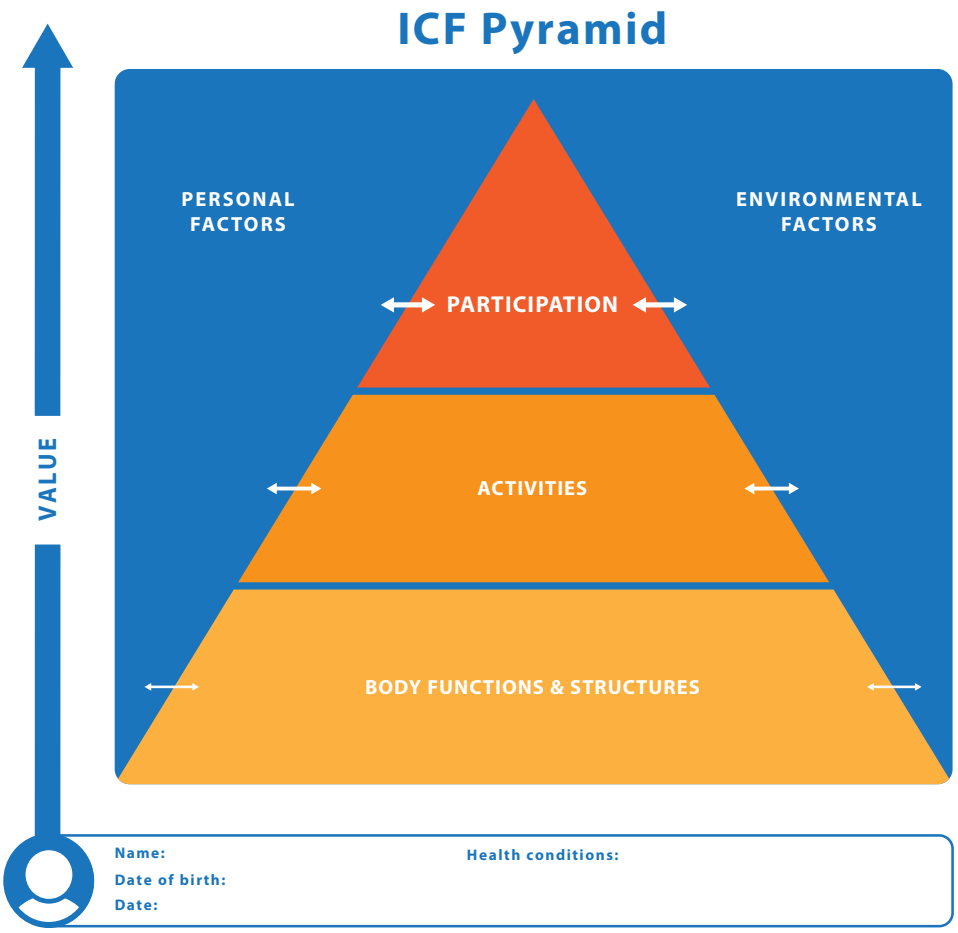

Figure 10.4: The ICF Pyramid, adapted from the ICF[49] to improve its applicability in stroke rehabilitation.

The ICF Pyramid (Figure 10.4) consists of the same components as the "regular" ICF. By adopting a pyramid shaped form, an explicit vertical hierarchical direction is created, facilitating its readability and clinical applicability. Participation is put on the top of the pyramid, being considered the ultimate goal of rehabilitation after stroke, and is built upon the foundations of "Body functions and Structures" and "Activities" respectively. The pyramid is surrounded by personal and environmental factors, and shows the growing contribution of these factors when ascending the pyramid. A person-centered approach is promoted by naming the pyramid after the person instead of the disease.

The ICF Pyramid can serve several purposes. First, it provides a more person-centered and uniform framework for clinicians to identify potential targets for rehabilitation interventions,

and underpins the goal-setting process during stroke rehabilitation due to its hierarchical structure. Second, it can function as a comprehensible psychoeducational tool and gives individuals with stroke insight into the different contributing factors, as the pyramid shape offers a natural metaphor and comprehensible visual display. Third, multidisciplinary teams and research groups could use the ICF Pyramid to select a suitable outcome measure to evaluate a particular intervention of interest. For example, if an intervention is carried out to improve a certain body function, the effect on the level of participation is probably smaller than the effect on the level of activities as the role of other factors (i.e. personal and environmental factors) increases when ascending the pyramid.

METHODOLOGICAL CONSIDERATIONS

The results of this Thesis are based on data from three different Stroke Cohort studies, i.e. the Stroke Outcome Measures Study, Restore4Stroke Cohort study28,50 and the RISE study.51 Each study has its strengths and limitations, which will be summarized below.

Study population

In all three studies, participants were recruited during stroke unit admission of hospitals in the Netherlands. As recruitment took place irresectable of discharge destination after hospitalization, the eligible study participants were a good representation of the general stroke population (the majority of participants being discharged home). As a consequence, the study samples largely consisted of mildly impaired stroke patients with mostly ischemic strokes, which is in line with the epidemiology of stroke.

However, the exclusion criteria (premorbid cognitive deficits and ADL dependency in the Restore4Stroke Cohort study, and inability to walk with supervision after discharge to the home setting and premorbid ADL dependency in the RISE study) may also have contributed to the underrepresentation of severely affected stroke patients. Also, informed consent was obtained in the first week after stroke onset in the Restore4Stroke Cohort study and the RISE study, which may not have been possible for more severely affected stroke patients. This may have negatively affected the generalizability of the results to more severely affected stroke patients and those with hemorrhagic strokes. Lastly, although post-stroke aphasia was not an exclusion criterion in the studies, only observational measures could be conducted if communication problems interfered with the capability of filling in questionnaires during the follow-up assessments. Since participation was the main outcome measure in this Thesis

and information on participation was obtained by questionnaires, individuals with post-stroke aphasia may also be underrepresented in our study results.

Study design

All three studies are multicenter studies with relatively large sample sizes. Also, the prospective and longitudinal designs of the Restore4Stroke and RISE cohort study, including long term follow-up (respectively 2 and 3–4 years after stroke) with multiple measurements over time, are among the main strengths of these studies. As the Stroke Outcome Measures Study has a cross-sectional study design, the responsiveness of the studied stroke outcome measures could not be examined.

In contrast to the Restore4Stroke and Stroke Outcome Measures study, the RISE study set discharge to the home setting after hospitalization/inpatient rehabilitation as baseline during follow-up (instead of stroke onset). Therefore, the time after stroke onset of the follow-up measurements differed across participants in the RISE study, which may complicate the interpretation of the results (since the component of spontaneous neurological recovery is time dependent) and may reduce its generalizability to the general stroke population.[52]

Statistics

As a wide variety of demographic factors, stroke characteristics, cognitive measures, psychological factors and data on movement behavior were obtained across the studies, the relationship between many different factors of interest and participation could be explored using multivariate statistics. By clustering multiple factors based on findings in previous literature (such as the psychological clusters[32] in Chapter 6 and movement behavior patterns[51] in Chapter 8), valuable insights into the complex and multifactorial nature of participation could be achieved. However, these clusters may also have decreased the clinical applicability of our findings, since it is complicated to trace back the contribution of separate components of the clusters (which could be interesting targets for rehabilitation interventions).

Furthermore, robust statistical techniques were used for longitudinal data analyses (mixed models and GEE) to explore the course of participation and its determinants over time, which allowed us to include all available data and took into account that the repeated observations within one subject are not independent. However, causality between determinants and participation could not be proven with the statistical techniques used in this Thesis, as an association does not imply causation.

Variables

Although a broad spectrum of factors was assessed in this Thesis, not all determinants of participation could be taken into account as the number of factors included in the analyses could not be infinite. In particular environmental factors were lacking among all three studies, while qualitative studies show that social support, relationships, physical environment and positive attitudes from others in the community towards people with stroke are important facilitators of participation after stroke.[53] Regrettably, these factors have rarely been examined in stroke research, as appropriate assessment tools for these purposes are often lacking.[53]

Furthermore, different measures have been used to assess participation and HRQoL across the studies in this Thesis. This broad scope allowed us to compare different PROMs measuring participation and HRQoL after stroke. On the other hand, the heterogeneity in outcome measures may have decreased the mutual comparability of the study results, although strong associations between the different questionnaires have been found.[54]

CLINICAL IMPLICATIONS

The findings of this Thesis emphasize the need to pay more attention to individuals with stroke who experience restrictions in participation or who are at risk for restrictions in participation. Although recent developments in the acute treatment of stroke (such as intravenous thrombolysis and mechanical thrombectomy) have led to higher rates of "favorable functional outcome" (defined as modified Rankin Scale 0–2 in clinical stroke trials),[3] a considerable number of these "mildly affected" individuals with stroke (according to the clinician) still experiences long term restrictions in participation. This shows the need for a paradigm shift in current stroke research and clinical practice, as the impact of stroke on the individual needs to be acknowledged in order to achieve "favorable outcome" according to the individual as well. Based on the results of this Thesis, three implications can be given to pursue this goal.

Clinical implications

1 Regular assessment of participation during follow-up assessments after stroke, preferably integrated in the regional stroke network using fixed timepoints after stroke independent of discharge destination. The USER-P-R is an appropriate instrument for this purpose. If restrictions in participation are identified, a comprehensive screening on influencing factors is indicated (the ICF Pyramid may serve as a useful tool) and referral to individually tailored rehabilitation interventions should be considered.

2 Early identification of individuals with stroke who are at risk for an unfavorable course of participation is important during follow-up assessments after stroke. Prolonged follow-up assessments could be considered if risk factors for long term restrictions in participation are present, such as mood problems, highly sedentary and inactive people, people aged over 70 years, cognitive complaints (especially in people aged under 70 years), and the absence of adaptive psychological factors. Modifiable factors such as mood problems or highly sedentary and inactive behavior should be managed in a timely manner to potentially prevent long term restrictions in participation. International consensus on a core set of screening and assessment tools post-stroke is needed to further boost the quality of stroke aftercare. Screening on mood problems and cognitive complaints can easily be achieved (by using the HADS and the CLCE-24, respectively), but a brief screening instrument on psychological factors is not available yet.

3 Assessment of patient-reported information in individuals with stroke is important, as it provides clinicians with relevant person-centered information on the impact of stroke and promotes value-based stroke care. Patient-reported information on participation and HRQoL does not only benefit clinical stroke care, but should also be considered as quality indicator in clinical stroke audits since the experiences of individuals with stroke are key to improve the quality of stroke care as a whole. The set of quality indicators should ideally reflect a person's level of functioning, thus incorporating measures on all levels of the ICF Pyramid (body functions, activities and participation).

CONCLUSIONS

Although participation improves on average up to one year after stroke onset, many individuals experience long term restrictions in participation. Old age, mood problems, the absence of adaptive psychological factors, cognitive problems and a sedentary and inactive lifestyle are determinants associated with worse participation after stroke. Early identification of individuals with stroke who are at risk for an unfavorable course of participation is important, as modifiable factors can be managed and follow-up assessments after stroke can be extended for those at risk for restrictions in participation. The USER-P-R is an appropriate instrument to measure restrictions in participation after stroke, and could both serve as screening tool during post-stroke follow-up assessments and as outcome indicator in clinical stroke audits. Regular assessment of participation after stroke (in post-stroke care, stroke audits and stroke research), taking into account the impact of stroke from the patients' perspective, would be a major step towards personalized stroke care.

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Chapter 11

Samenvatting
Summary in Dutch

Dit proefschrift gaat over de uitkomsten op het gebied van participatie van mensen die een beroerte hebben doorgemaakt. Beroertes zijn wereldwijd één van de meest voorkomende oorzaken van overlijden en van blijvende beperkingen. In Nederland krijgen jaarlijks ongeveer 45.000 mensen een beroerte, en naar verwachting zal dit aantal de komende jaren verder toenemen door de vergrijzende bevolking. Doordat de acute behandeling van een beroerte aanzienlijk verbeterd is in de afgelopen jaren (onder andere door de toepassing van nieuwe behandelingen zoals intraveneuze trombolyse en mechanische trombectomie), overleven steeds meer mensen een beroerte. Door deze ontwikkelingen hebben steeds meer mensen te maken met de langetermijngevolgen van een beroerte. Een beroerte leidt vaak niet alleen tot fysieke beperkingen, maar kan ook emotionele, cognitieve en psychosociale gevolgen hebben. Deze gevolgen hebben een negatieve invloed op de gezondheidsgerelateerde kwaliteit van leven, en kunnen er toe leiden dat mensen na een beroerte minder goed kunnen participeren in de maatschappij (bijvoorbeeld door beperkingen op het gebied van werk, hobby's en sociale activiteiten). Participatie is gedefinieerd door de International Classification, Disability and Health (ICF) als iemands betrokkenheid in een levenssituatie, en heeft onder andere betrekking op de dagelijkse activiteiten en sociale relaties van mensen. Revalidatie na een beroerte heeft als hoofddoel om de participatie van mensen na een beroerte te bevorderen.

Momenteel krijgt participatie echter nog relatief weinig aandacht in de zorg voor mensen met een beroerte en in het wetenschappelijk onderzoek naar de gevolgen van een beroerte. Van oudsher worden met name meetinstrumenten ingezet die door de clinicus gerapporteerd worden om de uitkomsten na een beroerte te evalueren. Om meer te weten over de participatiebeperkingen en de gezondheidsgerelateerde kwaliteit van leven die mensen na een beroerte ervaren, is het nodig om de persoon met de beroerte meer centraal te stellen. Daarom onderzoeken we in **deel 1** van het proefschrift hoe we participatie en gezondheidsgerelateerde kwaliteit van leven het beste kunnen meten bij mensen met een beroerte door middel van patiënt-gerapporteerde uitkomstmaten (PROMs). Hierdoor kunnen we hopelijk meer inzicht verkrijgen in de participatieproblemen waar mensen met een beroerte tegenaan lopen.

Om de participatie van mensen met een beroerte vervolgens verder te kunnen verbeteren, is er meer kennis nodig over het beloop van participatie na een beroerte en over de factoren die participatie positief of negatief beïnvloeden. In **deel 2** van het proefschrift onderzoeken we daarom het langetermijnbeloop van participatie na een beroerte, en kijken we naar factoren die dit beloop mogelijkerwijs beïnvloeden, zoals leeftijd, stemmingsklachten, psychologische factoren, cognitieve klachten en een inactieve leefstijl. Indien factoren een bewezen positieve

of negatieve invloed op de participatie van mensen met een beroerte hebben, zouden we in de toekomst door het stimuleren van deze positieve factoren of het voorkomen/tijdig behandelen van eventuele negatieve factoren, de langetermijnparticipatie van mensen met een beroerte kunnen verbeteren.

DEEL 1

De restrictie schaal van de *Utrecht Scale for Evaluation of Rehabilitation-Participation* (USER-P-R) is een veelbelovende vragenlijst waarin mensen kunnen aangeven in hoeverre zij beperkingen ervaren in participatie. In **hoofdstuk 2** wordt de validiteit (de mate waarin wordt gemeten wat we beogen te meten) van de USER-P-R nader onderzocht. De USER-P-R wordt hierbij onder andere vergeleken met andere veel gebruikte meetinstrumenten op dit gebied, zoals de *modified Rankin Scale* (mRS), *EuroQol 5-dimensional 5-level questionnaire* (EQ-5D-5L) en de *Patient Reported Outcomes Measurement Information System 10-Question Global Health Short Form* (PROMIS-10). De resultaten laten zien dat de USER-P-R goede meeteigenschappen heeft. De USER-P-R blijkt met name geschikt bij mensen met een beroerte die blijvende beperkingen ervaren sinds de beroerte. Mensen die geen beperkingen ervaren scoren namelijk al gauw de maximale score (een zogenaamd plafondeffect). Concluderend is de USER-P-R een valide vragenlijst om participatiebeperkingen te achterhalen bij mensen met een beroerte, en geschikt om bijvoorbeeld toegepast te worden op CVA nazorgpoli's.

De eerder genoemde EQ-5D-5L en PROMIS-10 zijn twee veelbelovende vragenlijsten om de gezondheidsgerelateerde kwaliteit van leven die mensen met een beroerte ervaren te meten, echter is nog niet duidelijk welke vragenlijst hier het beste in is. Daarom vergelijken we in **hoofdstuk 3** de meeteigenschappen van beide vragenlijsten. De resultaten laten zien dat beide vragenlijsten uitstekend in staat zijn om de gezondheidsgerelateerde kwaliteit van leven van mensen met een beroerte te evalueren, al scoort de PROMIS-10 gemiddeld genomen net iets beter. De PROMIS-10 blijkt met name geschikt voor mensen met een beroerte die weinig beperkingen ervaren, terwijl de EQ-5D-5L geschikter is bij mensen met een beroerte die veel beperkingen ervaren. Een mogelijke verklaring is dat de vragen van de PROMIS-10 meer gericht zijn op de algehele gezondheid, terwijl de vragen van de EQ-5D-5L zich meer richten op het detecteren van mogelijke problemen. In de praktijk kunnen het onderliggende doel en de populatie helpend zijn bij de keuze voor één van deze vragenlijsten om de ervaren gezondheidsgerelateerde kwaliteit van leven van mensen met een beroerte te meten.

Aangezien cognitieve klachten (zoals problemen in het geheugen, de concentratie of het aanpassingsvermogen) veel voorkomen bij mensen met een beroerte en vaak als hinderlijk worden ervaren, vergelijken we in **hoofdstuk 4** de validiteit van de EQ-5D-5L met en zonder de toevoeging van een cognitief domein (EQ-5D-5L+C). De resultaten laten zien dat de validiteit van de EQ-5D-5L met en zonder toevoeging van een cognitief domein niet substantieel verandert. Wel zien we dat meer dan de helft van de mensen met een beroerte cognitieve problemen rapporteert, en dat het aantal mensen met een maximale score lager ligt bij de EQ-5D-5L+C (een vermindering van het plafondeffect). Samenvattend adviseren we het gebruik van de EQ-5D-5L+C bij mensen met een beroerte, aangezien de EQ-5D-5L+C door de toevoeging van een cognitief domein een betere dekking geeft van de domeinen die belangrijk zijn voor de gezondheidsgerelateerde kwaliteit van leven na een beroerte.

DEEL 2

In **hoofdstuk 5** worden verschillen in participatie tussen mensen met een beroerte jonger en ouder dan 70 jaar beschreven. Verder hebben we voor beide leeftijdsgroepen apart bekeken welke factoren al vroeg na de beroerte kunnen voorspellen of er sprake zal zijn van een gunstige of een ongunstige participatie-uitkomst 1 jaar na de beroerte. De resultaten laten zien dat mensen die ouder zijn dan 70 jaar meer beperkingen in participatie ervaren een jaar na de beroerte dan mensen die jonger zijn dan 70 jaar, met name op het gebied van sport, huishoudelijke taken en activiteiten buitenshuis. Ook worden er andere voorspellers van langetermijnparticipatie geïdentificeerd in beide leeftijdsgroepen: bij mensen ouder dan 70 jaar blijken toenemende leeftijd, een ernstigere beroerte en meer angstklachten samen te hangen met een ongunstige participatie-uitkomst, terwijl bij mensen jonger dan 70 jaar het vrouwelijk geslacht, een ernstigere beroerte, meer cognitieve beperkingen en meer depressieve klachten samenhangen met een ongunstige participatie-uitkomst. Deze resultaten laten zien dat het belangrijk is om meer aandacht te besteden aan mensen met een beroerte die ouder zijn dan 70 jaar. Verder kunnen tijdige screening op participatie en leeftijdsafhankelijke voorspellers helpend zijn om mensen die een verhoogd risico lopen op een ongunstige participatie-uitkomst tijdig te identificeren, en eventuele behandelbare factoren tijdig te verhelpen.

In **hoofdstuk 6** wordt het beloop van participatie tot 4 jaar na het ontstaan van een beroerte beschreven. Tevens wordt de invloed van psychologische factoren (zoals persoonlijkheidskenmerken en copingstijlen) op dit beloop bestudeerd. De resultaten tonen dat het gemiddelde niveau van participatie verbetert tot 1 jaar na de beroerte, en nadien stabiliseert. Na

het eerste jaar van de beroerte houden veel mensen aanzienlijke beperkingen in participatie, met name op het gebied van dynamische activiteiten (waarin zowel fysieke als cognitieve componenten een rol spelen) zoals sport, activiteiten buitenshuis en huishoudelijke taken. Afwezigheid van adaptieve psychologische factoren (proactieve coping, zelfeffectiviteit, extraversie en optimisme) en stemmingsklachten zijn geassocieerd met slechtere participatie-uitkomsten tot 4 jaar na de beroerte. Het tijdig behandelen van stemmingsklachten en de ontwikkeling van interventies om adaptieve psychologische factoren te stimuleren tijdens de revalidatie zouden eventuele langetermijnbeperkingen in participatie kunnen voorkomen.

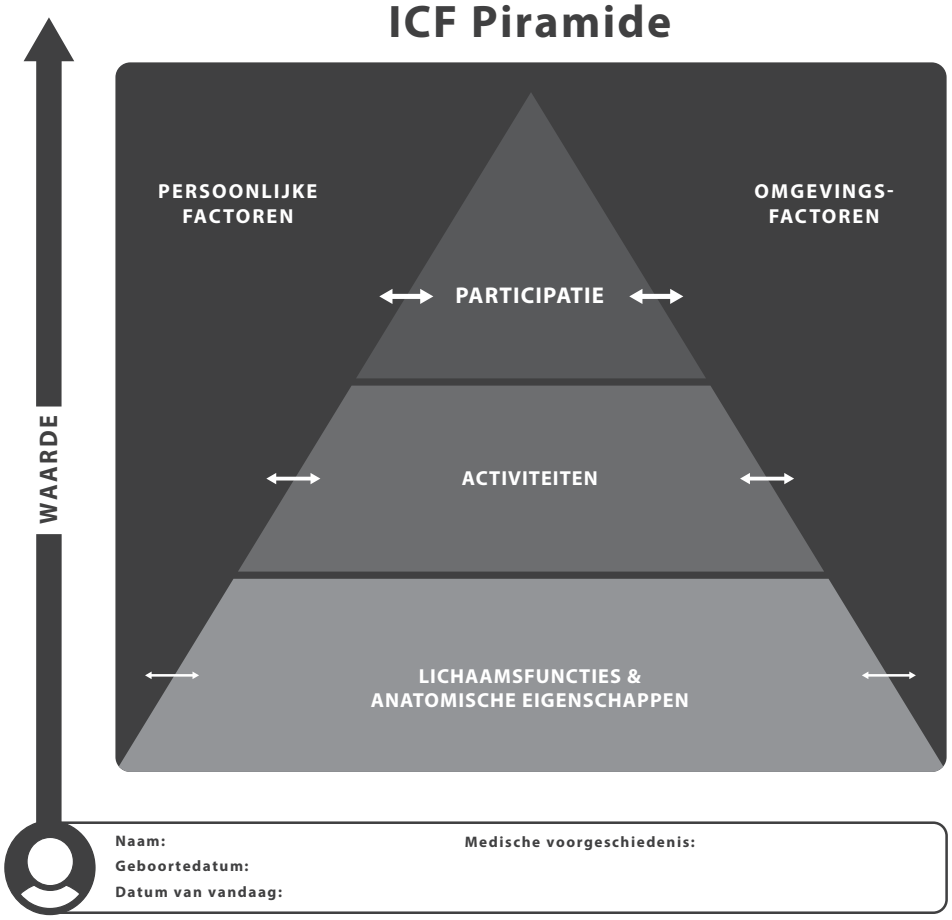
In **hoofdstuk 7** wordt getracht inzicht te verkrijgen in de relatie tussen verschillende scores voor cognitief functioneren en participatie na een beroerte. Het cognitief functioneren kan namelijk op vele verschillende manieren in kaart worden gebracht, maar welke wijze de voorkeur heeft om de relatie met participatie te onderzoeken is tot op heden onduidelijk. Zo kan een cognitieve screeningstest (zoals de MoCA) of een neuropsychologisch onderzoek verricht worden om objectieve cognitieve prestaties te meten, terwijl een zelfrapportagelijst (zoals de CLCE-24-C) afgenomen kan worden om de door de patiënt zelf ervaren cognitieve klachten te meten. De resultaten laten zien dat de door de patiënt zelf ervaren cognitieve klachten sterk geassocieerd zijn met beperkingen in participatie na een beroerte. Om die reden wordt geadviseerd om ook de door de patiënt zelf ervaren cognitieve klachten in kaart te brengen tijdens de nazorg voor mensen met een beroerte. Verder blijkt een combinatie van de door de patiënt zelf ervaren cognitieve klachten en twee specifieke neuropsychologische testen (op het gebied van visuospatiële perceptie en snelheid van informatieverwerking) het sterkst geassocieerd met participatie na een beroerte. Het meten van zowel de door de patiënt zelf ervaren cognitieve klachten als objectieve cognitieve prestaties wordt dan ook aanbevolen indien men de relatie tussen cognitief functioneren en participatie na een beroerte wil onderzoeken.

Beweeggedrag omvat zowel de mate waarin iemand inactief is (sedentair gedrag), als de mate waarin iemand licht, matig of intensief fysiek actief is, en is een potentieel interessant aangrijpingspunt voor revalidatie-interventies na een beroerte. Daarom wordt in **hoofdstuk 8** beschreven in hoeverre beweeggedrag het beloop van participatie na een beroerte beïnvloedt. De resultaten laten zien dat de zogenaamde sedentary prolongers, die weinig actief zijn en veel sedentair gedrag vertonen, het meest ongunstige participatiebeloop hebben na een beroerte. Tijdige identificatie van mensen met een beroerte die na thuiskomst weinig actief zijn en veel sedentair gedrag vertonen is daarom belangrijk, aangezien deze mensen risico lopen op langetermijnparticipatiebeperkingen. Helaas blijken mensen met een beroerte in de loop van de tijd risico te lopen om terug te vallen naar een inactieve leefstijl. Er is

dan ook meer onderzoek nodig naar de ontwikkeling van eerstelijns interventies voor deze doelgroep, met als doel om een duurzame verandering in beweeggedrag te bewerkstelligen en op deze manier langetermijnparticipatiebeperkingen te kunnen voorkomen.

Ondanks dat participatie de belangrijkste uitkomstmaat vormt in de revalidatiegeneeskunde, wordt participatie maar mondjesmaat als uitkomstmaat gebruikt in de zorg voor mensen met een beroerte en bij onderzoek naar de gevolgen van een beroerte. Uitkomsten op het gebied van gezondheidsgerelateerde kwaliteit van leven genieten vaak de voorkeur. In **hoofdstuk 9** wordt gekeken in hoeverre participatie-uitkomsten samenhangen met lange termijn gezondheidsgerelateerde kwaliteit van leven uitkomsten. De resultaten laten zien dat een gunstige participatie-uitkomst op 2 maanden na de beroerte voorspellend is voor een hogere gezondheidsgerelateerde kwaliteit van leven na 1 jaar. Dit resultaat toont wederom het belang van het meten van participatie bij mensen na een beroerte. Participatie-uitkomsten zijn bovendien niet alleen van meerwaarde als voorspellende factor voor gezondheidsgerelateerde kwaliteit van leven na 1 jaar, maar beschikken ook over evident klinisch nut. Zo zijn participatie-uitkomsten helpend bij het stellen van doelen tijdens de revalidatie en het bevorderen van gezamenlijke besluitvorming bij de nazorg voor mensen met een beroerte.

Tenslotte worden in **hoofdstuk 10** de belangrijkste bevindingen samengevat, en worden toepassingen van de resultaten bediscussieerd aan de hand van vier thema's die als een rode draad door het proefschrift lopen: (1) uitkomstmaten na een beroerte, (2) cognitief functioneren, (3) psychologische factoren en (4) persoonsgerichte zorg voor mensen met een beroerte. Belangrijke determinanten van participatie na een beroerte worden nader uitgelicht, waarbij diverse suggesties voor toekomstig onderzoek en klinische toepassingen de revue passeren. De "ICF Piramide", een aanpassing op het model van de ICF, kan hierbij fungeren als denkkader om persoonsgerichte zorg bij mensen met een beroerte na te streven, waarbij participatie een centrale rol vervult. Vervolgens worden methodologische overwegingen besproken aan de hand van de verschillende studiepopulaties (*Stroke Outcome Measures study*, *Restore4Stroke cohort study* en *RISE study*). Het hoofdstuk wordt afgesloten met een drietal aanbevelingen voor de klinische praktijk om persoonsgerichte zorg na een beroerte te bevorderen.


ICF Piramide
PERSOONLIJKE FACTOREN
OMGEVINGS-FACTOREN
PARTICIPATIE
ACTIVITEITEN
LICHAAMSFUNCTIES & ANATOMISCHE EIGENSCHAPPEN
WAARDE
Naam:
Geboortedatum:
Datum van vandaag:
Medische voorgeschiedenis:

Aanbevelingen voor de klinische praktijk

1 Het systematisch meten van participatie gedurende de nazorg van mensen met een beroerte (bijvoorbeeld door middel van de USER-P-R).

2 Tijdige screening op factoren die de langetermijnuitkomsten op het gebied van participatie na een beroerte nadelig beïnvloeden (zoals stemmingsproblematiek, de afwezigheid van adaptieve psychologische factoren, een inactieve leefstijl, en de aanwezigheid van cognitieve klachten), zodat behandelbare factoren in een vroeg stadium aangepakt kunnen worden en mensen die een verhoogd risico lopen op langdurige beperkingen in participatie langer kunnen worden gevolgd.

3 De toepassing van patiënt-gerapporteerde uitkomstmaten bij mensen met een beroerte uitbreiden (zowel in de zorg, het wetenschappelijk onderzoek als bij kwaliteitsregistraties), zodat er beter aangesloten kan worden bij de individuele waarden en ervaringen van mensen met een beroerte.

Chapter 12

Dankwoord

DANKWOORD

De afgelopen 6 jaar heb ik mij met veel plezier bezig gehouden met wetenschappelijk onderzoek, wat uiteindelijk tot dit proefschrift heeft geleid. Uiteraard had ik dit niet alleen gekund, onderzoek doen is teamwerk. Bij deze zou ik dan ook graag van de gelegenheid gebruik willen maken om die mensen die mij in deze periode geholpen en gesteund hebben hartelijk te bedanken.

Promotiecommissie

Achteraf gezien bleek een mailtje naar **Anne Visser-Meily** tijdens mijn laatste jaar van de geneeskundestudie, waarin ik naarstig op zoek was naar een wetenschappelijke stage, het startschot voor dit wat uit de hand gelopen studie/hobbyproject. Tot dat moment was mijn wetenschappelijke interesse nagenoeg non-existent, en was er geen haar op mijn hoofd die ook maar aan promoveren dacht (laat staan aan een academische carrière). Jouw tomeloze enthousiasme voor het wetenschappelijk onderzoek en de Revalidatiegeneeskunde zijn bewonderenswaardig en hebben mij al snel over de streep getrokken. Bedankt voor de mogelijkheden die je mij geboden hebt om mij binnen het onderzoek en de Revalidatiegeneeskunde te kunnen ontwikkelen tot waar ik nu sta, en voor het rotsvaste vertrouwen dat ik altijd ervaren heb.

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Veruit het grootste gedeelte van mijn promotietraject speelde zich af in de schaduw van mijn opleiding tot revalidatiearts. In deze periode vervulde **Vera Schepers** niet alleen de rol van copromotor, maar ook de rol van opleider. Met deze dubbele pet heb je een belangrijke rol gespeeld in mijn ontwikkeling als arts én als onderzoeker. Tijdens onze gesprekken had je altijd oog voor mijn persoonlijke welbevinden en stelde je mijn eigen doelen en ambities centraal. Jouw coachende rol heeft mij geholpen bij het maken van de juiste keuzes in mijn carrière, en ook bij het behouden van de juiste balans (zowel tussen opleiding en onderzoek als tussen werk en privé), bedankt hiervoor!

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Chapter 13

About the author

CURRICULUM VITAE

Joris de Graaf was born on September 1st 1991 in 's-Hertogenbosch, the Netherlands. He grew up in a little village called Tricht, and finished secondary school at Lek & Linge in Culemborg (VWO, cum laude). He started to study Medicine at the University of Utrecht in 2009. During his medical education, he developed a particular interest in Rehabilitation Medicine. In the final year of the medical program, he wrote his first article about participation after stroke, and conducted a research internship at the University of Edinburgh (Scotland) about exercise after stroke.

After obtaining his medical degree, he worked as a physician (ANIOS) at the Neurology department of the Zuwe Hofpoort Hospital and St. Antonius Hospital (Woerden). In March 2017, he started as a resident (AIOS) in Rehabilitation Medicine at De Hoogstraat Rehabilitation (Utrecht). During this training he continued conducting research, which resulted in the work described in this Thesis. He followed the research educational program "Clinical and Experimental Neuroscience" at the Graduate School of Life Sciences at University Utrecht.

During his medical training, he was involved in the development of the first national guideline for rehabilitation treatment in COVID-19 patients. In April 2021, the final month of his training, Joris was awarded the Livit Orthopedie Award ("most promising trainee in Rehabilitation Medicine"). Currently, he is attached to UMC Utrecht, with special interest in stroke, oncology and post-intensive care syndrome.

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