Predicting outcome in patients with chronic stroke: findings of a 3-year follow-up study

Ingrid van de Port

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Voor Mama

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Predicting outcome in patients with chronic stroke: findings of a 3-year follow-up study

Het voorspellen van lange termijn gevolgen na een beroerte

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de universiteit van Utrecht op gezag van de rector magnificus, prof. dr. W.H. Gispen, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 14 december 2006 des middags om 4.15 uur

door

Ingrid Gerrie Lambert van de Port
geboren op 3 december 1976 te Roermond

Promotor
Prof. Dr. E. Lindeman

Co-promotor
Dr. G. Kwakkel

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Contents

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General Introduction

Ingrid G.L. van de Port

Stroke is a leading cause of mortality and disability in the Western world. The number of stroke patients in the Netherlands has been estimated at 7.5 per 1000, resulting in 118,500 patients among the Dutch population in the year 2000. Demographic projections predict a substantial increase in the number of stroke patients in the near future: a 27% rise is expected over the 2000 – 2020 period, mainly due to the aging of the population[1]. The numbers of stroke survivors living with the consequences of a stroke will also continue to increase as mortality rates decrease[2], resulting in an augmented burden of chronic stroke for patients as well as health care and social services. In addition, costs relating to stroke will continue to rise. In 1999, about one billion euros were spent on care for stroke patients in the Netherlands[3]. After hospitalisation, about 10-15% of the Dutch stroke survivors are discharged to a rehabilitation centre for inpatient rehabilitation[4,5]. These patients usually have suffered a moderate to severe stroke, are relatively young and many had an active lifestyle before stroke. Rehabilitation is targeted on reducing disabilities and handicaps and preserving or restoring patients' autonomy and well-being. Despite rehabilitation, many survivors are facing the lifelong consequences of stroke. These sequels are usually complex and heterogeneous, and can result in problems across multiple domains of functioning. In recent years, there has been a growing awareness that stroke assessment must extend beyond the traditional outcome of mortality and neurological symptoms, and should include physical, psychological and social functioning. The International Classification of Functioning, Disability and Health (ICF)[6] also uses this biopsychosocial approach[7]. Since the 1980s, this biopsychosocial model has increasingly been applied in health care and research, especially in rehabilitation medicine. Outcome on the ICF activities and participation levels is most relevant for chronic stroke patients when they need to function in the community again.

Although the consequences of stroke are chronic, studies focusing on the long-term consequences of stroke beyond the first year have been scarce. Long-term follow up studies can help to understand the natural course of body functions, activities and participation after stroke. In particular acknowledging that a number of questions asked by patients and their relatives are related to the long-term prognosis of activities and participation. Prognostic models in which clinically relevant outcome is predicted by valid determinants may be helpful to address these questions. It has been found that reducing the uncertainty about the functional prognosis seems to improve quality of life[8]. Identification of risk factors related to outcome can help to provide adequate health services and support patients and relatives in preparing for their future lives. In addition, risk profiles make it possible to select patients who are susceptible to deterioration of activities over time[9]. The models can also help to adjust care to patients' needs and to anticipate the need for home adjustments and community support[10,11]. Several reviews have focused on prognostic factors for survival[12] and functional outcome in stroke[10,13,14]. A wide range of determinants for outcome have been identified, which is partly due to the existing heterogeneity in stroke populations and to differences in outcome measurements. Moreover, there is not much evidence for the accuracy of various determinants of functional outcome, since many prognostic studies have been characterised by considerable methodological problems[10,12,14].

Mobility

One of the major goals during rehabilitation is to restore walking function and to prevent deterioration in patients' ability to walk independently and safely, and failing to achieve this objective is perceived as one of the key problems in chronic stroke. Fortunately, Jorgensen et al. showed that 64% of the survivors had independent walking function at the end of hospital rehabilitation. The recovery of walking function mainly occurred within the first 11 weeks after stroke[15]. Despite the finding that a substantial part of the stroke patients will regain independent walking, recent studies showed that only about one fifth[16] to two thirds[17] of patients manage to walk independently in the community again. Besides lower gait velocities and shorter covered distances[18-20], hemiplegic gait is accompanied by greater energy costs than that of healthy age-matched controls[21,22]. All these factors lead to impaired ambulation in the community. Not much research has been done on mobility outcome in the chronic stage after stroke. It remains unclear whether gains that are made during rehabilitation can be sustained after discharge. Although gains made in ADL function seem to persist, some studies have suggested that mobility declines over the years, although results reported in the literature have been contradictory[23-30]. It has been shown that, on average, patients maintained the functional gains they had made between 6 and 12 months after stroke onset. Focusing on individual patients, however, it has been suggested that about one third of all patients with incomplete recovery showed either significant functional improvement or deterioration in comfortable walking speed beyond 6 months after stroke[30].

Since a decline in mobility outcome might result in a loss of ADL independency, decreased endurance and social isolation, it would be valuable to be able to identify patients who are at risk for such deterioration. The study by Kwakkel et al.(2002)[30] and that by Paolluci (2001)[27] investigated possible predictors of changes in outcome, but they were unable to identify determinants that could explain a substantial part of the variation in the chronic post-stroke phase. Both authors mainly focused on determinants that were related to patient and stroke characteristics and to physical outcome. They did not, for instance, include factors like depression and fatigue, even though both are common complaints after stroke.

Depression and Fatigue

A recent review showed that depressive symptoms are present in about one third of the stroke population[31], and that between 38% and 68% of the patients report fatigue[32-36]. The role of these two factors in long-term outcome has not been thoroughly investigated however. Some studies have suggested that depression is negatively associated with functional outcome, i.e. activities of daily living (ADL)[37-45] and health-related quality of life (HRQoL)[43]. Studies on fatigue have suggested that this problem may independently affect functional outcome after stroke[33,35,36,46]. The small number and poor comparability of studies is partly due to the fact that different definitions and measures have been used to determine depression and fatigue. Fatigue in particular lacks an unambiguous definition that validly reflects the multidimensional qualities of this symptom[47-49]. Also, studies have examined different patient populations, and chronic stroke patients have hardly been studied. In addition, most studies that have assessed both depression and fatigue were cross-sectional, showing frequencies at different time points. Thus far, only a few studies have evaluated the cumulative incidence of depression over a prolonged period[50-52]. Since it has been suggested that depression[50,53] and fatigue[54] are time-dependent, longitudinal studies would be useful to evaluate the course over a longer period after stroke and evaluate the impact of these symptoms on outcome. One might suggest that, especially in chronic stroke patients, factors like depression and fatigue are of great concern. It is particularly when patients need to function in their own community again that these symptoms may result in a substantial reduction in activities, restrictions in participation and decreased quality of life.

Care

Providing the right care to chronic patients is a challenge, since the consequences of a stroke are diverse. Generally, most attention is paid to care in the acute and subacute phases after stroke. However, many of these patients need care over a much longer period of time to cope with the consequences of their stroke[4]. It is therefore important that the care that is provided meets the demands of the individual patient. Thus far, few studies have investigated the appropriateness of health care by analysing discrepancies between health care demands and the use of health care[55-57]. Some of these studies suggested that care provision was not meeting all of the needs, resulting in the perception of unmet needs by a relatively high percentage of patients[55-58]. Identifying determinants related to the perception of unmet demands can help to guide the care to the right patients.

FuPro-Stroke study

The FuPro-Stroke study (the Functional Prognostication and disability study on stroke) was part of the larger FuPro research programme, in which the functional prognosis of four neurological diseases (Multiple Sclerosis, Traumatic Brain Injury, Amyotrophic Lateral Sclerosis and stroke) is being investigated. This programme is coordinated by the department of Rehabilitation Medicine of the VU Medical Center in Amsterdam, and supported by the Netherlands Organisation for Health Research and Development (ZonMW programme on Rehabilitation, No. 1435.0020). The FuPro-Stroke study was a prospective cohort study conducted in four Dutch rehabilitation centres. Between April 2000 and July 2002, patients with stroke were recruited at the start of inpatient rehabilitation and were followed up for one (part I, V.P.M. Schepers) to three years (part II, I.G.L. van de Port) post stroke. All subjects had been hospitalised before admission to the rehabilitation centre. Patients were included in the following rehabilitation centres: De Hoogstraat, Utrecht; Rehabilitation Centre Amsterdam, Amsterdam; Heliomare, Wijk aan Zee; Blixembosch, Eindhoven.

Inclusion criteria were: age over 18, first-ever supratentorial stroke located on one side (cortical and subcortical infarctions, intracerebral haemorrhages or subarachnoid haemorrhages). Stroke was defined according to the World Health Organisation (WHO) criteria as “rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin”[59]. Exclusion criteria were a pre-stroke Barthel Index below 18 (range 0-20) and insufficient Dutch language skills. Patients with aphasia were not excluded from this study, and proxy ratings were used for these patients when necessary and possible. Subjects were included and assessed in the first week of inpatient rehabilitation, and again at 6, 12 (part I) and 36 (part II) months after their stroke. A subpopulation was also assessed at 24 months post stroke for the MOVE study (I. van Wijk)[60]. However, these data have not been used in the present thesis.

The consequences of stroke were assessed at the level of body functions and structures, activity and participation by means of validated and reliable outcome measures. Whereas the first part of the FuPro-Stroke study (by V.P.M. Schepers) mainly focused on clinimetrics and determinants of outcome during the first year after stroke[61], the aims of the second part were to investigate the long-term prognosis of chronic stroke in terms of outcome up to 3 years after stroke onset. Therefore, the following research questions are addressed in the present thesis:

Firstly: What determinants can predict mobility outcome one year after stroke and is it possible to derive a valid prognostic model for mobility outcome at one year post stroke? (Chapter 2) Secondly: Who is susceptible to deterioration in mobility outcome from one to three years post stroke and what risk factors determine deterioration in mobility outcome from one to three years post stroke? (Chapter 3) Thirdly: How is gait speed, as an important derivative of walking ability, related to community ambulation in chronic stroke? (Chapter 4) Fourthly: What is the evidence from the literature of the effect of lower limb strengthening, cardio-respiratory fitness training and gait-oriented circuit training on gait, gait-related activities and health-related quality of life in patients with stroke? (Chapter 5) Fifthly: What factors can be identified that predict the presence of depression in the long term after stroke? (Chapter 6) Sixthly: Is fatigue an independent determinant that significantly affects the longitudinal course of activities of daily living, instrumental activities of daily living, and health-related quality of life from 6 months to 3 years after stroke? (Chapter 7) Finally: Do patients with chronic stroke perceive unmet demands and, if so, are we able to identify the underlying risk factors? (Chapter 8)

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2

Predicting mobility outcome one year after stroke: a prospective cohort study

Ingrid G.L. van de Port, Gert Kwakkel, Vera P.M. Schepers, Eline Lindeman

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Abstract

Objective To develop a prognostic model to predict mobility outcome one year post-stroke.

Design Prospective cohort study in patients with a first-ever stroke admitted for inpatient rehabilitation.

Patients A total of 217 patients with stroke (mean age 58 years) following inpatient rehabilitation in 4 rehabilitation centres across the Netherlands.

Methods Mobility was measured using the Rivermead Mobility Index at one year post-stroke. Included independent variables were: patient and stroke characteristics, functional status, urinary incontinence, sitting balance, motor and cognitive function. Univariate and multivariate linear regression analyses were performed in a model-developing set (N=174) and the model was validated in cross-validation set (N=43).

Results Total Rivermead Mobility Index score at one year post-stroke was predicted by functional status, sitting balance, time between stroke onset and measurement, and age. The derived model predicted 48% of the variance, while validation in the cross-validation set resulted in an adjusted R^2 of 0.47.

Conclusion The present prospective study shows that outcome of mobility one year after stroke can be predicted validly by including functional status, sitting balance, moment of admission to the rehabilitation centre after stroke onset and age.

Introduction

Stroke is the most important cause of morbidity and long-term disability in Europe and 40% of the patients with stroke need active rehabilitation services[1]. Regaining mobility is a primary goal of patients with stroke during rehabilitation, since it is a key factor in becoming independent in daily functioning. Predicting mobility (i.e. independent physical movement within the environment[2]), especially for the long-term, is essential to be able to inform patients and their families about the consequences of the stroke when a patient has to function in the community again.

Most studies on outcome prediction in a rehabilitation-based stroke population have focused on activities of daily living (ADL)[3-11]. Important predictors of functional outcome were age[5-7;9], stroke severity[6], motor impairment[3], sitting balance[4], urinary incontinence[9], co-morbidity[9] and disability at the start of the rehabilitation period[4-7;9-11].

Only a few studies have been performed on prognostication of mobility-related outcomes after stroke. Mobility outcome, at 10 months post-stroke, was found to be best explained by self-efficacy, age and mobility at discharge from geriatric rehabilitation[12]. In a community-based cohort, the ADL independency at admission to the stroke unit was the single predictor of walking ability at discharge[13]. Age, sitting balance and bowel control were predictive factors for the walking item of the Barthel Index (BI) at discharge from the hospital[14]. Sanchez et al.[11] classified patients into 3 subgroups, viz. a motor, a motor-sensitive and a motor-sensitive with haemianopia group. This classification, plus pareses and age determined ambulation at 6 months post-stroke. Another study[15] found that advanced age and severity of pareses were valid predictors of ambulation, also at 6 months post-stroke. Comfortable walking speed at 6 months post-stroke was best predicted by motor function, sitting balance and social support at 2 weeks post-stroke.

Unfortunately, the studies are not fully comparable, due to differences in definition and with that, in measures used, the timing post-stroke and a number of methodological shortcomings[16]. Also, Meijer et al.[17] concluded, after reviewing the literature, that summarizing prognostic factors for ambulation and ADL was not feasible. They suggested that further research was needed on prognostification of stroke outcome in the subacute phase.

The aim of the present study was to derive a prognostic model for an inpatient rehabilitation cohort, in order to predict mobility outcome 1 year post-stroke.

Methods

Design

Between April 2001 and April 2003 patients with stroke receiving inpatient rehabilitation were recruited for the Functional Prognosis after stroke study (i.e. FuPro-Stroke). This prospective cohort study was conducted in 4 Dutch rehabilitation centres. The medical ethics committees of University Medical Centre Utrecht and the participating rehabilitation centres approved the FuPro-Stroke study. All patients included gave their informed consent. A proxy gave informed consent if the patient could not communicate.

Subjects

All patients were included at the start of their inpatient rehabilitation in 1 of the 4 rehabilitation centres across the Netherlands. All patients had been hospitalised before admission to the rehabilitation centre. Inclusion criteria were: age over 18, first-ever stroke (cerebral infarctions or intra-cerebral haemorrhages) and a supratentorial lesion located on one side. Stroke was defined according to the WHO definition[18]. Exclusion criteria were pre-stroke BI lower than 18(0-20), insufficient Dutch language skills and subarachnoid haemorrhages. Patients for whom the time between stroke onset and measurement was more than 100 days were excluded from analysis.

Dependent variables

The definition of mobility is equivocal, and can be given from different perspectives and in different terms[2]. The used outcome measure for mobility was the Rivermead Mobility Index (RMI)[19]. The RMI is a further development of the Rivermead Motor Assessment, consisting of 14 questions and 1 observation. The items are scored dichotomously (0-1) and were summated. Total scores range from 0 to 15 and a higher score reflects better mobility. The questions can be answered by patients or carers[19]. It is a simple and short outcome measure to determine mobility. The RMI is valid and reliable[19;20], responsive to change[21] in patients with stroke and its items cover a wide range of activities, from turning over in bed to running.

Independent variables

Independent variables were chosen on the basis of the results of previous studies and on clinical grounds. The following independent variables were included: sex, age, type of stroke, hemisphere, co-morbidity, living status, hemianopia, aphasia, inattention, functional status, urinary incontinence, sitting balance, motor function, cognition and time between stroke onset and the first measurement. An independent observer collected data concerning the type of stroke (infarctions or haemorrhages) and its location, presence of hemianopia, co-morbidity (the presence of cardiovascular and/or respiratory diseases, diabetic mellitus and co-morbidity of the locomotor system) and living status (living alone or not). Inattention was measured by the letter cancellation task[22] and was scored positive when the patient scored 2 omissions or more at one side, compared with the other side. The total score (0-20) of the activities of daily living (ADL) BI[23] was used to describe functional status. Urinary incontinence was assessed with the corresponding BI item. Although the item was originally scored on a 3-point scale (continent, occasional accident (maximum once a day), incontinent), the score was dichotomised for the present analyses (0=continent, 1=incontinent or occasional accident). The Trunk Control Test (TCT) is valid and reliable in stroke patients[24] and was used to assess sitting balance. The corresponding item was dichotomised: 0 for patients not able to sit independently, vs 1 for patients able to sit independently. The Motricity Index (MI) is a valid and reliable measure[24] and was used to determine motor function of the arm (MI arm) and the leg (MI leg). Scores ranged from 0 (no activity) to 33 (maximum muscle force) for each dimension. Cognitive status was assessed with the Mini Mental State Examination (MMSE)[25]. Aphasia was defined with the Token Test (short form)[26] and the Utrecht Communicatie Onderzoek (UCO)[27]. Patients scoring 9 errors or more on the Token Test and/or scoring less than 4 on the UCO were considered aphasic. Since only communicative patients completed the MMSE, a dichotomous variable for cognition was developed on the basis of a positive score on the MMSE score or on the existence of aphasia. The cognition variable was scored positive if MMSE ≤ 23 or patients were classified as aphasic.

Procedure

After admission to the rehabilitation centre (t0) and at one year (t1) post-stroke, patients were visited by a research assistant. Baseline values were obtained within 2 weeks after t0 by collecting data from medical charts, face-to-face interviews and physical and cognitive examination. For patients who could not communicate, information was gained by interviewing a member of the nursing staff.

At t1, patients were visited by a research assistant for an assessment at home or at the institution where they were staying. The RMI was completed and for patients who could not communicate, a proxy was interviewed. Most often this was the patients' spouse and occasionally a member of the nursing staff if the patient was institutionalised.

Data analysis

Data from all patients were entered into a computer database and analysed with the SPSS statistical package (version 12.0). Multiple linear regression analysis was used to predict RMI score. The data set was split non-randomly into a model-developing set and a cross-validation set, based on time of inclusion. The model-developing set, comprising the first 174 patients included (80%), was used to derive the prognostic model, whose validity could be tested in the cross-validation set, comprising the last 43 patients (20%)[28]. Univariate regression analysis of the model-developing set was used to select significant determinants ($p < 0.1$) for the subsequent development of the multivariate linear regression model. This selection, with a more liberal significance level, increased the sensitivity for selection of true predictors and limited the bias in the selected coefficients. These candidate determinants were tested for multicollinearity to prevent over-parametrization of the prediction model. The variables were cross-tabulated, and if the correlation coefficient was >0.7, the variable with the lowest correlation coefficient, in relation to the outcome measure, was omitted from the analysis[29]. The remaining significant variables were used in a backward multivariate linear regression analysis. Collinearity diagnostics (i.e. eigenvalues, condition index) were applied for each variable to control for unstable estimates and make sure that the proportion of variance for a particular variable was unique and not due to other variables in the model. A condition index greater than 10 was interpreted as indicating the presence of collinearity[30]. The final model was validated by calculating the explained variance in the cross-validation group. After cross validation the model was re-fitted in the total (model-developing + cross-validation) data set. Each hypothesis was tested with a two-tailed analysis, using 0.05 as the level of significance.

Results

At t0, 308 patients were included in the FuPro-Stroke study. After the patients with a subarachnoid haemorrhage had been excluded, 274 patients remained. At t1, 235 patients were interviewed. Seven patients had died within the first year after stroke, 12 patients had had a recurrent stroke, and were therefore excluded from follow-up, 17 patients refused participation and 3 could not be traced. Median time between stroke onset and t1 was 52.0 weeks (interquartile range = 51-53). Nine patients were excluded because the time interval between stroke onset and first measurement was more than 100 days. In addition, there were 9 missing values for co-morbidity, therefore, complete datasets were available for 217 patients. Mean age was 58 years, and 65% were men. Mean time between stroke onset and t0 was 45 days (SD=16) (Table 1). Treatment availability was

more or less the same for all patients in our population and applied according to the Dutch stroke guidelines. All patients received multidisciplinary rehabilitation therapy consisting of physical and occupational therapy, speech-language pathology, psychology and therapeutic recreation for 5 days a week.
At t1, 2 patients (1%) were still in the rehabilitation centre and 9 (4%) were living in a nursing home. Thirty-eight patients (18%) could not communicate at t1 and, therefore, proxy ratings for the RMI were obtained from the spouse (97%) or the nursing staff (3%). In the complete dataset mean RMI score was 12.0 (SD= ± 3.1) at t1. Sixteen percent of the patients scored a maximum RMI score of 15. After data splitting on the basis of the time of inclusion, 174 patients (80%) were assigned to the model-developing set and 43 (20%) patients to the cross-validation set. Baseline characteristics of the patients included in both sets are illustrated in Table I.

Univariate analysis

Univariate analysis showed significant associations between, on the one hand, RMI at t1, and, on the other hand, age, cognition, type of stroke, inattention, co-morbidity, urinary incontinence, functional status (BI), sitting balance (TCT), motor function (MI arm, MI leg) and time between stroke onset and the moment of measurement at t0 in the model-developing set (Table 2).
The BI, MI arm and MI leg scores showed high collinearity (Spearman's Rank correlation coefficients ranging from 0.72 to 0.74). Because the BI showed the strongest association with the RMI score, the BI was used in the multivariate regression analysis.

Multivariate analysis

The backward linear regression analysis constructed a model with age, type of stroke, time between stroke onset and measurement, sitting balance and functional status as predictive factors (Table 2). Collinearity diagnostics showed a high condition index of 18.7 for the type of stroke. This variable was therefore excluded from the final regression model. Functional status, sitting balance, time between stroke onset and measurement, and age were valid predictors in the final model (Y= 10.75+0.30xBI+2.65x sitting balance-0.04xdays between stroke onset and measurement-0.05xage). The explained variance of the model was 0.50 (adjusted R^2=0.48) in the model-developing sample. The found adjusted R^2 of the model in the cross-validation sample was 0.47 and 84% of the patients were correctly classified within ±2 RMI-units (mean RMI=12.4, 95% confidence interval (CI) = 11.8-13.0). After re-fitting the model in the total data-set, the mean value of the RMI was 12.1, with a 95% CI for mean of 11.8-12.4. Eighty-one percent of the patients were correctly classified within ±2 RMI-units.

Table 1. Patient characteristics at admission (t0), total group and model-development and cross-validation group.

	Total n=217	Model developing n=174	Cross-validation n=43
Gender (% female)	35	36	30
Mean (SD) age (years)	58 (11)	58 (11)	55 (11)
Living status (% living alone)	23	24	21
Co-morbidity † (% present)	79	79	80
Type of stroke (% haemorrhage)	17	17	16
Hemisphere (% right)	47	48	44
Mean time (SD) between stroke onset and t0 (days)	45 (16)	45 (16)	45 (14)
Haemianopia (% present)	19	20	14
Aphasia (% present)	30	31	26
Median (IQR) MMSE*	27 (3)	27 (4)	27 (3)
Cognition (% cognitive problems and/or aphasia)	42	44	30
Inattention (% present)*	35	37	29
Urinary incontinence (% present)	28	31	16
Median (IQR) Motricity Index (arm)	47 (65)	50 (63)	39 (67)
Median (IQR) Motricity Index (leg)	48 (38)	53 (38)	42 (43)
Sitting balance (% present)	84	85	81
Median (IQR) Barthel Index	13 (7)	13 (7)	14 (6)

MMSE: Mini Mental State Examination (0-30, ≤23 indicates cognitive problems); Aphasia was determined by the short form Token Test (≥ 9 errors indicates presence of aphasia); Sitting balance was present when the score on the sitting item of the Trunk Control Test was 25; Urinary incontinence was present when the corresponding item on the Barthel Index was scored as 0 or 1. Inattention was defined as 2 omissions or more on one side, compared with the other side, in the letter cancellation task.

* n= 151, 120, 32, respectively

† the presence of cardiovascular and/or respiratory diseases, diabetic mellitus and co-morbidity of the locomotor system

Table 2. Univariate and multivariate linear regression analysis: standardized Beta coefficients of independent variables assessed at admission for inpatient rehabilitation and Rivermead Mobility Index (RMI) score at 1 year post-stroke (n=174)

Determinants	**Univariate analysis**		**Multivariate analysis**		
	Standardized Beta	**p-value**	**Standardized**	**p-value Beta**	**% explained variance**
Gender (female)	-0.042	0.580			
Age*	-0.188	0.013	-0.177	0.001	3%
Living alone	-0.121	0.113			
Comorbidity (present)*	-0.147	0.053			
Type of stroke (haemorrhage)*	0.176	0.020			
Hemisphere (right)	-0.052	0.499			
Mean time between stroke onset and admission (days)*	-0.247	0.001	-0.209	<0.001	4%
Haemianopia (present)	0.094	0.217			
Cognition (impaired cognition)*	-0.231	0.002			
Inattention (present) †	-0.277	0.002			
Urinary incontinence (present)*	-0.264	<0.001			
MI (arm)	0.450	<0.001			
MI (leg)	0.466	<0.001			
Sitting balance (present)*	0.540	<0.001	0.293	<0.001	8%
BI*	0.575	<0.001	0.437	<0.001	33%

*Included in the multivariate analysis. MI was not included due to collinearity with BI.

MI = Motricity Index (range 0-100); TCT = Trunk Control Test (range 0-100); TT = Token test, short form (range 0-20); BI = Barthel Index (range 0-20). The multivariate model included BI, sitting balance, time between stroke onset and measurement and age and explained 48% of the total variance.

† Inattention was not included in the multivariate analysis, because only patients without aphasia completed the letter cancellation task (n=120)

Discussion

Mobility outcome was optimally predicted by functional status, sitting balance, time between stroke onset and first measurement, and age at admission to inpatient rehabilitation. It is important to note that more than two-thirds of these relatively young patients were not able to walk independently, according to the BI mobility item, suggesting that prognostication of mobility outcome was justified. The final model explained 48% of the variance of the outcome on RMI score at t1, which is comparable to other prognostic research. In a previous study sitting balance, MI leg score and social support explained 49% of the variance in comfortable walking speed at 6 months post stroke[15]. For a smallest detectable difference of 2 points[31], the model was able to predict the scores with an accuracy of 81%. This underpins the robustness of found determinants. This model is slightly higher compared to another study in which 77% of the patients were correctly classified on the Functional Ambulation Categories (FAC)[11]. To our knowledge, the present prospective study is the largest prognostic study aimed to forecast long-term outcome of mobility for patients admitted in a stroke rehabilitation ward.

The strongest predictor (33%) in our model was functional status (BI), which is in agreement with previously published studies evaluating functional outcome[6;7;9;11]. One study on mobility outcome showed that functional status (BI) at admission to the hospital was the single predictor for walking ability in a multivariate model[13]. The strong predictive value of functional status for mobility outcome was expected, in view of the close interrelationship between BI and RMI[19;20].

Sitting balance was another independent factor associated with RMI, suggesting that balance control is highly specific to control of mobility[20]. This finding is in agreement with those of Duarte and colleagues[4], who showed that trunk balance while sitting is closely associated with gait velocity and walking distance. Similarly, Kwakkel et al.[15], showed that sitting balance in the first week post-stroke was an independent determinant for predicting comfortable walking speed at 6 months. Another study showed that balance, determined by the sit and reach test, explained 33% of the variance of Functional Independence Measure (FIM) mobility score at discharge[32]. The present study shows that just assessing the sitting balance, as tested by 30 seconds of sitting unsupported following the TCT test, is an important predictor for outcome of mobility after stroke.

Time between stroke onset and measurement was a valid predictor in our study, suggesting that shorter intervals between stroke onset and admission are associated with better RMI scores at 1 year post stroke. The average onset to admission interval in the present study was 45 days, which is comparable to other European studies[33], but seems longer compared to American[34]. Our result seems to confirm previous studies, in which an earlier start of inpatient rehabilitation was found to be related to better outcomes in the longer term[7]. Hypothetically, this relationship could be partialled out by correcting for differences in functional status at admission and other patient characteristics. However, in contrast to what might be expected, patients who had a longer onset to admission interval did not have a lower BI score at admission to inpatient rehabilitation (r=-0.283 vs partial correlation r=-0.277). Unfortunately, we were not able to include variables considering functional status and patient characteristics (i.e. co-morbidity and medical complications) during hospital stay. These variables might have had an influence on the time interval between stroke onset and admission.

According to other studies of functional outcome in a rehabilitation population[5-7;9;11;33], age is also an independent factor. Previous prospective studies have shown that older age was negatively related to mobility outcome at discharge from the hospital[14] as well as to long-term outcome after stroke[11,15]. Age has also been found to be a valid long-term predictor of FIM mobility outcome in elderly stroke patients[12]. In our study, age played a small but independent role in mobility outcome, which shows that even in this relatively young stroke population, age affects the prognosis of recovery of mobility. Motor function was found to be a determinant for mobility outcome in stroke patients[35]. In the present study MI was highly correlated to BI and therefore not included in the multivariate analysis. However, because of this high association and since BI is a predictor for mobility outcome, it is reasonable to assume that motor function might be a predictor for mobility outcome in this study as well.

Unfortunately, comparison between prognostic studies is often impeded by differences in selecting a uniform set of outcome measures for developing prediction models, as well as in the way they are defined. Secondly, determinants and outcomes are measured at different time intervals post-stroke, depending on the stroke population involved. Thirdly, most prognostic studies showed several methodological shortcomings[16]. Only a few used multivariate analysis, calculated the explained variance of outcome, or validated the model. Due to a lack of validation, most derived prediction models probably overestimate the accuracy of prediction. In the present study, the regression model was validated in a non-random sample. Non-random splitting is a tougher test than random splitting, since random splitting leads to a data set that is the same apart from chance variation[28].

Although we explained a substantial part of the variance with our model, still half of the variation stays unexplained. Many variables were assessed, but for pragmatic reasons no other variables, such as RMI at t0, were assessed and included in the analysis. Also, factors such as post-discharge therapy and home exercise programs were

not analysed in the present study. In addition, further investigation is needed to validate the present model in an early phase post stroke. Finally, it is important to note that the model is tested for a relatively young stroke population admitted in rehabilitation setting. Therefore, generalisation of the present model with respect to age might be limited. It should be noted, however, that the patients who dropped out and were not included the model developing, were not significantly different from those who were included, except that the drop-outs showed more aphasia.
In the present study, the RMI was used as an outcome measure, which may be arbitrary. Although, 16% of the patients scored the maximum score of 15, this ceiling was judged as acceptable, since a ceiling effect of higher than 20% is considered to be significant[36]. In our opinion, the RMI is a useful measure covering a wide range of mobility items. Nevertheless, we encourage development of new outcome measures for mobility in chronic stroke without the presence of ceiling effects.
In conclusion, the present study shows that it is possible to derive a valid model, which includes predictors that are easy to assess and commonly collected in rehabilitation, and explains a substantial proportion of variation in long-term mobility outcome. In our opinion the model may serve as a guide to support clinicians in their stroke management to predict outcome of mobility at one year after stroke.

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3

Susceptibility to deterioration of mobility long-term after stroke: a prospective cohort study

Ingrid G.L. van de Port, Gert Kwakkel, Iris van Wijk, Eline Lindeman

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Abstract

Background and Purpose The aim of the present study was to identify clinical determinants able to predict which individuals are susceptible to deterioration of mobility from 1 to 3 years after stroke.

Methods Prospective cohort study of stroke patients consecutively admitted for inpatient rehabilitation. A total of 205 relatively young, first-ever stroke patients were assessed at 1 and 3 years after stroke. Mobility status was determined by the Rivermead Mobility Index (RMI), and decline was defined as a deterioration of ≥2 points on the RMI. Univariate and multivariate logistic regression analyses were performed to identify prognostic factors for mobility decline. The discriminating ability of the model was determined using a receiver operating characteristic curve.

Results A decline in mobility status was found in 21% of the patients. Inactivity and the presence of cognitive problems, fatigue, and depression at 1 year after stroke were significant predictors of mobility decline. The multivariate model showed a good fit (Hosmer–Lemeshow test $P > 0.05$), and discriminating ability was good (area under the curve 0.79).

Conclusions Mobility decline is an essential concern in chronic stroke patients, especially because it might lead to activities of daily living dependence and affects social reintegration. Early recognition of prognostic factors in patients at risk may guide clinicians to apply interventions aimed to prevent deterioration of mobility status in chronic stroke.

Introduction

Because decreased mobility is one of the major concerns for patients surviving a stroke, improving mobility is one of the main goals of stroke rehabilitation. Previously published studies suggest that mobility-related outcome improves after rehabilitation treatment[1–4]. However, it remains unclear whether improvements made during rehabilitation can be sustained long term after stroke[5,6]. The general view is that little recovery is to be expected 6 months after stroke[7,8]. Unfortunately, the course of mobility status in the chronic stage (ie, beyond 6 months after stroke) has hardly been studied, and the results have been contradictory. Whereas some studies found that patients maintain their levels of functional status or even improve over time[1,9], others observed that patients show a gradual deterioration in functional status in this chronic poststroke stage[2,10]. Kwakkel et al[5] showed that patients, on average, maintained the functional gains they had made from 6 to 12 months after stroke onset. However, about one third of all patients with incomplete recovery showed either significant functional improvement or deterioration in comfortable walking speed. Apparently, the absence of a significant average change in a stroke population does not reflect the individual improvement or deterioration of patients.

Especially, deterioration of walking ability long term is regarded as a major problem, resulting in a loss of activities of daily living (ADL) independency and social isolation. A number of randomized studies have shown that mobility improves by therapeutic interventions aimed at improving gait in chronic stroke patients[11–15]. Therefore, it is highly useful to identify those patients who are susceptible to long-term deterioration. However, to date, there have only been few reports in the literature on research to identify factors able to predict which patients will show significant change[2]. Therefore, the purpose of the present study was to identify clinical determinants able to predict the individuals who are susceptible to deterioration in mobility from 1 to 3 years after stroke.

Materials and Methods

Subjects

Subjects were stroke patients included in the first week of inpatient rehabilitation in 4 main rehabilitation centers in the Netherlands to participate in the longitudinal functional prognosis after stroke study (FuPro-Stroke study). All subjects had been hospitalized before admission to the rehabilitation center. Inclusion criteria were: >18 years of age, first-ever stroke, and a supratentorial lesion located on 1 side. Stroke was defined according to the World Health Organization definition[2,16]. Exclusion criteria were a prestroke Barthel Index (BI) <18 (0 to 20) and insufficient command of Dutch.

Dependent Variable

Mobility was assessed by the Rivermead Mobility Index (RMI)[17]. The RMI is a simple and short outcome measure, consisting of 14 questions and 1 observation. It is valid and reliable[17–20], unidimensional[21], and responsive to change[19,22]. Its items cover a wide range of activities, from turning over in bed to running. The items are scored dichotomously (0 –1) and summated, with a higher score reflecting better mobility (0 –15). The questions can be answered by patients or carers.[17] We considered a decline of ≥2 points on the RMI as the 95% confidence limits of measurement error (ie, error threshold)[17]. The change score was dichotomized into 1 for "deterioration" (a decline of ≥2 points) and 0 for "improvement or no change beyond the error threshold."

Independent Variables

The independent variables used in this study were clustered into 4 domains: patient and stroke characteristics, physical factors, psychological/ cognitive factors, and social factors. The patient and stroke characteristics included gender, age, level of education, type of stroke, hemisphere, aphasia, and inattention. The physical factors included motor function, ADL independence, and level of activity. Psychological and cognitive factors included cognitive status, depression, and fatigue. Social factors considered were living alone and social support.

Data were collected on the type of stroke (infarction or hemorrhage) and its location. Aphasia was defined using the Token Test (short version)[23] and the Utrecht Communication Observation (Utrechts Communicatie Onderzoek [UCO])[24]. Patients scoring ≥9 errors on the Token Test or scoring <4 on the UCO were considered aphasic. Inattention was measured by the letter cancellation task and was scored positive when the patient had ≥2 omissions at 1 side compared with the other side.

The Motricity Index (MI)[25] was used to determine the motor functions of arm (MI arm) and leg (MI leg). Scores range from 0 (no activity) to 33 (maximum muscle force) for each dimension, with a maximum total score of 100. Scores were dichotomized, and scores between 0 and 75 on the MI leg dimension or between 0 and 76 on the MI arm dimension indicated no optimal range of motion, whereas higher scores indicated optimal range of motion. Functional status was determined by the ADL BI[26]. Total score (0 –20) of the BI was dichotomized into "dependent" (BI<19 points) and "independent" (BI 19 to 20 points). The Frenchay Activities Index (FAI)[27] was used to determine the level of activity.

Total scores ranged from 0 to 45 and were dichotomized into 0 to 15 as inactive and 16 to 45 as moderately/highly active.
Cognitive status was assessed with the mini mental state examination (MMSE)[28]. Scores vary from 0 (severe cognitive problems) to 30 (no cognitive problems), and the MMSE was completed only by nonaphasic patients. Scores were dichotomized and cognitive problems were regarded as present when MMSE was ≤23. Depression was measured by the Center for Epidemiologic Studies-Depression (CES-D)[29] and dichotomized into "non-depressed" (CES-D <16 points) and "depressed" (CES-D ≥16 points)[30]. Fatigue was determined by the Fatigue Severity Scale (FSS)[31]. The FSS consists of 9 questions, and total scores range between 9 and 63. The mean score (total score/9) was dichotomized into "nonfatigued" (FSS <4 points) and "fatigued" (FSS ≥4 points)[32].
Social support was determined by the shortened version of the Social Support List (SSL-12)[33], which consists of 12 questions about the frequency of social support in different situations. Scores on individual items range from 1 to 4, with a maximum score of 48. The sum score on this scale was dichotomized into <25 for no or minimal social support and 25 to 48 for moderate to high social support.

Procedure

At 1 (t1) and 3 (t2) years after stroke, patients were visited by a trained research assistant for an assessment at home or at the institution where the patient resided. For non-communicative patients, proxies were interviewed, usually the patients' spouses. The medical ethics committees of University Medical Center Utrecht and the participating rehabilitation centers approved the FuPro-Stroke study. All patients included gave their informed consent, whereas a proxy gave informed consent if a patient was not communicative.

Statistics

Data were analyzed with the SPSS statistical package (version 12.0). Mobility scores at 1 and 3 years after stroke were compared by means of the Wilcoxon signed rank test. Univariate analyses were conducted by calculating odds ratios to identify statistically significant candidate factors relating to mobility decline. Variables with a P value <0.2 were selected for use in the multivariate analyses. A more liberal significance level increased the power for selecting true predictors and limited the bias in the selected coefficients. Subsequently, significant independent variables were used in a multivariate backward logistic regression analysis to predict mobility outcome. Only determinants with a significance level <0.1 were allowed into the final model. Goodness of fit of the multivariate logistic model was tested with the Hosmer–Lemeshow test, and a receiver operating characteristic (ROC) curve was used to test the predictive properties of the developed regression model. A two-tailed significance level of 0.05 was used.

Results

At 1 year after stroke, 264 patients were assessed. During follow-up, 13 patients died, 33 patients withdrew, and 13 patients were lost to follow-up (moved, residing outside the Netherlands). Baseline characteristics of the patients included at 3 years after stroke were not significantly different from those who had ended their participation in the study except for age, MMSE, and FAI (Table 1).
At 3 years, 205 patients were assessed, and RMI data were available for 202 patients. Mean age at t1 was 57 years (SD=11), and 59% were men. Of the patients, 76% were living with a partner, 2% were still residing at a rehabilitation center, and 4% were institutionalized.

Table 1. Patient characteristics at 1 year after stroke for patients included and not included in the 3-year follow-up assessment

Patient Characteristic	Included (n=205)	Not Included (n=59)
Gender, % male	59	68
Age, % >65*	25	39
Living alone, %	24	26
Hemisphere, % right	46	46
Typeofstroke, % infarction	72	78
Aphasia, % present	18	25
MMSE, % ≤23*	11	26
MIleg, % impaired	59	71
BI, % dependent	39	44
CES-D, % depressed	30	39
FSS, % fatigued	68	73
FAI, % inactive*	32	45

*P<0.05 in χ^2 test for cross tabs. n=No. of subjects.

Table 2. **Univariate and multivariate analyses using decline of mobility as outcome measure**

	Univariate Analysis (n=Variable)				Multivariate Analysis (n=152)			
Independent Variables	B (ß Coefficient)	SE	OddsRatio (95%CI)	*P* Value	B (ß Coefficient)	SE	OddsRatio (95%CI)	*P* Value
Patient/stroke characteristics								
Age, >65	0.14	0.39	1.15 (0.54–2.45)	0.72				
Sex, female	-0.44	0.36	0.65 (0.32–1.32)	0.23				
Type of stroke, infarction	-0.04	0.38	0.96 (0.45–2.03)	0.91				
Education level, university	-0.59	0.48	0.55 (0.22–1.42)	0.22				
Inattention	0.22	0.46	1.24 (0.50–3.08)	0.64				
Physical factors								
Motor function, impaired*	0.82	0.39	2.27 (1.07–4.84)	0.03				
ADL, dependent*	0.66	0.35	1.93 (0.98–3.81)	0.06				
Level of activity, inactive*	1.16	0.37	3.17 (1.55–6.52)	0.00	0.98	0.45	2.67 (1.10–6.47)	0.03
Psychological and cognitive factors								
Cognition, MMSE impaired*	1.01	0.54	2.75 (0.96–7.85)	0.06	1.17	0.67	3.23 (0.87–12.02)	0.08
Depression, present*	1.24	0.40	3.44 (1.57–7.54)	0.00	1.05	0.44	2.85 (1.19–6.81)	0.02
Fatigue, present*	1.19	0.57	3.30 (1.09–9.99)	0.04	1.04	0.62	2.83 (0.83–9.60)	0.09
Social factors								
Living alone*	0.50	0.38	1.65 (0.79–3.45)	0.18				
Social support, absent	-0.38	0.47	0.69 (0.27–1.71)	0.42				
Constant, multivariate					-2.96			

n=No. of subjects; SE=standard error of the estimate.
*P<0.2 in univariate analysis.

Mobility decline was found in 43 patients (21%), whereas 146 patients (72%) had maintained their mobility status, and 13 patients (7%) had improved between 1 and 3 years after stroke. RMI change scores ranged from -12 (decline) to +4 (improvement). The median RMI score at t1 and t2 was 13 (interquartile range 3). Ceiling effects were relatively high at t1 (20%) and t2 (14%) but were not considered to be significant[34]. The Wilcoxon signed rank test showed a statistically significant decrease in RMI score between 1 year and 3 years after stroke ($z=-4.58$; $P<0.05$). Five percent of the patients experienced a recurrent stroke, and 46% received physiotherapy during follow-up.
Univariate analysis showed statistically significant associations between mobility decline and motor function of the leg (MIleg), ADL independency (BI), level of activity (FAI), cognitive function (MMSE), depression (CES-D), fatigue (FSS), and living alone ($P=0.2$; Table 2).
Multivariate logistic regression analysis showed that level of activity, cognitive problems, fatigue, and depression at 1 year after stroke were statistically significant predictors of mobility decline between 1 and 3 years after stroke (Table 2). The multivariate model showed a good fit (Hosmer–Lemeshow test $P>0.05$). Discriminating ability of the model was good, as shown by the area under the ROC curve (0.8)[35].

Discussion

The present study shows that about one fifth of the chronic stroke victims deteriorated significantly in terms of mobility status between 1 and 3 years after stroke. Patients who had a poor level of activity, had cognitive problems, reported about fatigue, and had depressive feelings at 1 year after stroke were highly susceptible to deterioration of mobility in the next 2 years. To our best knowledge, the present study is the largest prospective cohort study to date to investigate longterm deterioration of mobility in chronic stroke patients.
Longitudinal studies on changes long term after stroke have thus far been scarce[2,5,10,36,37], and most studies have concentrated on ADL outcome and mean changes. However, mean changes do not reflect individual changes in patients. One study that focused on long-term individual changes in mobility, as measured by the RMI, suggested that 43% of the stroke patients deteriorated in terms of mobility status[2]. Deterioration was defined as a decline of 1 point on the RMI, whereas in the present study, deterioration was defined as any change beyond the 95% limits of measurement error on RMI[17,38]. Also, Paolucci et al included patients who were more severely impaired and used a follow-up period with the variable end point of 1 year after discharge, which restricts the comparability with our study.

Interestingly, our prediction model shows that mobility decline is most strongly associated with psychological and cognitive factors and not, as might be expected, with physical factors such as lower limb strength. These findings are in agreement with a number of prospective cohort studies. Zinn et al suggested that cognitive impairments attenuated instrumental ADL recovery[39]. Depression has been found to be a significant factor in poor mobility[38] and ADL outcome[40–43] after stroke. Recognizing depression is particularly important for clinicians because about one third of all stroke patients experience depression[44]. Another common symptom of stroke patients is poststroke fatigue[45–47]. However, the impact of fatigue on poststroke recovery remains unclear in the literature[46]. It has been suggested that the presence of fatigue accounts for more functional limitations[31] and predicts decreased functional independence,[45] but prospective cohort studies have so far been lacking.

Our results suggest that the negative impact of depression and fatigue in stroke patients should not be underestimated[45]. Not only are these variables associated with poor functional outcome and mobility, it is also important to note that this relationship is probably not unidirectional, suggesting that poor mobility itself will contribute to the vicious circle by reducing the patients' level of activity and increasing their feelings of fatigue and depression.

It is possible that factors such as medication intake and the use of health care services between 1 and 3 years after stroke might have influenced outcome. However, receiving physical therapy during follow-up was not statistically significantly related to deterioration in mobility in our population. Also, the occurrence of a recurrent stroke between 1 and 3 years after stroke was not statistically significantly related to mobility decline (χ^2; $p<0.05$). Regarding the generalizability of our results, it is important to note that only patients were included who received inpatient rehabilitation in the first year after stroke. However, it is especially in this relatively young and moderately disabled population that a decline in mobility status will be of major concern. Therefore, deriving a model in this population is highly relevant and valuable. It should be noted that the patients who were not included in the study showed significantly more cognitive problems and were less active than those included (Table 1). Because these are risk factors, mobility might actually decline in even more chronic stroke patients than the 21% we identified.

Conclusion

We can conclude that about one fifth of stroke patients show a significant decline in mobility status in the longer term after their stroke. It is important to identify factors predicting a decline, such as depression and fatigue. Reducing the severity of these risk factors by providing pharmacological treatment[38] or rehabilitation programs[48] may lower the risk of mobility decline. Moreover, intensive physical training programs, aimed at improving walking competency of chronic stroke patients, have proved to increase mobility status[6,11,13,15].

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4

Community ambulation in chronic stroke: how is it related to gait speed?

Ingrid G.L. van de Port, Gert Kwakkel, Eline Lindeman

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Abstract

Objective To explore the strength of the association between gait speed and community ambulation and to investigate if this association was significantly distorted by other variables, viz. age, living alone, history of falls, the use of assistive walking devices, executive function, depression, fatigue, motor function, standing balance, and walking endurance.
Design Cross-sectional, multi-center study at three years post stroke.
Setting Four rehabilitation centers across the Netherlands.
Patients Total of 102 first ever stroke patients following inpatient rehabilitation.
Interventions Not applicable.
Main outcome measure(s) Community ambulation was determined by a self-administered questionnaire consisting of four categories. Gait speed was assessed by the 5 m walking test.
Results Twenty-six percent of the patients were non-community walkers or limited community walkers. The optimal cut-off point for community ambulation was 0.66 m/s. Although gait speed was significantly related to community ambulation, this association was confounded by balance, endurance, and the use of an assistive waking device. These factors reduced the regression coefficient of gait speed by more than 15%.
Conclusion Ability to walk in the community is determined by several factors. Assessing gait speed alone may underestimate patients' ability to walk in their own community.

Introduction

Despite the finding that a substantial proportion of stroke patients regains independent gait[1], recent studies showed that only about one fifth to two thirds[2-4] of the patients manage to walk independently in the community again. A qualitative study showed that loss of independent ambulation, especially outdoors, was one of the most disabling aspects for stroke patients[5]. In addition, Lord found that the ability to 'get out and about' in the community was considered to be either essential or very important by 75% of stroke patients[4].

Currently, attempts are being made to evaluate community ambulation with well-defined outcome measures, and gait speed has often been used as a proxy measure[6]. Gait speed is a reliable and objective measure of recovery of walking ability[7] and walking performance[8-10]. In addition, gait speed has been found to be the most sensitive parameter to objectify change[11] and has often been established as the most pronounced marker to show effects in interventions trials to improve walking competency[12-18].

Despite the robustness of gait speed as an outcome measure, the relationship between gait speed and walking independence and distance is not unequivocal. Although it has been suggested that gait speed is a useful and discriminative measure for different ambulation levels[2,4,19], a review by Lord and coworkers found a moderate relationship and concluded that gait speed does not consistently reflect community ambulation. Therefore, relying on gait speed as a proxy measure was suggested to be inappropriate[6].

The above findings suggest that regaining sufficient walking speed is not the only factor that determines the ability of hemiplegic stroke patients to walk in their own community. Theoretically, the relationship between gait speed on the one hand and community walking on the other might be confounded by other physical, cognitive, and mental factors, such as lack of confidence and fear, social support, feelings of fatigue and depression, or lacking the necessary physical condition[20-23].

The first aim of the present study was to explore the strength of the association between gait speed and community ambulation. Subsequently, we investigated if this association was significantly confounded by other variables related to both gait speed and the capacity for community walking. On the basis of existing evidence from the literature and clinical considerations, we hypothesized that potential covariates that could confound the relationship between gait speed and community ambulation in patients with chronic stroke would be age, living alone[20], history of falls, the use of assistive walking devices[24], executive function[21], depression, fatigue[20], motor function, control of standing balance[19,20,25], and walking endurance[4].

Methods

Subjects

Patients were recruited for the Functional Prognosis after Stroke (FuPro-Stroke) study in four Dutch rehabilitation centers. Inclusion criteria for the FuPro-Stroke study were: age over 18, first-ever stroke, and a supratentorial lesion located on one side (cortical infarctions, subcortical infarctions, intracerebral hemorrhages or subarachnoid hemorrhages). Stroke was defined according to the WHO definition. Exclusion criteria were pre-stroke Barthel Index lower than 18 (0-20) and insufficient Dutch language skills. For the present analyses, only communicative patients were included, since non-communicative patients were unable to complete some parts of the questionnaires.
This prospective cohort study was approved by the medical ethics committees of UMC Utrecht and the participating rehabilitation centers. All patients included gave their informed consent.

Procedure

Data were collected at three years post stroke. Patients were visited by a trained research assistant for a face-to-face interview, either at home or at the institution where they resided.
Community ambulation was measured according to Lord by a self-administered questionnaire and served as the dependent variable in the association model[4]. Four categories could be distinguished, based on whether the patient could walk outside (1) only with physical assistance or supervision, (2) e.g. as far as the car or mailbox in front of the house without physical assistance or supervision, (3) in the immediate environment (e.g. down the road, around the block) without physical assistance or supervision; (4) to stores, friends or activities in the vicinity without physical assistance or supervision. Patients allocated to the fourth category were considered community walkers, which includes the ability to confidently negotiate uneven terrain, shopping venues, and other public venues. Others were regarded as non-community walkers (category 1) or limited community walkers (categories 2 and 3). Patients who did not walk outside at all were also classified as non-community walkers.
Gait speed (m/s) was measured by the 5 m walking test (5MWT) and served as the independent variable in the association model. The 5MWT was chosen since the tests were conducted indoors and space was limited. In addition, a standing start was chosen, since a rolling start would require more space. The assessor walked alongside the patients and timed them with a hand-held digital stopwatch. Patients were instructed to walk at their usual (comfortable) walking speed, and they were timed from the

moment the first foot crossed the starting line until the first foot crossed the finish line. Patients were allowed to use walking devices where needed. The mean speed over three attempts was calculated. If it was not possible to conduct the walking test over 5 m, gait speed was not assessed.

Variables that were considered as possible co-variates in the association model were age, living alone, history of falls, the use of assistive walking devices, executive function, depression, fatigue, motor function, control of standing balance, and walking endurance. History of falls was retrospectively determined by asking patients if they had experienced one or more falls during the previous six months (yes=1, no=0). In the case of memory problems, a proxy was asked to answer the question. Executive function was measured by the time needed to complete part B of the Trail Making Test (TMT)[26]. This involves complex visual scanning, motor speed, and (divided) attention. The participant has to connect 25 encircled numbers and letters, as quickly as possible, alternating between numbers and letters (1-a-2-b-3-c etc.). The assessor did not correct the errors made by the patient and the total time needed was divided by the number of correct connections. This ratio (time/correct connections) was dichotomized on the basis of the median score and used as a measure of executive function. Depression was measured by the Center for Epidemiologic Studies-Depression scale (CES-D)[27] and dichotomized into 'non-depressed' (CES-D <16 points) and 'depressed' (CES-D ≥16 points)[28]. Fatigue was determined by the Fatigue Severity Scale (FSS)[29,30]. The FSS consists of nine questions and total scores range between 9 and 63 points. The mean score (total score/9) was dichotomized into 'non-fatigued' (FSS <4 points) and 'fatigued' (FSS ≥4 points)[31]. The Motricity Index (MI)[32] was used to determine motor function. Scores range from 0 (no activity) to 100 (maximum muscle force) and were dichotomized into non-optimal range of motion (MI <76) and optimal range of motion (MI ≥76). Balance was determined by the Berg Balance Scale (BBS)[33]. The BBS evaluates a person's ability to perform 14 functional balance tests. The summed score of the BBS ranges from 0 to 56 points. A cut-off score of 45 was used (≤ 45=impaired)[33]. Walking endurance was reflected by question 3g of the Short Form 36 (SF36)[34] questionnaire (i.e., 'are you able to walk more than one kilometer'), and dichotomized into limitations (scores 1 and 2) and no limitations (score 3).

Statistical analysis

All variables were examined by descriptive statistics. A Receiver Operating Characteristics (ROC) curve was constructed to establish the diagnostic validity of gait speed in discriminating between community walkers and non-community walkers. An optimal cut-off point was determined and the area under the curve (AUC) was calculated. The AUC can be interpreted as the probability of correctly identifying community walkers versus non-community walkers. The area ranges from 0.5 (no accuracy in discriminating community walkers from non-community walkers) to 1.0 (perfect accuracy)[35]. Positive (PPV) and negative predictive values (NPV) were calculated to determine the proportion of patients with a walking speed above the cut-off score who were community walkers (PPV) and the proportion with a walking speed below the cut-off score who were non-community walkers (NPV).

Univariate logistic regression analysis was used to determine the relation between community ambulation and gait speed. Subsequently, other candidate covariates associated with both gait speed and community walking were added to the model. If the regression coefficient of gait speed with community walking changed by more than 15% after the variable had been added to the model, the variable was considered to be a covariate that confounded the relationship between gait speed and community walking.

We used a two-tailed significance level of 0.05 for all statistical tests applied (SPSS version 13.0).

Results

Data regarding community walking were available for 102 stroke patients. Gait speed data of 12 patients could not be collected because there was not enough space in their place of residence to conduct the 5 m test. After non-communicative patients had been excluded, 72 complete datasets were available for analyses. Sixty-four percent of the patients were male. Mean age was 59 years (SD=10) and the majority had suffered an infarction (67%) (Table 1) .

Based on the self-administered questionnaire, 8 patients were not able to walk outside without supervision or assistance, 3 patients walked as far as the car or mailbox in front of the house, 8 patients walked the immediate outside vicinity (eg around the block), and 53 patients walked outside to stores, friends or activities in their neighborhood without physical assistance or supervision. These results indicate that 26% of the patients were non-community walkers or limited community walkers and 74% of the patients were considered unlimited community walkers.

Mean gait speed was 0.74 m/s (SD=0.30). ROC analysis revealed a high diagnostic validity in terms of distinguishing between community walkers and non-community walkers, with an AUC of 0.85. A cut-off score of 0.66 m/s correctly allocated 93% (PPV) of the patients to the group of unlimited community walkers and 57% (NPV) were correctly classified as non-community walkers.

Univariate logistic regression analysis, with the dichotomized gait speed score as the independent variable, showed that gait speed was significantly related to community ambulation, with an odds ratio of 18.2 (95% CI: 4.5-73.2).
Subsequently, we investigated the association between gait speed and community walking while controlling for the other variables. Balance control, motor function, walking endurance, and the use of assistive devices distorted the relation between walking speed and community ambulation, as it changed the regression coefficient of gait speed by more than 15% (Table 2). However, gait speed remained a significant determinant of community ambulation after the confounders had been added to the model. No significant distortion was found for age, living alone, history of falls, executive function, fatigue, or depression.

Table 1. Patient characteristics at three years post stroke (n=72)

Patient Characteristic	%
Gender (male)	64
Age (>65)	26
Hemisphere (right)	56
Type of stroke (infarction)	67
Living alone	24
Walking device	14
TMT (impaired executive function)	50
CES-D (depressive symptoms)	10
FSS (fatigued)	46
MI (no optimal range of motion)	61
BBS (balance problems)	22
Walking endurance (impaired)	63

TMT=Trail Making Test, CES-D= Center for Epidemiologic Studies-Depression, FSS= Fatigue Severity Scale, MI = Motricity Index, BBS= Berg Balance Scale

Table 2. Multivariate logistic regression analysis with community walking as outcome measure (n=72). Printed in bold are the percentages above the 15% change in beta coefficient.

Variables in the model	Confounder β (SE)	Gait speed β (SE)	Proportional change in the coefficient of gait speed
Gait speed		2.903 (0.710)	
Candidate confounders			
Balance (impaired)	-2.140 (0.780)*	2.140 (0.776)*	**26.3%**
Motor function (impaired)	-1.841 (1.146)	2.287 (0.754)*	**21.2%**
Walking endurance (impaired)	-2.003 (1.127)**	2.412 (0.738)*	**16.9%**
Walking device (yes)	-2.001 (0.947)*	2.467 (0.742)*	**15.0%**
Age (>65)	1.601(0.824)**	3.220 (0.759)*	10.9%
Fatigue (present)	-0.994 (0.699)	3.134 (0.761)*	8.0%
Living alone (yes)	2.209 (1.152)**	2.970 (0.736)*	2.3%
Depression (present)	-0.669(1.118)	2.956 (0.724)*	1.8%
History of falls	-0.414(0.829)	2.918 (0.713)*	<1%
Trail Making Test	0.012 (0.723)	2.908 (0.770)*	<1%

SE=standard error

*p<0.05

**p<0.1

Discussion

Our results show that in a relatively young, moderately disabled stroke population, 26% of the patients were non-community walkers or limited community walkers. Gait speed was significantly related to community ambulation, and a cut-off point of 0.66 m/s was optimal to distinguish between community walkers and non-community walkers. This cut-off point might be too pessimistic, since NPV was 57%. Despite being classified as non-community walkers because of a gait speed lower than 0.66 m/s, 43% of the patients were community walkers by Lord's classification. This shows that patients with a low walking speed are particularly difficult to classify by gait speed alone[4,9,36].

Gait speed was the most powerful discriminative measure of community ambulation. Previously reported threshold gait speeds for community ambulation have varied between 0.8m/s and 1.2m/s[2,22,23]. Although the reason why the optimal cut-off point in the present study was lower than those previously reported, remains unknown, Taylor and colleagues have already suggested that the threshold of 0.8 m/s for community ambulation might be too high. In their chronic stroke population, patients did walk in the community despite lower gait speeds[37]. It might be hypothesized that our chronic patients use more compensatory strategies which they have learned over the years. Also, fear may have been overcome and walking aids may be used to greater effect than in the early phase after stroke.

Although gait speed is an important determinant of community walking, the present study also shows that it was not the sole determinant of community ambulation. The relation between gait speed and community ambulation was confounded by control of standing balance, motor function, walking endurance, and the use of walking devices. Therefore, rehabilitation should not only focus on improving gait speed, but also on other factors that are relevant to becoming an independent community walker. This finding further suggests that clinicians need to be careful in classifying community walkers on the basis of gait speed alone. Patients with a slow walking speed in particular seem to be able to compensate by an appropriate use of walking aids and sufficient control of balance.

The results we found are in agreement with those of other studies[4,20,22] suggesting that the ability to walk in the community requires more than gait speed alone. The role of control of standing balance for mobility outcome is in line with the literature[20,25]. In our study, the relation between gait speed and community walking became weaker after balance was added to the model, which suggests that balance control is an independent compensatory factor enabling patients to walk in the community despite lower gait speeds. In the same way, motor function also weakened the association between gait speed and community walking. In contrast to Shumway-Cook[38], who suggested that endurance was less important for successful community ambulation in older adults, our results are in agreement with the findings by Lord and colleagues, who found that walking endurance was an important factor, highly associated with outdoor mobility[4]. It has previously been suggested that the minimum walking endurance required for community walking was 300 to 500 m[22,23]. The use of assistive devices also confounded the relation in our study, presumably since the use of a walking aid increases the ability to walk in the community despite lower gait speed. Although patients are often stimulated not to use assistive walking devices, community ambulation can be improved by providing them with appropriate walking aids for outdoor use. Recently, a controlled trial by Logan and colleagues found that providing walking aids helps patients to increase outdoor mobility[24].

The present study was subject to some limitations. First, there might be other variables that distort the relation between gait speed and community ambulation, for example lack of confidence and fear. Although we did include falling characteristics in the model, we were unable to analyze the role of fear of falling. Second, we chose to assess community ambulation according to Lord's self-administered questionnaire[4], which has not been validated. In the present study, endurance was determined by one question of the SF36. Although this question is a very relevant one for community ambulation, other valid and more responsive measures could have been chosen. Third, the 15% change in the beta coefficient of gait speed that we used to decide whether a factor was a covariate is an arbitrary value. Finally, the present study was conducted cross-sectionally in a relatively small sample. It has previously been shown that mobility outcome is not stable but decreases gradually over time in about 20% of chronic patients[39]. Like mobility outcome, community ambulation might also be time-dependent. Therefore, future studies should focus on longitudinal relationships in patients with chronic stroke.

Conclusion

Community ambulation is a relevant but complex outcome. Simply improving the gait speed of stroke survivors during rehabilitation is not sufficient for them to regain community walking. Balance, motor function, endurance, and the use of assistive walking devices are important factors that may distort the relationship between gait speed and community ambulation.

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5

Effects of exercise training programs on walking competency after stroke: a systematic review

Ingrid G.L. van de Port, Sharon Wood-Dauphinee,
Eline Lindeman, Gert Kwakkel

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Abstract

To determine the effectiveness of training programs that focus on lower limb strengthening, cardio-respiratory fitness or gait-oriented tasks in improving gait, gait-related activities and health-related quality of life (HRQoL) after stroke. Randomized controlled trials (RCTs) were searched for in the databases of Pubmed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, DARE, PEDro, EMBASE, DocOnLine and CINAHL. Databases were systematically searched by two independent researchers. The following inclusion criteria were applied: (1) participants were people with stroke, older than 18 years; (2) one of the outcomes focused on gait-related activities; (3) the studies evaluated the effectiveness of therapy programs focusing on lower limb strengthening, cardio-respiratory fitness or gait-oriented training; (4) the study was published in English, German or Dutch. Studies were collected up to November 2005, and their methodological quality was assessed using the PEDro scale. Studies were pooled, and summarized effect sizes were calculated. Best-evidence synthesis was applied if pooling was impossible. Twenty-one randomized contolled trails were included, of which 5 focused on lower limb strengthening, 2 on cardio-respiratory fitness training (e.g., cycling exercises) and 14 on gait-oriented training. Median PEDro score was 7. Meta-analysis showed a significant medium effect of gait-oriented training interventions on both gait speed and walking distance, whereas a small, non-significant effect size was found on balance. Cardio-respiratory fitness programs had a non-significant medium effect size on gait speed. No significant effects were found for programs targeting lower limb strengthening. In the best-evidence synthesis strong evidence was found to support cardio-respiratory training for stair-climbing performance. While functional mobility was positively affected, no evidence was found that activities of daily living, instrumental activities of daily living or HRQoL were significantly affected by gait-oriented training. This review shows that gait-oriented training is effective in improving walking competency after stroke.

Introduction

Stroke is a major cause of disability in the developed world, often resulting in difficulties in walking. According to the Copenhagen Stroke Study, 64% of survivors walk independently at the end of rehabilitation, 14% walk with assistance and 22% are unable to walk[1]. Since independent gait is closely related to independence in Activities of Daily Living (ADL), achieving and maintaining the ability to walk in the home and in the community is an important aim of stroke rehabilitation[2].

Saunders and colleagues evaluated the evidence for the effects of strength training, cardio-respiratory training and mixed training programs on gait. They suggested that programs concentrating on cardio-respiratory fitness resulted in improved scores for walking ability and maximum walking speed. They also noted that studies including strength and mixed training have been few, and inconclusive[3].

Recently, there has been increasing interest in combinations of strength and cardio-respiratory training, in which gait and gait-related tasks are practiced using a functional approach[4-6]. Salbach and colleagues suggested that high-intensity task-oriented practice may enhance 'walking competency' in patients with stroke better than other methods[5], even in those patients in which the intervention was initiated beyond 6 months post stroke[5,7]. Walking competency was defined as "the level of walking ability that allows individuals to navigate their community proficiently and safely"[5]. In addition, there is growing evidence that the link between physical training and improved cardio-respiratory fitness, as established in the general population, can be extrapolated to persons who are disabled by stroke[8].

To optimize the treatment of those with stroke, it is necessary to systematically evaluate the effects of the different training programs that aim to restore walking competency. We, therefore, conducted a systematic review of the literature on the effects of lower limb strength training, cardio-respiratory fitness training and gait-oriented training on gait, gait-related activities and health-related quality of life in those who had sustained a stroke.

Methods

Literature search

Potentially relevant studies were identified through computerized and manual searches. Electronic databases (Pubmed, Cochrane Central register of Controlled Trials, Cochrane Database of Systematic Reviews, DARE, Physiotherapy Evidence Database (PEDro), EMBASE, DocOnLine (Database of the Dutch Institute of Allied Health Care) and CINAHL (1980 through November 2005)) were systematically searched by two independent researchers (IvdP, WE). The following MeSH headings and keywords were used for the electronic databases: cerebrovascular accident, gait, walking, exercise therapy, rehabilitation, neurology and randomized controlled trial. Bibliographies of review articles, narrative reviews and abstracts published in proceedings of conferences were also examined. Studies were included if they met the following inclusion criteria: (1) participants were patients with stroke older than 18 years; (2) one of the study outcomes focused on gait-related activities; (3) the studies evaluated the effectiveness of therapy programs focusing on lower limb strengthening, cardio-respiratory fitness or gait-oriented training; (4) the study was published in English, German or Dutch; (5) the design was a randomized controlled trail (RCT). Studies were collected up to November 2005. Studies evaluating specific neurological treatment approaches (not specifically focusing on lower limb training), applying gait manipulations, for example by using specific devices such as body weight supported training, virtual reality or electrical stimulation, were excluded. Cross-over designs were treated as RCTs by taking only the outcomes after the first intervention phase. The full search strategy is available on request from the corresponding author.

Definitions

In the present review, stroke was defined according to the WHO definition as an acute neurological dysfunction of vascular origin with sudden (within seconds) or at least rapid (within hours) occurrence of symptoms and signs corresponding to the involvement of focal areas in the brain[9].

RCT was defined as a clinical trial involving at least one test treatment and one control treatment, in which concurrent enrolment and follow-up of the test- and control-treated groups is ensured and the treatments to be administered are selected by a random process, i.e. the use of a random-numbers table or concealed envelopes (Pubmed 1990).

Gait-related activities were defined in the present study as activities involving mobility-related tasks, such as stair walking, turning, making transfers, walking quickly and walking for specified distances. Lower limb strength training was defined as prescribed exercises for the lower limbs, with the aim of improving strength and muscular endurance, that are typically carried out by making repeated muscle contractions resisted by body weight, elastic devices, masses, free weights, specialized machine weights, or isokinetic devices[3]. Cardio-respiratory fitness training was defined as that aiming to improve the cardio-respiratory component of fitness, typically performed for extended periods of time on ergometers (e.g. cycling, rowing), without aiming to improve gait performance as such[3]. We defined gait-oriented training as that intended to improve gait performance and walking competency in terms of different parameters of gait (e.g., stride and stepping frequency, stride and step length), gait speed and/or walking endurance.

Methodological quality
Two independent reviewers (IvdP and WE) assessed the methodological quality of each study using the PEDro scale[10,11] (Table 1). In the case of persistent disagreement, a third reviewer made the final decision after discussions with the primary reviewers. PEDro scores were used as a basis for best-evidence syntheses and to discuss the methodological strengths and weaknesses of the studies.

Quantitative analysis
Data contained in the abstract (numbers of patients in the experimental and control groups, mean difference in change score and standard deviation (SD) of the outcome scores in the experimental and control groups at baseline) were entered in Excel for Windows. If necessary, point estimates were derived from graphs presented in the article. Outcomes were pooled if the studies were comparable in terms of the type of intervention (i.e., lower limb strengthening, cardio-respiratory fitness or gait-oriented training), and if they assessed the same construct. Pooled SD_i was estimated using the baseline SDs of the control and experimental groups. The effect size g_i (Hedges' g) for individual studies was assessed by calculating the difference in mean changes between the experimental and control groups, divided by the pooled SD_i of the experimental and control groups at baseline[12]. If additional information was required, we contacted the authors or derived SDs from t- or F-statistics, p-values or post-intervention distributions.
Because g_i tends to overestimate the population effect size in studies with a small number of patients, a correction was applied to obtain an unbiased estimate: g_u (unbiased Hedges' g). The impact of sample size was addressed by estimating a weighting factor w_i for each study and applying greater weight to effect sizes from studies with larger samples, which resulted in smaller variances. Subsequently, g_u values of individual studies were averaged to obtain a weighted summarized effect size (SES), while the weights of each study were combined to estimate the variance of the SES[13]. SES was

expressed as the number of standard deviation units (SDUs) and a confidence interval (CI). The fixed effects model was used to decide whether the SES was statistically significant. The homogeneity (or heterogeneity) test statistic (Q-statistic) of each set of effect sizes was examined to determine whether studies shared a common effect size from which the variance could be explained by sampling error alone[14,15]. Since the Q-statistic underestimates the heterogeneity in a meta-analysis, the percentage of total variation across the studies was calculated as I^2, which gives a better indication of the consistency between trials[16]. When significant heterogeneity was found (I^2 values > 50%)[16], a random effects model was applied[14]. For all outcome variables, the critical value for rejecting Ho was set at a level of 0.05 (two-tailed). Based on the classification by Cohen, effect sizes below 0.2 were classified as small, those from 0.2 to 0.8 as medium and those above 0.8 as large[15].

Best-evidence synthesis

A best-evidence synthesis was conducted if pooling was impossible due to differences in outcomes, intervention category and/or numbers of studies found. Using criteria based on the methodological quality score of the PEDro scale, we classified the studies as 'high-quality' (4 points or more) or 'low-quality' (3 points or less)[7]. Subsequently, studies were categorized into four levels of evidence, based on van Tulder et al.[17]

1) Strong evidence: provided by generally consistent findings in multiple, relevant, high-quality RCTs;
2) Moderate evidence: provided by generally consistent findings in one, relevant, high-quality RCT and one or more relevant low-quality RCTs;
3) Limited evidence: provided by generally consistent findings in one, relevant, high-quality RCT or in one or more relevant low-quality RCTs;
4) No or conflicting evidence: no RCTs are available or the results are conflicting.

If the number of studies that showed evidence was less than 50% of the total number of studies found within the same methodological quality category, this was regarded as no evidence[18].

Results

The initial search strategy identified 486 relevant citations. Based on title and abstract we excluded 440 studies, since, for example, studies were not randomized, used an intervention that not fitted within our definition, or the study was conducted in different patient population. Forty-six full-text articles were selected. Of these, three

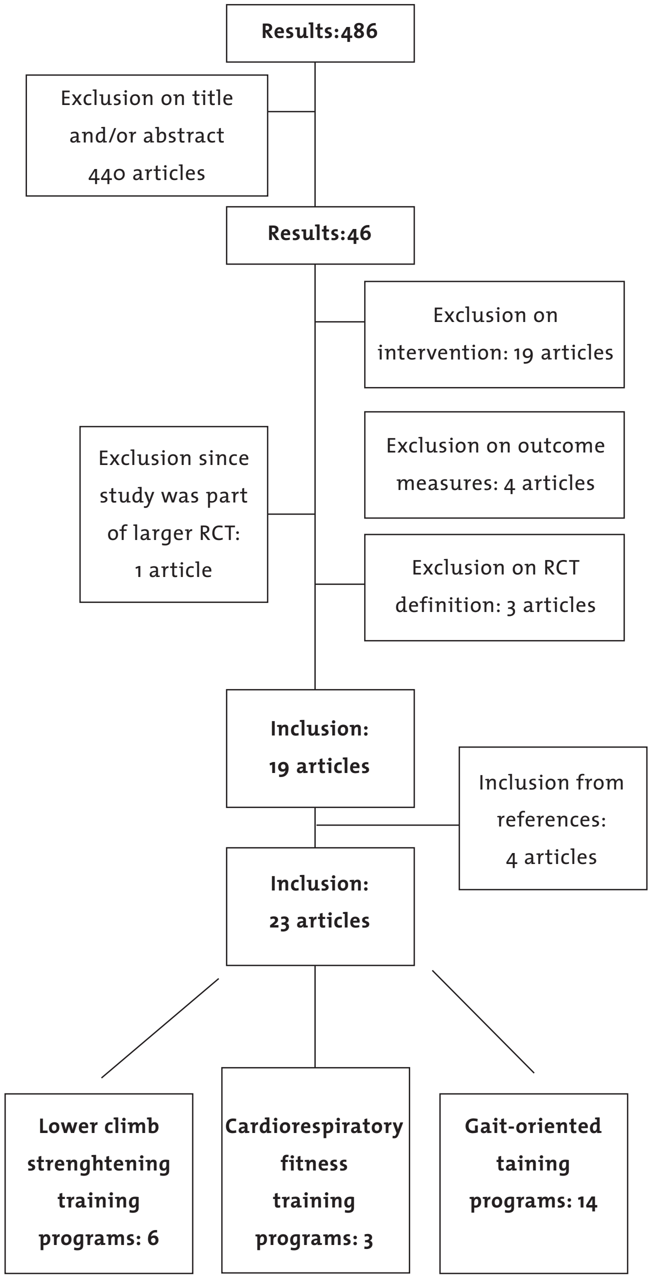
Table 1. The 11 items of the PEDro scale for methodological quality

1.	Eligibility criteria specified	Yes / No
2.	Random allocation	Yes / No
3.	Concealed allocation	Yes / No
4.	Baseline prognostic similarity	Yes / No
5.	Participant blinding	Yes / No
6.	Therapist blinding	Yes / No
7.	Outcome assessor blinding	Yes / No
8.	More than 85% follow-up for at least one primary outcome	Yes / No
9.	Intention-to-treat analysis	Yes / No
10.	Between- or within-group statistical analysis for at least one primary outcome	Yes / No
11.	Point estimates of variability given for at least one primary outcome	Yes / No

more were excluded since the studies were not RCTs[19-21] and four were excluded because the outcome measures did not reflect gait-related activities[22-24]. Another 19 studies were excluded because the intervention did not meet the criteria[25-44] and one study was excluded since it focused on a subgroup of a larger RCT[45]. Screening of references of the articles led to another four studies[46-49] being included. In total, 23 studies were included in the present systematic review (Figure 1).The selection included six RCTs that focused on strength training of the lower limb[46-48,50-52], three that concentrated on cardio-respiratory fitness[53-55] and 14 that targeted gait-oriented training[4,5,49,56-66]. Two RCTs concentrating on the effects of cardio-respiratory fitness employed the same population[53,54]. One of these[53] was used in our meta-analysis, while the second study was used to obtain additional information. Despite being a RCT, the study by Lindsley et al. was excluded because of lack of information[48]. Table 2 shows the main characteristics of the 21 studies included in the present meta-analysis.

The studies centered on lower limb strength training included 240 participants, of whom 121 were assigned to the intervention group. Sample sizes ranged from 20[46,47] to a maximum of 133 participants[51]. Time between stroke onset and the start of the intervention ranged from three months[46] to a mean of four years[47]. Studies focusing on cardio-respiratory fitness training included 104 participants, of whom 53 were assigned to the intervention group. Individual study sample sizes were 12[55] and 92 participants[53], respectively. Time between stroke onset and the start of the intervention ranged from a mean of 16 days[53] to more than one year[55]. The studies focusing on gait-related

Figure 1. Flow-chart included studies



training included 574 participants, of whom 332 were assigned to the intervention group. Individual sample sizes ranged from 9[58] to a maximum of 100 participants[4]. Time between stroke onset and the start of the intervention varied between eight days[65] to a mean of eight years[66].

Methodological quality

PEDro scores ranged from 4 to 8 points, with a median score of 7 (Table 3). All studies, except for one[46] specified the eligibility criteria. In no study was the therapist blind to group status. This was as expected, since the therapists had to conduct the therapy, therefore they cannot be blinded. All studies applied statistical analysis to group differences and reported point estimates and measures of variability. All studies, except the work by Glasser[46], Teixeira-Salmela[66], Dean[58] and Macko[63] and their colleagues, scored a minimum of 6 points. RCTs centered on lower limb strengthening scored a median of 7 points (range 4–8). The two RCTs focusing on cardio-respiratory fitness both scored 6 points[53]. A median of 7 points (range 4–8) was scored by RCTs targeting gait-oriented training.

Quantitative analysis

Pooling was possible for balance (4 RCTs, N=274)[4,5,49,59], gait speed (17 RCTs, N=692)[4,5,46,47,50,52,53,55,56,58,59,61-66] and walking distance (13 RCTs, N=743)[4,5,49-53,56-60,63]. Balance was determined by the Berg Balance Scale (BBS)[67] in all studies. Gait speed was measured over distances ranging from 5 to 30 meters[65]. Walking distance was assessed by the 2-minute[51] or 6-minute[4,5,49,52,56-60,68] walk test. Only Katz and colleagues[53] asked the patients to walk as far as they could.

One study on cardio-respiratory training[53] failed to report baseline SDs, so we used the SD of the post-intervention measurement to calculate g_i (Figures 2 and 3). Another study[59] on gait-oriented training did not provide baseline SDs either, so SDs were derived from p-values. The study by Richards and colleagues included two control groups. We decided to include the early control group (ECON) in our review, since the number of patients who completed this trial was larger than that in the other control group (CON)[65].

Lower limb strengthening

Four studies[46,47,50,52] targeting lower limb strengthening (N=107) measured gait speed. A heterogeneous non-significant SES was found compared to the control groups (SES [random] -0.13 SDU; CI -0.73 to 0.47; Z=-0.43, p=0.667, I^2=57.1%). Three studies (N=200)[50-52] determined walking distance and found a homogenous non-significant SES compared to control groups (SES [fixed] 0.00 SDU; CI -0.28 to 0.28; Z=0.02, p=0.98, I^2=21%).

Table 2. Characteristics of the studies included in the review

Study	N (E/C)	Time since stroke (mean days at inclusion)	Intervention
Lower Limb strengthening training			
Glasser 1986	20 (10/10)	3-6 months (137)	I: Therapeutic exercise programme based on neurophysiological and development theories and gait training + isokinetic training. C: Therapeutic exercise program based on neurophysiological and development theories and gait training.
Kim et al. 2001	20 (10/10)	> 6 months (1460)	I: Maximal concentric isokinetic strength training. C: Passive range of motion.
Bourbonnais et al. 2002	25 (12/13)	Chronic (1096)	I: Motor re-education program for the paretic lower limb, based on the use of a static dynamometer. C: Motor re-education program for the paretic upper limb, based on the use of a static dynamometer.
Moreland et al. 2003	106 (54/52)	< 6 months after stroke (38)	I: Conventional therapy + progressive resistance exercises performed with weights at the waist or on the lower extremities. C: Conventional therapy.
Ouellette et al. 2004	42 (21/21)	6 months to 6 years after stroke (874)	I: High-intensity resistance training program consisting of bilateral leg press, unilateral paretic and nonparetic knee extension, ankle dorsiflexion, and plantarflexion. C: bilateral range of motion and upper body flexibility exercises.
Cardio-respiratory training			
Katz et al. 2003	90 (46/44)	Subacute (16)	I: Regular therapy and leg cycle ergometer training. C: Conventional therapy.
Chu et al. 2004	12 (7/5)	> 1 year post stroke (1315)	I: Intervention group participating in a water-based exercise program that focused on leg exercise to improve inclusive cardiovascular fitness and gait speed. C: Arm and hand exercise while sitting.

Intensity	Outcome	Author's Conclusion
5 wks; 5 days a week; 2 hours a day	Functional Ambulation Profile (FAP), ambulation time	Differences in ambulation times and FAP scores were non-significant.
6 wks; 3 times a week; 45 min	Lower limb strength, gait speed, stair climbing speed, quality of life (SF36)	Intervention aimed at increasing strength did not result in differences in walking between groups.
6 wks; 3 times a week	Motor function (FM), finger-to-nose movements, gait speed, timed up-and-go, walking distance	Treatment of the lower limb produces an improvement in gait velocity and walking speed.
During rehabilitation (mean 8 wks); 3 times a week; 30 min	Disability (CMSA Disability Inventory), gait speed	Progressive resistance training was not effective compared to the same exercises without resistance.
12 wks; 3 times a week	Lower extremity muscle strength, peak muscle power, walking distance, stair climbing, chair rising, gait speed, functional limitation and disability (LLFDI), depression (GDS), quality of life (SIP)	Progressive resistance training safely improves lower limb strength in the paretic and non paretic limb and results in reductions in functional limitations and disabilities.
8 wks; first 2 wks: 5 times a week; 30 min; last 6 wks: 3 times a week; 30 min	Walking distance, gait speed, workload, exercise time	Stroke patients in the subacute stage improved some of their aerobic and functional abilities, including walking distance, after submaximal aerobic training.
8 wks; 3 times a week; 60 min	Gait speed, balance (BBS)	The experimental group attained significant improvement compared to the control group in cardiovascular fitness and gait speed.

Study	N (E/C)	Time since stroke (mean days at inclusion)	Intervention
Gait-oriented training			
Richards et al. 1993	27 (10/8/9)	Acute (about 10 days)	I: Intensive and focused approach incorporating the use of tilt table and limb-load monitor, resisted exercise with a Kinetron isokinetic device, and a treadmill. C1: started early and was as intensive as for the experimental group but included more traditional approaches to care (ECON) C2: therapy composed of similar techniques as provided to the other control group. This one started later, and was not as intensive (CON).
Duncan et al. 1998	20 (10/10)	Subacute (61)	I: Therapist-supervised home-based exercise program to improve strength, balance and endurance. C: Usual care.
Teixera-Salmela et al. 1999	13 (6/7)	>9 months (2799)	I: Program consisting of warm-up, aerobic exercises (graded walking plus stepping or cycling), lower extremity muscle strengthening, cooling down. C: No intervention.
Dean et al. 2000	12 (6/6)	> 3 months (658)	I: Circuit program including workstations designed to strengthen the muscles in the affected leg in a functional way and practicing locomotion-related tasks. C: Similar organization and delivery as the experimental group, except that it was designed to improve the function of the affected uppers limb.
Liston et al. 2000	18(10/8)		I: Treadmill retraining with the instruction to walk for as long as patients felt comfortable. C: Conventional physiotherapy.

Intensity	Outcome	Author's Conclusion
Exp: 5 wks; 10 times a week; 50 min ECON: 5 wks; 10 times a week; 50 min CON: 5 wks; 5 times a week; 40 min	Balance (FM-B), motor function (FM), ambulation (BI), balance (BBS), gait speed	Group results demonstrated that gait velocity was similar in the three groups.
12 wks; 3 times a week; 90 min	Motor function (FM), balance (BBS), gait speed, walking distance, ADL, instrumental ADL, quality of life	The experimental group showed greater improvement of neurological impairment and lower extremity function. Lower extremity scores and gait velocity were significantly different.
10 wks, 3 times a week; 60-90 min	Muscle strength and tone, level of physical activity (HAP), quality of life (NHP), gait speed	The combined program of muscle strengthening and physical conditioning resulted in gains in all measures of impairment and disability.
4 wk; 3 times a week; 60 min	Gait speed, walking distance, timed up-and-go, sit-to-stand, step test	This task-related circuit training improved locomotor function in chronic stroke. Walking distance, gait speed and the step test showed significant improvements between groups.
4 wks; 3 times a week; 60 min	Sit-to-stand, gait speed, balance, ADL, Nine Hole Peg test	Improvements were seen, but there were no statistically significant differences in gait between the conventional and treadmill re-training groups.

Study	N (E/C)	Time since stroke (mean days at inclusion)	Intervention
Laufer et al. 2001	25 (13/12)	< 90 days (34.2)	I: Physiotherapy treatment + ambulation on a motor-driven treadmill at comfortable walking speed. C: physiotherapy treatment + ambulation on floor surface at a comfortable speed using walking aids, assistance and resting periods as needed.
Pohl et al. 2002	60 (20/20/20)	> 4 weeks (114.6)	I1: Conventional physiotherapy + Limited Progressive Treadmill Training (LTT). I2: Conventional physiotherapy + Structured Speed-Dependent Treadmill Training (STT). C: Physiotherapeutic gait therapy based on the latest principles of proprioceptive neuromuscular facilitation and Bobath concepts.
Ada et al. 2003	27 (13/14)	6 months- 5 years (822)	I: Both treadmill and overground walking, with the proportion of treadmill walking decreasing by 10% each week. C: Low-intensity, home exercise program consisting of exercises to lengthen and strengthen lower-limb muscles, and train balance and coordination.
Duncan et al. 2003	92 (44/48)	30-150 days (76)	I: Exercise program designed to improve strength and balance and to encourage more use of the affected extremity. C: Usual care.
Blennerhassett et al. 2004	30 (15/15)	Subacute (43)	I: Mobility-related group activities including endurance tasks and functional tasks. C: Upper limb group activities including functional tasks.

Intensity	Outcome	Author's Conclusion
3 wks, 5 times a week; 8-20 min	Standing balance, functional mobility (FAC), gait speed, gait cycle	Treadmill training may be more effective than conventional gait training in improving gait parameters such as functional ambulation, stride length, percentage of paretic single stance period and gastrocnemius muscular activity.
4 wks, 12 sessions; 30 min	Gait speed, cadence, stride length, functional mobility (FAC)	Structured STT in post-stroke patients resulted in better walking abilities than LTT or conventional physiotherapy.
4 wks; 3 times at week; 30 min	Gait speed, step length and width, cadence, quality of life (SA-SIP30)	The intervention program significantly increased walking speed and walking capacity compared with the control group.
12 wks; 3 times a week; 90 min	Lower extremity muscle and grip strength, motor function (FM), upper extremity function, balance (BBS), endurance, gait speed, walking distance	This structured, progressive exercise program produced gains in endurance, balance and mobility beyond those attributable to spontaneous recovery and usual care.
4 wks; 5 times a week; 60 min	Upper limb function (MAS, JTHFT), step test, timed up-and-go, walking distance	Findings support the use of additional task-related practice during inpatient stroke rehabilitation. The mobility group showed significantly better locomotor ability than the upper limb group.

Study	N (E/C)	Time since stroke (mean days at inclusion)	Intervention
Eich et al. 2004	50 (25/25)	<6 weeks (44)	I: Individual physiotherapy Bobath-oriented + treadmill training. C: Individual physiotherapy, Bobath-oriented.
Salbach et al. 2004	91 (44/47)	Chronic (228)	I: Ten functional tasks designed to strengthen the lower extremities and enhance walking balance, speed and distance. C: Upper extremity activities.
Macko et al. 2005	61 (32/29)	> 6 months after stroke (1125)	I: Progressive task-oriented modality to optimize locomotor relearning, providing cardiovascular conditioning. C: Conventional therapy.
Pang et al. 2005	63 (32/31)	> 1 year (1881)	I: Progressive fitness and mobility exercise program designed to improve cardio-respiratory fitness, balance, leg muscle strength and mobility. C: Seated upper extremity program.

E/C=experimental vs. control group; I=intervention group; C=control group; ECON=early control group; wks=weeks; min=minutes; FAP=Functional Ambulation Profile, SF36= Social Functioning 36, FM=Fugl Meyer; BBS=Berg Balance Scale, FM-B=Fugl Meyer balance, CMSA=Chedoke-McMaster Stroke Assessment, LLFDI= Late Life Function and Disability Instrument, GDS= Geriatric Depression Scale, SIP= Sickness Impact Profile, BI=Barthel Index,

Cardio-respiratory fitness training

Two studies involving cardio-respiratory training[53,55] (N=104) assessed gait speed. A homogeneous non-significant SES was found compared to control groups (SES [fixed] 0.36 SDU; CI -0.03 to 0.75; Z=1.83, p=0.07, I^2=0%).
Since only one study analyzed the effect of cardio-respiratory training on balance[55] and one on walking distance[53] these results are described in the best evidence syntheses.

Gait-oriented training

Four studies assessed balance after gait-oriented training[4,5,49,59] and found a homogenous non-significant SES (SES [fixed] 0.19 SDU; CI –0.05 to 0.43; Z=1.59, p=0.11, I2=0%). Twelve studies centered on gait-oriented training (N=501)[4,5,56,58,59-66] evaluated gait speed and found

Intensity	Outcome	Author's Conclusion
6 wks; 5 times a week; 60 min	Gait speed, walking distance, gross motor function (RGMF), walking quality	Addition of aerobic treadmill training to Bobath-oriented physiotherapy resulted in significant improvement in gait speed and walking distance.
6 wks; 3 times a week	Timed up-and-go, balance (BBS), gait speed, walking distance	The task-oriented intervention significantly improved gait speed and walking distance.
6 months; 3 times a week; 40 min	Gait speed, walking distance, endurance, functional mobility (RMI), Walking Impairment Questionnaire (WIQ)	Both functional mobility and cardio-vascular fitness improved more after the intervention than after conventional care.
19 wks; 3 times a week; 60 min	Muscle strength, balance (BBS), endurance, walking distance, physical activity (PAS)	The intervention group had significantly greater gains in cardio-respiratory fitness, mobility and paretic leg strength.

HAP= Human Activity Profile, NHP=Notthingham Health Profile, SA-SIP30= Stroke Adapted-Sickness Impact Profile 30; MAS=Modified Ashworth Scale; JTHFT=Jebsen Taylor Hand Function Test, RGMF=Rivermead Gross Motor Function, RMI=Rivermead Mobility Index, WIQ=Walking Impairment Questionnaire, PAS=Physical Activity Scale

a homogenous significant SES (SES [fixed] 0.45 SDU; CI 0.27 to 0.63; Z=4.84, p<0.01, I^2=31.3%). In addition, nine studies (N=451)[4,5,49,56-60,63] assessed the effect of gait-oriented training on walking distance. A heterogeneous significant SES was found compared to the control groups (SES [random] 0.62 SDU; CI 0.30 to 0.95; Z=3.73, p<0.01, I^2=61.2%).

Best evidence syntheses

Lower limb strengthening

Two high-quality studies on lower limb strengthening[47,52] selected stair climbing as a secondary outcome measure. Although they used different measures to determine stair climbing performance, both studies concluded that changes in stair climbing did not

Table 3. **PEDro scores for each RCT**

Study	1	2	3	4	5	6	7	8	9	10	11	Total score
Lower limb strengthening training												
Glasser 1986	No	1	0	0	0	0	0	1	0	1	1	4
Kim et al. 2001	Yes	1	0	1	1	0	1	1	1	1	1	8
Bourbonnais et al. 2002	Yes	1	1	1	0	0	0	1	0	1	1	6
Moreland et al. 2003	Yes	1	1	1	0	0	1	1	1	1	1	8
Ouellette et al. 2004	Yes	1	0	1	0	0	1	1	1	1	1	7
Cardio-respiratory fitness training												
Katz et al. 2003	Yes	1	0	1	0	0	1	1	0	1	1	6
Chu et al. 2004	Yes	1	0	1	0	0	1	1	0	1	1	6
Gait-oriented training												
Richards et al. 1993	Yes	1	0	1	0	0	1	1	0	1	1	6
Duncan et al. 1998	Yes	1	1	1	0	0	0	1	1	1	1	7
Teixera et al. 1999	Yes	1	0	0	0	0	0	1	0	1	1	4
Dean et al. 2000	Yes	1	1	0	0	0	0	0	0	1	1	4
Liston et al. 2000	Yes	1	0	1	0	0	1	1	1	1	1	7
Laufer et al. 2001	Yes	1	0	1	0	0	1	1	0	1	1	6
Pohl et al. 2002	Yes	1	0	1	0	0	1	1	0	1	1	6
Ada et al. 2003	Yes	1	1	1	0	0	1	1	1	1	1	8
Duncan et al. 2003	Yes	1	1	1	0	0	1	1	1	1	1	8
Blennerhassett et al. 2004	Yes	1	1	1	0	0	1	1	1	1	1	8
Eich et al. 2004	Yes	1	1	1	0	0	1	1	1	1	1	8
Salbach et al. 2004	Yes	1	1	1	0	0	1	1	1	1	1	8
Macko et al. 2005	Yes	1	1	1	0	0	0	0	0	1	1	5
Pang et al. 2005	Yes	1	1	1	0	0	1	1	1	1	1	8

significantly differ between the experimental and control groups. One study also evaluated health-related quality of life (HRQoL) by means of the Short Form-36 (SF-36), and concluded that there was no significant difference between the groups[47]. These findings provide strong evidence that programs focusing on lower limb strengthening do not produce greater improvement in stair climbing ability than conventional care. Moreover, there was limited evidence that programs of lower limb strengthening are not superior to conventional care in improving HRQoL.

Cardio-respiratory fitness training

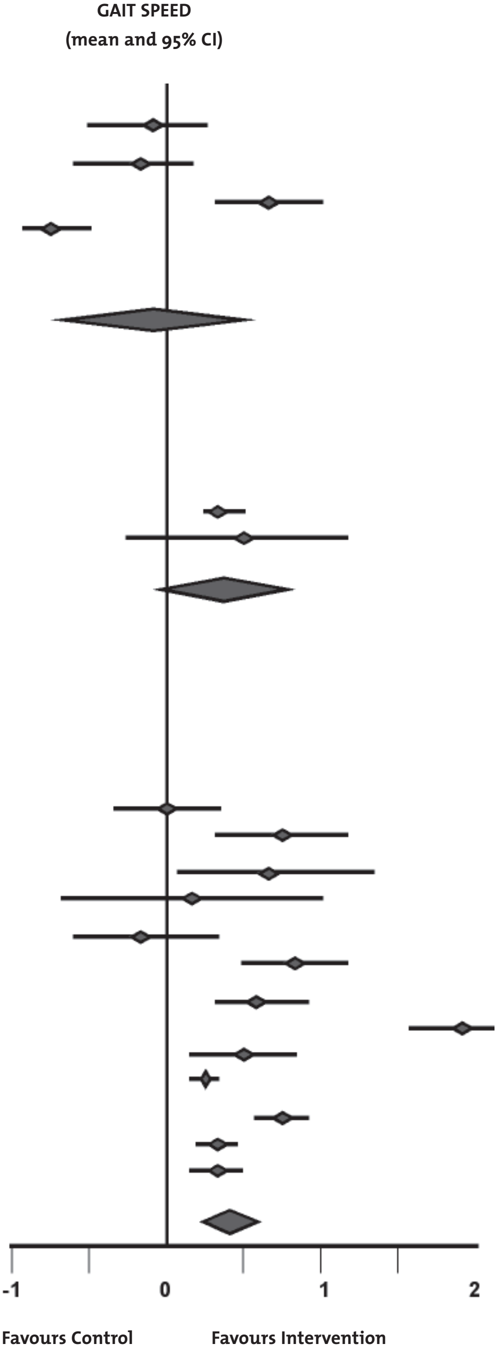
There is limited evidence that cardio-respiratory training negatively affects balance[55] and limited evidence for a positive impact of cardio-respiratory training on walking distance[53]. One high-quality study[53] on cardio-respiratory fitness training also assessed stair climbing by asking the patients to climb as many stairs as possible at comfortable speed. The experimental group performed significantly better than the control group, suggesting limited evidence in favor of cardio-respiratory training for improving stair climbing.

Gait-oriented training

Standing balance showed no statistically significant differences between control and experimental groups in two high-quality studies focusing on gait-oriented training [61,62]. Two high-quality studies, however, presented statistically significant differences between groups on the Functional Ambulation Category[61,64], whereas another high-quality study failed to find significant results in favor of gait-oriented training on the Rivermead Mobility Index[63]. The high-quality studies also found no significant effects of gait-oriented training on outcomes such as ADL[59,62,65], instrumental ADL[4,62] or HRQoL of life[56,59], although one low-quality study did find significant differences in quality of life between groups[66]. Finally, one high-quality study concluded that there were no significant differences on walking quality between the control and experimental groups[60].

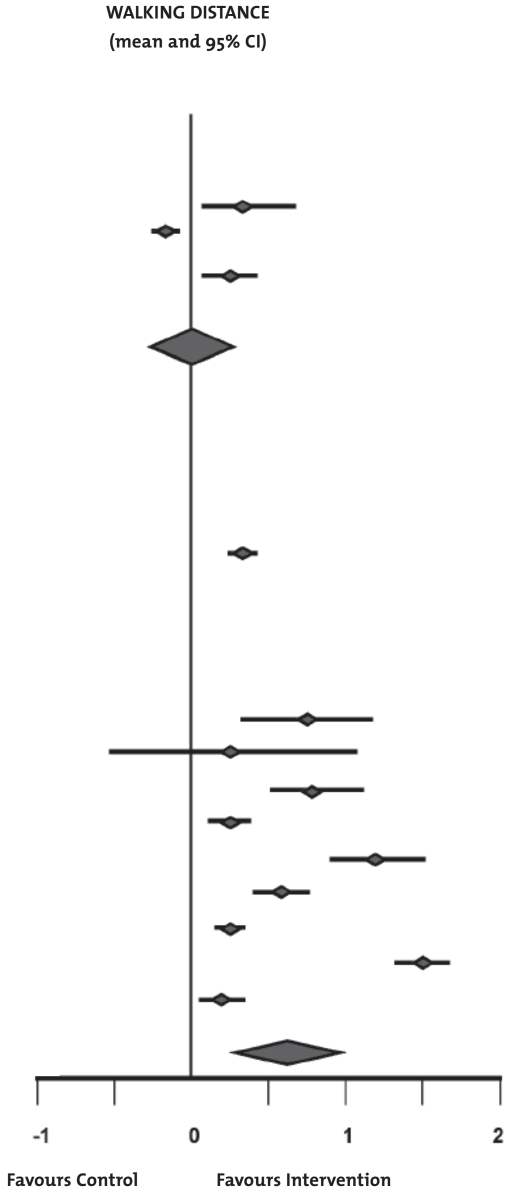
The above findings provide strong evidence that standing balance, ADL, IADL or quality of life are not significantly more improved by gait-oriented training than by conventional care. Strong evidence was found for improved functional mobility after gait-oriented training, whereas limited evidence was found that there is no effect of gait-oriented training on walking quality.

Figure 2. **Summarized effect size of gait speed**



Lower limb strengthening training			
Glasser 1986	N=20	-0.11	[-0.50-0.28]
Kim 2001	N=20	-0.19	[-0.58-0.20]
Bourbonnais 2002	N=25	0.64	[0.31-0.96]
Quelette 2004	N=42	-0.74	[-0.93--0.54]
S.E.S. (random effects model)	**N=107**	**-0.13**	**[-0.73-0.47]**
Cardio-respiratory training			
Katz 2003b	N=92	0.35	[0.26-0.44]
Chu 2004	N=12	0.47	[-0.21-1.15]
S.E.S. (fixed effects model)	**N=104**	**0.36**	**[-0.03-0.75]**
Gait oriented training			
Richards 1993	N=27	0.00	[-0.33-0.33]
Duncan 1998	N=20	0.78	[0.37-1.19]
Teixera-Salmela 1999	N=13	0.70	[0.07-1.33]
Dean 2000	N=9	0.14	[-0.75-1.02]
Liston 2000	N=18	-0.14	[-0.58-0.31]
Laufer 2001	N=25	0.83	[0.49-1.15]
Pohl I 2002	N=30	0.61	[0.31-0.91]
Pohl II 2002	N=30	1.94	[1.59-2.30]
Ada 2003	N=27	0.50	[0.20-0.79]
Duncan 2003	N=100	0.23	[0.15-0.31]
Eich 2004	N=50	0.75	[0.59-0.91]
Salbach 2004	N=91	0.31	[0.22-0.40]
Macko 2005	N=61	0.30	[0.17-0.43]
S.E.S. (fixed effects model)	**N=501**	**0.45**	**[0.27-0.63]**

Figure 3. **Summarized effect size of walking distance**



Lower limb strengthening training			
Bourbonnais 2002	N=25	0.36	[0.04-0.68]
Moreland 2003	N=133	-0.14	[-0.20--0.08]
Quelette 2004	N=42	0.25	[0.06-0.44]
S.E.S. (fixed effects model)	**N=200**	**0.00**	**[-0.28-0.28]**
Cardio-respiratory training			
Katz 2003b	N=92	0.32	[0.23-0.41]
Gait oriented training			
Duncan 1998	N=20	0.73	[0.32-1.14]
Dean 2000	N=9	0.24	[-0.65-1.12]
Ada 2003	N=27	0.79	[0.49-1.10]
Duncan 2003	N=100	0.28	[0.20-0.36]
Blennerhassett 2004	N=30	1.30	[1.02-1.59]
Eich 2004	N=50	0.62	[0.46-0.78]
Salbach 2004	N=91	0.27	[0.18-0.36]
Macko 2005	N=61	1.51	[1.37-1.66]
Pang 2005	N=63	0.19	[0.07-0.32]
S.E.S. (random effects model)	**N=451**	**0.62**	**[0.30-0.95]**

Discussion

This systematic review included 21 high-quality RCTs. The results showed positive, significant effects of gait-oriented training on gait speed and walking distance, whereas no significant effects were found on balance control as measured by the BBS. Although there is evidence that the BBS is a responsive tool[69] there is some discussion about the clinical implication of the changes assessed by the BBS[70]. The significant SES for gait-oriented training programs corresponds to a mean improvement of 0.14m/s for gait speed and 41.2 m on the 6-minute walk test. The small number of studies that evaluated cardio-respiratory fitness training using non-functional approaches, by means of leg cycle ergometers and water-based exercises, also found positive effects on gait speed. In contrast, programs focusing on lower limb strengthening alone failed to show significant effects on gait speed and walking distance.

In agreement with the above findings, a best-evidence synthesis showed that lower limb strength training did not affect outcomes such as stair climbing or HRQoL, whereas strong evidence was found for a favorable effect of cardio-respiratory training on stair climbing performance. In addition, there is some evidence that cardio-respiratory training negatively affects balance[55] and has a positive impact on walking distance[53]. Finally, strong evidence was found that balance, ADL, IADL or HRQoL were not significantly affected by gait-oriented training, although functional mobility was positively impacted. However, these conclusions need to be interpreted with some caution, since the authors used ordinal scales to assess balance and ADL which they treated as continuous scales, reporting means and CI's.

The main finding of the present review is that programs focusing on cardio-respiratory and gait-oriented training are more beneficial in improving walking competency than programs centered on strengthening. This finding supports the general view of motor learning that exercise regimens mainly induce specific treatment effects, suggesting that gait and gait-related activities should be directly targeted. In other words, the training programs need to focus primarily on the relearning of functional gait-related skills that are relevant to the individual patient's needs[7,71]. Since gait speed over a short distance overestimates walking distance in a 6 minute walk test[72], one should realize that improving gait speed does not automatically result in improvements in walking distance. This underlines the fact that training should be task-specific. The lack of evidence to support the relationship between strength gains and improvements in walking ability[47,64] also suggests that, despite the significant improvement in strength, therapy-induced improvements do not automatically generalize to significant gains in gait performance[47,52,73].

The mechanisms underlying therapy-induced improvements in gait performance are not yet well understood. Recent electroneurophysiological studies in which the EMG activity of the paretic muscles was serially recorded[45] and studies recording improvements in standing balance[74,75] have shown that task-related improvements were poorly related to physiological gains on the paretic side. Closer associations have been found with compensatory adaptive changes on the non-paretic side, such as increased anticipatory activation of muscles of the non-paretic leg[75], strategies using increased weight-bearing above the non-paretic leg while standing[74] or stride lengthening of the non-paretic leg[32] while walking. In other words, there is growing evidence that functional improvements are closely related to the use of compensatory movement strategies in which patients learn to adapt to existing impairments[45]. Since it is still unclear which compensatory characteristics are most closely related to gains in walking competency, longitudinal kinematic and neurophysiologic studies are needed for a better understanding of the underlying mechanisms of functional improvement.

Although only two studies focusing on the effect of cardio-respiratory fitness interventions (without walking) on gait speed could be included, a positive effect on walking speed was found, however this effect was not statistically significant. This is in accordance with the Cochrane review of Saunders and colleagues[3]. The only study that assessed the effect of cardio-respiratory training on walking distance, showed that cardio-respiratory training was beneficial in improving distance walked[53]. These results are in agreement with the findings in the recently conducted review of Pang[76]. Obviously, improving aerobic capacity as a reflection of physical condition is an important factor in restoring walking competency, since it has been suggested that the energy costs of walking are substantially higher in people with stroke than in normal individuals[77]. These high energy demands are frequently associated with less efficient motor control in hemiplegic compared to healthy subjects, resulting from the use of compensatory or adaptive movement strategies to perform functional tasks such as walking[77,78]. Energy expenditure required to perform routine ambulation is increased approximately 1.5- to 2.0-fold in hemiparetic stroke patients compared to normal control subjects[79]. The lower walking speeds observed in patients with hemiparesis (30 m/min) consume approximately the same amount of oxygen (10 ml/kg/min)[80] as healthy people require when walking approximately twice as fast (i.e., 60 m/min)[81]. However, the number of studies investigating energy expenditure after stroke is limited.

The present review also suggests that enhancing walking endurance by improving physical condition seems to be less specific, since progressive bicycling programs resulted in significant gains in walking endurance[45]. Progression in training programs seems to be an important aspect of improving walking endurance[5]. The fact that balance is also improved by cardio-respiratory training might also suggest that it would be beneficial in improving gait speed and walking distance, since balance is highly related to independent gait[53,82]. However, more RCTs are needed to allow conclusions on the effects of non-specific cardio-respiratory training on walking competence.

Further improvement of stroke rehabilitation could be achieved by identifying which patients benefit most from supervised[83] physical fitness training programs. Salbach et al. indicated that most effects were gained in the group of patients with a moderate walking deficit[5]. Another study suggested that persons with severe depressive symptoms may be particularly responsive to therapeutic intervention[22]. Recently, Lai and co-workers concluded that depressive symptoms do not restrict gains in functional outcome as a result of physical exercise. They also suggested that exercise may help reduce post-stroke depressive symptoms[84]. Recently, we found that the presence of depressive symptoms, fatigue, reduced cognitive status and an inactive lifestyle are important factors related to a gradual decline in mobility over time[85]. In other words, these variables can be used to identify those patients who are at risk for mobility decline, since function-oriented training is effective in improving walking competency. The moment at which these gait-oriented treatments are introduced seems not to be restricted to a particular phase after stroke or a particular type of stroke.

Although this systematic review aimed at identifying all relevant trials, the study was subject to certain limitations. Firstly, the review did not include papers written in languages other than English, German or Dutch, or studies focusing on body weight support treadmill training programs. In addition, the definitions of strengthening, cardio-respiratory fitness and gait-oriented training we used were arbitrary.

Conclusion

This review shows that gait-oriented training, targeting improved strength and cardio-respiratory fitness is the most successful method to improve gait speed and endurance. This is an important finding for clinical practice, since about 20% of all chronic stroke patients show a significant decline in mobility status in the long run. Future studies should elucidate whether a functional training program can improve walking competency in patients who are susceptible to a decline in mobility such as the very old, those severely compromised and those who are depressed. In addition, current debate is concentrating on whether the critical variable for therapeutic efficacy is task-specificity or the intensity of the effort involved in therapeutic activities (increased volume, increased level of participation, increased intensity)[86], aspects which need further investigation. Future studies should establish whether the improvements in gait speed and walking distance that have been described are of clinical relevance for independent community ambulation. In addition, the long-term effects of these training interventions need to be investigated.

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6

Determinants of depression in chronic stroke: a prospective cohort study

Ingrid G.L. van de Port, Gert Kwakkel, Margje Bruin, Eline Lindeman

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Abstract

Purpose The aim of the study was to identify factors that are significantly related to depression in chronic stroke patients.

Methods Prospective cohort study of stroke patients admitted for rehabilitation. A total of 165 first ever stroke patients over 18 years of age were assessed at one and three years post stroke. Depression was determined by the Centre for Epidemiologic Studies Depression Scale (CES-D). Patients with scores ≥ 16 were classified as depressed. Bivariate and multivariate logistic regression analyses were used to identify prognostic factors for depression.

Results At three years post stroke, 19% of the patients were depressed. Bivariate analysis showed significant associations between post-stroke depression and type of stroke, fatigue, motor function of the leg and arm, activities of daily living (ADL) independency and instrumental ADL. Multivariate logistic regression analysis showed that depression was predicted by one-year instrumental ADL and fatigue. Sensitivity of the model was 63%, while specificity was 85%.

Conclusions The present prospective cohort study showed that depression three years after stroke can be predicted by instrumental ADL and fatigue one year post stroke. Recognition of prognostic factors in patients at risk may help clinicians to apply interventions aimed at preventing depression in chronic stroke.

Introduction

Depression is a common symptom in stroke patients, with a prevalence ranging between 25% and 79%[1]. A recent systematic review found a pooled estimate of the occurrence of depression among all stroke patients of 33%. Depression occurred in early, medium and late stages of recovery[2].

Post-stroke depression (PSD) has been negatively associated with functional outcome, i.e. activities of daily living (ADL)[3-10]; and health related quality of life (HRQoL)[11]. Unfortunately, it is as yet unclear what determinants predict PSD, since the published studies have reported variable findings. To date, prognostic studies have shown that a history of previous depression[12], stroke severity[13,14], lesion location[15], functional status [12,16-19], neuroticism[16], younger age[17] and female gender[14,20] were related to PSD. In contrast, older age[14] and male gender[13] were also found to be predictive. The differences in reported determinants may be due to a number of factors. First of all, prognostic studies have used different definitions and measures to determine depression. Furthermore, studies have varied widely in terms of population characteristics and the timing of the assessment of depression and outcome post stroke. Finally, methodological flaws due to inappropriate start and end-points, co-interventions and drop-outs may have biased the relationships found, in particular, acknowledging that none of the prognostic studies did (cross)-validate their developed prediction model.

Berg et al.[13] suggested that depressive symptoms are likely to emerge at longer times, and therefore emphasised the importance of follow-up studies beyond 18 months to explore the real outcome of depressive stroke patients. Bogousslavsky[7] described that emotional behavioural changes shortly after stroke are often confused with depression. He suggested that significant PSD is more common in the chronic phase after stroke. He also introduced the issue of post-stroke fatigue, which might be associated with PSD but which has also been proven to be distinct from it.

In view of the above findings, the first aim of the present study was to identify factors that are significantly related to depression in patients suffering from chronic stroke. Subsequently, a multivariate, logistic regression model was developed based on the findings one year post stroke, to predict the presence of depression three years post stroke.

Subjects and Methods

Design

Between April 2000 and July 2002, stroke patients were recruited for the Functional Prognosis after Stroke Study (FuPro-Stroke Study). This prospective cohort study was conducted in four Dutch rehabilitation centres and patients were included after admission to inpatient rehabilitation. The medical ethics committees of UMC Utrecht and the participating rehabilitation centres approved the FuPro-Stroke study. All patients included gave their informed consent. At one year and three years post stroke, data were collected by means of face-to-face interviews and physical and cognitive examinations.

Subjects

All subjects had been hospitalised before admission to the rehabilitation centre. Stroke was defined according to the WHO definition[21]. Stroke patients included were over 18 years of age and had suffered their first supratentorial stroke located on one side (cortical and subcortical infarctions, intracerebral haemorrhages or subarachnoid haemorrhages), as diagnosed by means of MRI or CT scan. Patients with lesions related to a trauma or tumour were excluded, as were patients who suffered disabling conditions with consequences for daily functioning (premorbid Barthel Index < 18), and patients with insufficient command of Dutch. For the present analysis, patients with aphasia were also excluded, since they were unable to complete the Centre for Epidemiologic Studies Depression Scale (CES-D). The presence of aphasia was assessed by the Token Test (short version)[22] and the Utrecht Communication Observation [Utrechts Communicatie Onderzoek][23]. Patients scoring nine errors or more on the Token Test and/or scoring less than four on the UCO were considered aphasic. At three years post stroke 42 of the 217 patients were aphasic and excluded for assessment of the CES-D.

Dependent variable

Post-stroke depression (PSD) was assessed by the CES-D[24]. This outcome measure consists of 20 items, with a minimum score of 0 and a maximum score of 60, and has proved to be valid and reliable for stroke populations[25,26]. Total scores on the CES-D were dichotomised into ‘non-depressed’ (CES-D <16) and ‘depressed’ (CES-D ≥16)[25].

Independent variables

Independent variables used in this study were chosen on the basis of results of previous studies and on clinical grounds. The following independent variables were included:

gender, age, living status, time between stroke onset and admission, type of stroke, hemisphere, fatigue and functional status.
Type of stroke was dichotomised into infarction (cortical ischemia, subcortical lacunar and other subcortical infarction) and haemorrhage (intracerebral haemorrhage and subarachnoid haemorrhage). Fatigue was assessed by the Fatigue Severity Scale (FSS)[27], a nine-item scale with total scores ranging from 9 to 63. The FSS was originally developed to determine the impact of fatigue in patients with multiple sclerosis[27], but has also been used in stroke patients[28,29]. Internal consistency (Cronbach's α) was determined at .89[30]. The mean score (total score / 9) was dichotomised into 'non-fatigued' (FSS < 4 points) and 'fatigued' (FSS ≥ 4 points)[31]. The Frenchay Activities Index (FAI)[32] is a valid[32,33] and reliable[34,35] measure that was used to assess instrumental ADL. Total scores of the FAI range from 0 to 45. According to previous studies these scores were dichotomised into inactive (0-15) and moderately / highly active (16-45)[36,37]. The Barthel Index (BI)[38] was used to determine activities of daily living (ADL). Validity and reliability of the BI have been well investigated[38,39]. The total score (0-20) of the BI was dichotomised into 'independent' (BI = 19/20) and 'dependent' (BI <19)[40]. The Motricity Index (MI) is valid and reliable[41] and was used to determine the motor functions of arm (MI arm) and leg (MI leg). Scores ranged from 0 (no activity) to 100 (maximum muscle force) for each dimension. We dichotomised the total scores into scores between 0 and 75 on the MI leg dimension or between 0 and 76 on the MI arm dimension, indicating no optimal range of motion, and higher scores, indicating optimal range of motion.

Statistics
Data for all patients were entered into a computer database and analysed with the SPSS statistical software package (version 13.0).
Univariate regression analysis was used to select significant determinants ($p<0.2$) of PSD, and for the subsequent development of a multivariate logistic regression model for the prediction of PSD. The significant determinants were tested for multicollinearity to prevent overparametrisation of the prediction model. If the correlation coefficient was >0.7, the variable with the lowest correlation coefficient, relative to the outcome measure, was omitted. The remaining significant independent determinants were used in a multivariate, backward logistic regression analysis. Only determinants with a significance level below 0.1 were allowed into the final model. Goodness of fit of the multivariate logistic model was tested with the Hosmer-Lemeshow test. Also, the area under the receiver operating characteristics (ROC) curve, and sensitivity and specificity were measured.

Results

In total, 165 patients were assessed. At one year post stroke, their mean age was 57 years (SD = 11), 55% of the patients were male, and 29% were living alone (Table 1). Complete datasets for the regression analyses were available for 145 patients. At three years post stroke, 19% of the patients were depressed.

Bivariate Analysis

The bivariate analysis showed significant associations between PSD and type of stroke, fatigue (FSS), motor function of the leg and arm (MI arm and MI leg), ADL (BI) and instrumental ADL (FAI) ($p<0.2$) (Table 2). A more liberal significance level was used to increase the power for true predictor selection. MI arm and MI leg showed high collinearity (Spearman's correlation coefficient >0.7). MI leg was used in the multivariate regression analysis because it had the strongest association with PSD.

Multivariate Analysis

The backward logistic regression analysis showed that instrumental ADL (FAI) and fatigue (FSS) were statistically significant predictors of depression three years after stroke ($p < 0.1$) (Table 2). The multivariate model showed a good fit (Hosmer-Lemeshow test $p>0.05$). The area under the ROC curve was 0.7. Sensitivity was 63%, while specificity was 85%. The model correctly classified 76% of the patients.

Table 1. Baseline patient characteristics one year post stroke

	n=165
Gender (female)	74 (45%)
Mean age (years)	57 (SD=11)
Marital status (living alone)	48 (29%)
Education (University)	35 (21%)
Type of stroke (haemorrhage)	51 (31%)
Hemisphere (right)	91 (55%)
Mean time between stroke onset and admission (days)	36 (SD=23)
Depression (present)*	41 (27%)
Fatigue (present)*	104 (68%)
Motor function – arm (no optimal range of motion)	78 (48%)
ADL-status (dependent)	53 (32%)
Level of activity (% inactive)**	41 (26%)

n= number of subjects, SD= standard deviation, *n=152,**n=156

Table 2. Bivariate and multivariate logistic regression analyses

	Bivariate analysis				Multivariate analysis (n=145)			
	B (ß coefficient)	S.E.	p-value	Odds (95%CI)	B (ß coefficient)	S.E.	p-value	Odds (95%CI)
Gender (female)	-0.06	0.40	0.89	0.95 (0.44 - 2.06)				
Age (>65 years)	0.01	0.46	0.98	1.01 (0.41 – 2.46)				
Partner (yes)	-0.35	0.42	0.41	0.71 (0.31 – 1.62)				
Level of education (university)	-0.45	0.53	0.39	0.64 (0.23 – 1.79)				
Type of stroke (infarction) *	0.80	0.49	0.10	2.22 (0.85 – 5.77)				
Time between CVA and rehabilitation	-0.01	0.10	0.40	0.99 (0.97 – 1.01)				
Hemisphere (right)	-0.07	0.40	0.86	0.93 (0.43 – 2.02)				
Fatigue (present)*	1.32	0.64	0.04	3.72 (1.06 – 13.06)	1.05	0.65	0.10	2.86 (0.80 – 10.29)
ADL (dependent)*	0.69	0.41	0.09	1.99 (0.89 – 4.42)				
Motor function – arm (impaired) *	0.60	0.41	0.14	1.83 (0.82 – 4.09)				
Motor function – leg (impaired)*	0.59	0.42	0.17	1.80 (0.78 – 4.14)				
Level of activity (inactive) *	1.18	0.44	0.01	3.24 (1.38 – 7.63)	0.90	0.47	0.06	2.47 (0.97 – 6.26)
Constant					-2.58			

n= number of subjects, SE= standard error of the estimate, * Significant one-year determinants of post-stroke depression at three years ($p < 0.2$)

Discussion

The present study showed that type of stroke, fatigue (FSS), motor function of the leg and arm (MI), ADL (BI) and instrumental ADL (FAI) were bivariately related to depression three years after stroke. The multivariate logistic regression model included one-year fatigue and instrumental ADL as statistically significant factors associated with depression three years post stroke.

Interestingly, our prediction model showed that the presence of fatigue is one of the two valid predictors of the development of three-year PSD. Until now, prospective cohort studies investigating determinants of post-stroke depression did not include fatigue. However, an association between post-stroke fatigue and PSD has been demonstrated in a number of previous studies[29,42,43]. There is a certain amount of overlap between PSD en post-stroke fatigue, partly because fatigue is often accompanied with depression. On the other hand, a number of studies have shown that fatigue can also occur in the absence of depression[7,29,44]. Patients experiencing fatigue as measured by the FSS are impeded in their daily activities and responsibilities, which may create feelings of depression[12,18,19]. Furthermore, the social life of stroke patients may be impeded by symptoms of fatigue, which can be an independent predictor of PSD[45,46].

The prediction model in the present study also included instrumental ADL, indicating that IADL limitations were a risk factor for developing PSD. This may be due to the kind of activities measured by the FAI. It can be hypothesised that stroke patients become socially isolated when disability after stroke makes it impossible to visit friends and family, make short trips and actively pursue hobbies. Moreover, a lack of activities during the day can create a sense of emptiness, especially if someone is unable to engage in leisure activities or have a job[47]. Furthermore, not being able to accomplish everyday activities that one was able to accomplish before stroke causes frustration. Although most studies on determinants of PSD have included ADL independency, they did not include instrumental ADL. The present study shows that activities that require a certain level of initiative from stroke patients, such as shopping and actively pursuing hobbies, should also be considered, besides the basic activities of daily living that are measured by instruments like the Barthel Index.

The moderate area under the ROC curve showed that the model was not fully able to correctly identify the depressed and non-depressed patients. Sensitivity was moderate (63%), but specificity was high (85%), which means that the patients who did not develop depression were correctly identified by the model. In total 76% of the patients were classified correctly. The model only consisted of two determinants, and although we tested several other potential factors, there are probably other determinants that also play a role in developing depression. We did not determine factors like previous depression and co-interventions such as psychopharmaceuticals or psychotherapy, which might cause bias. Pre-stroke depression might be an important determinant related to the development of depression after stroke, as demonstrated in previous studies[12,48]. Also, aphasic stroke patients were excluded since they are unable to complete the CES-D. Depression may well be an issue especially in aphasic patients. Recently, new instruments have been developed for screening depression in aphasics, such as the Stroke Aphasia Depression Questionnaire[49,50] and the Aphasic Depression Rating Scale[51]. However, these instruments await further validation. Further investigation is needed to check the validity of the developed model by cross-validation in an independent stroke population.

The present study investigated the predictors of PSD in a multivariate logistic regression model in a large sample of chronic stroke patients, and showed that fatigue and instrumental ADL should be taken into account as possible predictors of PSD. So far, few prognostic studies on the predictors of PSD have been conducted and identifying strong predictors for post stroke depression is difficult[13,19]. What is needed now is prognostic research with a longitudinal design, in which the origins and the development of PSD over time can be studied by repeated measurements. In particular, acknowledging that most symptoms such as feelings of depression and fatigue, as well as ADL and IADL are heavily dependent on the moment of assessment after stroke.

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7

Is fatigue an independent factor associated with activities of daily living, instrumental activities of daily living, and health-related quality of life in chronic stroke?

Ingrid G.L. van de Port, Gert Kwakkel, Vera P.M. Schepers, Caroline T.I. Heinemans, Eline Lindeman

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Abstract

Background To determine the longitudinal association of poststroke fatigue with activities of daily living (ADL), instrumental ADL (IADL), and perceived health-related quality of life (HRQoL) and to establish whether this relationship is confounded by other determinants.

Methods A prospective cohort study of stroke patients consecutively admitted for inpatient rehabilitation was conducted. ADL, IADL, and HRQoL were assessed in 223 patients at 6, 12, and 36 months after stroke. Fatigue was determined by the Fatigue Severity Scale. Random coefficient analysis was used to analyze the impact of fatigue on ADL, IADL, and HRQoL. The association between fatigue and outcome was corrected for potential confounders, i.e. age, gender, comorbidity, executive function, severity of paresis and depression. The covariate was considered to be a confounder if the regression coefficient of fatigue on outcome changed by >15%.

Results Fatigue was significantly related to IADL and HRQoL, but not to ADL. The relation between fatigue and IADL was confounded by depression and motor impairment. Depression biased the relation between fatigue and HRQoL, but fatigue remained independently related to HRQoL.

Conclusions Fatigue is longitudinally spuriously associated with IADL and independently with HRQoL. These findings suggest that in examining the impact of poststroke fatigue on outcome, one should control for confounders such as depression.

Introduction

Poststroke fatigue is a common complaint in many stroke patients, with prevalence rates reported in the literature ranging from 38% to 68%[1-5]. However, research of fatigue is hampered due to the lack of an unambiguous definition that validly reflects the multi-dimensional qualities of this symptom[6-8]. Despite the assumed negative impact of poststroke fatigue on functional outcome, few studies have investigated this symptom[7,9]. A few studies have suggested that fatigue is an important invalidating symptom which may independently affect functional outcome after stroke[1,2,4,10]. For example, Glader et al.[2] showed that fatigue was associated with increased dependency in activities of daily living (ADL; both primary and secondary) and with higher case fatality. In addition, it has been suggested that the impact of fatigue is severest on physical domains[1,3]. Unfortunately the studies that focused on the impact of fatigue on functional outcome did not control for the influence of possible confounding factors, such as depression, which are related to the symptom of fatigue itself as well as to the outcome variable[11]. In addition all studies determined the impact of fatigue on functional outcome at an arbitrarily selected moment after stroke, whereas it has been shown that fatigue is a time-dependent factor[12]. Therefore, longitudinal models with repeated measurements are more appropriate to investigate the relationship between poststroke fatigue and functional outcome than the traditional methods of regression analysis, in which the impact of fatigue on functional outcome is assumed to be fixed.

Since the effect of poststroke fatigue on the level of ADL, instrumental ADL (IADL) and perceived health related quality of life (HRQoL) had never been the subject of a longitudinal study, the first aim of the present prognostic study was to investigate the longitudinal bivariate relationship of poststroke fatigue with ADL, IADL, and HRQoL between 6 and 36 months after stroke. We hypothesized that the influence of post-stroke fatigue would be more strongly associated with the more energy-consuming ADLs, like social and household activities, and with perceived HRQoL, than with purely basic ADLs. In addition we wanted to establish whether this longitudinal association between fatigue on the one hand and ADL, IADL and HRQoL on the other was confounded by other factors. On the basis of existing evidence from the literature and on clinical grounds, we hypothesized that younger age[1,9], female gender[2,3,13], comorbidity[1], neuro-psychological impairments[5,6,14-17], severer hemiplegia[1,7,18], and depressive feelings[1,4,10] would be significantly associated with fatigue, as well as with ADL, IADL, and HRQoL, and might distort the relationship between fatigue and outcome in chronic stroke.

Materials and Methods

Design

From April 2000 to July 2002, stroke patients receiving inpatient rehabilitation were recruited for the Functional Prognosis after Stroke study (FuPro-Stroke). For this prospective cohort study patients were recruited in 4 Dutch rehabilitation centers. The medical ethics committees of University Medical Center Utrecht and the participating rehabilitation centers approved the FuPro-Stroke study. All patients included gave their informed consent.

Subjects

The subjects were stroke patients included in their first week of inpatient rehabilitation to participate in the FuPro-Stroke study. They had all been hospitalized before admission to the rehabilitation center. Inclusion criteria were: (1) age >18; (2) first-ever stroke, and (3) a supratentorial lesion located on 1 side. Patients with the following stroke subtypes were included: cortical and subcortical infarction, intracerebral hemorrhage, and sub-arachnoid hemorrhage. Stroke was defined according to the World Health Organization criteria as 'rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin'[19]. Exclusion criteria were: (1) prestroke Barthel Index (BI) <18 (0–20) and (2) insufficient command of Dutch. The present study also excluded patients with aphasia, since they were unable to complete the questionnaire measuring fatigue.

Measurement

Dependent Variables

The BI was used as a valid and reliable measure to determine functional ability for 10 ADL functions[20]. The total score, which was used to describe ADL function, ranges from 0 (ADL-dependent) to 20 (ADL-independent).

IADL was assessed with the Frenchay Activities Index (FAI)[21]. The FAI consists of 15 items and is considered to be a valid and reliable measure for stroke patients[22]. Each item is scored on a 4-point scale (0–3), and the possible total score ranges from 0 (inactive) to 45 (highly active). The FAI was not assessed for patients who were still in inpatient rehabilitation.

Perceived HRQoL was determined by the Sickness Impact Profile 68 (SIP68)[23]. All questions were scored dichotomously and the total scores are presented as a percentage of maximum dysfunction, ranging from 0–100%, with a higher score indicating poorer perceived HRQoL.

Fatigue
The Fatigue Severity Scale (FSS) was used to assess fatigue. It was originally developed to determine the impact of fatigue in patients with multiple sclerosis[24], but has also been used in stroke patients[1]. The FSS is brief and simple and consists of 9 items with the scores of each item ranging from 1 to 7. The total score of the FSS is the mean of the 9 items[24]. Recently the FSS showed an internal consistency (Cronbach's α) of .89[12]. In a reliability study with 2 independent observers and 18 stroke patients, FSS had an intra-class correlation coefficient of 0.82. Patients with an FSS score of ≥ 4 points were considered fatigued[24,25].

Potential confounders
Confounding was defined as the distortion in the observed association between fatigue and outcome (i.e., ADL, IADL and HRQoL) due to factor(s) associated with both fatigue and outcome[11]. For this purpose various time-independent and time-dependent variables were considered as potential confounders that might distort the relationship between fatigue and ADL, IADL, and HRQoL in the association model.
The time-independent variables were age, gender and comorbidity. Comorbidity was scored positive when one or more of the following diseases were present: cardiovascular and respiratory diseases, diabetic mellitus and non stroke-related disability of the locomotor system.
The following time-dependent variables were included: depression, impairment of executive function and severity of hemiplegia.
The total score (range 0–60) on the Center for Epidemiologic Studies Depression Scale (CES-D) was used to determine depression[26]. Executive function was determined by the time needed to complete part B of the Trail Making Test (TMT)[26,27]. This involves complex visual scanning, motor speed and attention. The participant has to connect 25 encircled numbers and letters, as quickly as possible, alternating between numbers and letters (1-a-2-b-3-c, etc.). The Motricity Index (MI) was used to determine motor function[28]. A total score was calculated as the mean of the arm and leg dimensions (range 0–100).

Procedure
The longitudinal relation between fatigue on the one hand and ADL, IADL and HRQoL on the other was investigated at 3 measurement moments. At 6 (t1), 12 (t2) and 36 months (t3) after stroke, the patients were visited by a research assistant, who collected data by means of face-to-face interviews and physical and cognitive examination.

Statistics

The longitudinal relationship between fatigue on the one hand and ADL, IADL, and HRQoL on the other was evaluated by means of random coefficient analyses (RCA; MLwiN version 2.0). In longitudinal studies the repeated measurements are correlated and clustered within the individuals and the measurements. RCA[29-32] takes into account that the repeated observations within 1 subject are dependent of each other. In contrast to traditional methods of longitudinal data analysis (e.g., MANOVA), RCA does not require complete datasets, and both the number of observations per individual and the time between observations may vary. In MLwiN, the intercept is assumed to be randomly distributed between subjects.

Initially, bivariate longitudinal regression analyses were conducted with the BI, FAI, and SIP68 scores as dependent variables and the FSS score as the independent variable, to test our first hypothesis. Subsequently the effect of fatigue on ADL, IADL and HRQoL was investigated while controlling for time-independent (gender, age and comorbidity) and time-dependent (depression, executive function and motor impairment) covariates as potential confounders in the longitudinal association model. If the regression coefficient of fatigue changed by >15% after controlling for the added variable in the model, the added covariate was considered to be a confounder. If the relationship between fatigue and outcome was still significant after controlling for the detected confounder, new candidate confounders were added to the model. A 2-tailed significance level of 0.05 was used for all tests.

Results

Table 1 represents a cohort of 223 patients, of whom 60% were men. The mean age of the patients included in the analysis at t1 was 57 years (SD= 11). The observed FSS scores increased from 4.5 at 6 months to 4.7 at 12 months and then declined to 4.3 at 36 months after stroke. At 6 months after stroke, 68% of the patients were fatigued, compared to 74% and 58% at 12 and 36 months after stroke, respectively. In total 580, 514, and 578 of the 669 scores were available for random coefficient modeling of ADL, IADL and HRQoL, respectively.

Bivariate RCA

Fatigue was not statistically significantly associated with BI between 6 and 36 months after stroke (p=0.320), whereas significant associations were found for FAI (p=0.032) and SIP68 (p=0.000; Tables 2, 3).

Table 1. Patient characteristics at 6 months (n=223)

Gender, % male	59.6
Age, mean ± SD	57.3 ± 11.1
Living status, % partner	73.5
Type of stroke, % infarction	72.2
Hemisphere, % right	53.8
Comorbidity, % present	78.9
TMT median, s (n=216)	176 (range 41-600)
MI, mean ± SD	66.3 ± 25.7
CES-D, mean ± SD (n=220)	10.6 ± 7.8
FSS, mean ± SD	4.4 ± 1.2
BI, mean ± SD	18.0 ± 2.5
FAI, mean ± SD (n=164)	18.6 ± 8.1
SIP68, mean ± SD	29.7 ± 14.3

Confounding factors

Instrumental ADL

The proportional change in the regression coefficient of FSS after inclusion of the assumed confounders in the regression model for predicting FAI is presented in Table 2, in hierarchal order. Adding depression (CES-D) to the model resulted in the largest proportional change (60.1%) in the regression coefficient of FSS. After controlling for CES-D, no significant relationship between FSS and IADL was found (β=-0.232, SE=0.283, $p>0.05$). Controlling the model for motor function (MI) caused a significant reduction of 20.6% in the FSS regression coefficient (β=-0.462, SE=0.257, $p>0.05$). No significant changes were found after controlling for age, gender, time needed to complete the TMT or co morbidity.

Health Related Quality of Life

Table 3 presents the association between FSS and SIP68 after correcting for possible confounders. The proportional reduction of the regression coefficient of the FSS was 37.6% after CES-D had been added to the model. However, the FSS remained significant in the longitudinal regression model (β=1.725, SE=0.423, $p<0.05$). In addition no significant change was found in the relationship between FSS and SIP-68 after other potential confounders had been added to the multivariate regression model. No significant bias was found for age, gender, time needed to complete the TMT, severity of hemiparesis, or comorbidity.

Table 2. Bivariate multilevel regression model to test the effect of confounders on the predictive value of fatigue for IADL (n=223)

Variables in the model	Confounder ß	FSS ß	Proportional change in the coefficient of FSS
FSS		-0.582 (0.271)*	
Candidate confounders			
CES-D	-0.190 (0.047)*	-0.232 (0.283)	60.1%
MI	0.165 (0.017)*	-0.462 (0.257)	20.6%
Gender (1 = female)	4.646 (1.113)*	-0.635 (0.286)*	9.1%
TMT total time	-0.020 (0.004)*	-0.625 (0.273)*	7.4%
Comorbidity (1 = present)	-3.377 (1.118)*	-0.566 (0.269)*	2.7%
Age	-0.150 (0.048)*	-0.579 (0.270)*	<1%

The figures in parentheses represent SE; * $p < 0.05$

Table 3. Bivariate multilevel regression model to test the effect of confounders on the predictive value of fatigue for HRQoL (n=223)

Variables in the model	Confounder ß	FSS ß	Proportional change in the coefficient of FSS
FSS		2.765 (0.418)*	
Candidate confounders			
CES-D	0.593 (0.071)*	1.725 (0.423)*	37.6%
TMT total time	0.030 (0.006)*	2.963 (0.421)*	7.2%
MI	-0.338 (0.025)*	2.847 (0.380)*	2.9%
Age	0.164 (0.080)*	2.767 (0.418)*	<1%
Comorbidity (1 = present)	5.862 (1.822)*	2.768 (0.416)*	<1%
Gender (1 = female)	-2.114 (1.882)	2.786 (0.418)*	<1%

The figures in parentheses represent SE; * $p < 0.05$

Discussion

Fatigue was present in 68% of the patients at 6 months after stroke, whereas 74% of the patients were fatigued at 1 year and 58% at 3 years after stroke. This study shows for the first time that, longitudinally, poststroke fatigue is an important covariate that is significantly associated with IADL and HRQoL, but not with basic ADLs, between 6 and 36 months after stroke. This finding confirms our first hypothesis that poststroke fatigue is more strongly related to the more complex, energy-consuming ADLs (IADL), such as shopping and using public transport, as well as to perceived HRQoL, than to basic ADLs such as dressing and making transfers. However, the present study also showed that the association between fatigue and IADL became nonsignificant after controlling for depression and severity of hemiparesis, suggesting that these 2 factors determine the relationship between fatigue and IADL in chronic stroke. Depression was also the strongest confounder distorting the longitudinal association between fatigue and perceived HRQoL. However, even after controlling for depression, fatigue remained a significant factor that is independently associated with HRQoL. The latter finding suggests that fatigue is an isolated symptom which is to a large extent independently related to perceived HRQoL in patients with chronic stroke.

The above results are in line with those of cross-sectional studies investigating the relationship between fatigue on the one hand and IADL[2] and HRQoL[4] on the other. Unfortunately these studies used different outcome measures and did not systematically control for potential confounders such as depression. Since depressed patients may experience fatigue or loss of energy nearly every day, and since they show markedly diminished interest in activities such as interpersonal and social activities[33], it is conceivable that depression is a confounder in the relations between fatigue and IADL and between fatigue and HRQoL. In addition fatigue is one of the criteria for a major depressive disorder according to DSM-IV. However, both variables have also been observed as symptoms that were present independently[1,3,14,15]. It may be questioned whether the association between depression and fatigue that we found could have been caused by the existing overlap between the measures. However, we used the CES-D to establish depression, to prevent the same questions being addressed in both measurements. Only 1 of the 20 items in the CES-D (‘My sleep was restless’) might be related to fatigue, but none of the items of the FSS measure depression. In other words the association we found is unlikely to be explained by an overlap in questions between the 2 measurements. Besides depression the relation between fatigue and IADL was also influenced by motor impairment. The literature provided evidence that poor motor function is related to fatigue[1] and poorer IADL[34,35]. Such a relationship is not inconceivable, since patients with

severe hemiparesis need more energy for extended ADLs and tire more easily than those with a minor hemiparesis.
Demographic factors such as age, gender and comorbidity did not significantly bias the longitudinal relation between fatigue and IADL or HRQoL. Executive function did not bias the longitudinal relationship either, although some studies have suggested that cognitive status was related to both fatigue[7,15] and HRQoL[17]. Naess et al.[10] concluded that cognitive status, as measured by the MMSE, was not related to fatigue, but they argued that MMSE does not evaluate executive functioning and was therefore not related to fatigue. Since we used the TMT, we did determine executive function, including attention and concept shifting. However, the association between fatigue and IADL and HRQoL was not confounded.
An important advantage of using RCA is that it is possible to analyze measurements over time and to correct for the dependency between repeated measurements within subjects[29]. Previous studies have focused mainly on the cross-sectional relation between fatigue and outcome by calculating correlation coefficients. However, it has been suggested that fatigue is a time-dependent variable[12] and the use of multilevel analysis allows one to account for the existing time dependency. In addition RCA does not require complete datasets, which is an important advantage, since traditional methods based on analysis of variances (i.e., MANOVA) cannot deal with missing values when analyzing results of longitudinal studies[29]. We therefore believe that investigating the longitudinal relationship between time-dependent symptoms such as fatigue, depression and HRQoL may reflect the existing relationship more robustly and accurately than performing naïve regression analysis at arbitrarily selected moments after stroke.
There are also some limitations to investigating the impact of poststroke fatigue on outcome. Firstly the main problem is how to define fatigue, and as a result fatigue has been assessed in different ways[7,9], making comparisons between studies difficult. Secondly we were unable to distinguish mental and physical aspects of fatigue in the present study, acknowledging that this should be an important topic for further research. Thirdly the possible confounders in our study were included on the basis of previous literature and on clinical grounds, the choice remains in a way arbitrary. In addition other determinants that may distort the relationship, such as psychopharmaca, psychotherapy and coping style[2,3,14], were not considered in the present study. Fourthly we were not able to correct for lesion site, while literature data show some evidence that patients with brain stem strokes suffer more from fatigue[7,10]. Finally the 15% change in the ß-coefficient of FSS that we used to decide whether a factor was a confounder is an arbitrary value. However, even using a 20% change in the regression coefficient would not have influenced the present findings.

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8

Identification of risk factors related to perceived unmet demands in patients with chronic stroke

Ingrid G.L. van de Port, Geertrudis A.M. van den Bos,
Marlous Voorendt, Gert Kwakkel, Eline Lindeman

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Abstract

Purpose To investigate the prevalence of unmet demands concerning autonomy and participation and to identify risk factors related to these unmet demands in chronic patients with stroke.

Method A cross-sectional study in 147 patients three years after stroke. We assessed perceived unmet care demands in relation to problems of participation and autonomy measured by the Impact on Participation and Autonomy Questionnaire (IPAQ). Sociodemographic and health characteristics were analysed as potential risk factors for the prevalence of unmet demands, using multivariate regression analysis.

Results A total of 33% of the patients perceived at least one unmet demand in one of the IPAQ domains. Risk factors significantly related to the presence of unmet demands were younger age, motor impairment, fatigue and depressive symptoms. Findings indicate that the model including these factors was fairly accurate in identifying patients having unmet demands and those not having unmet demands.

Conclusions Unmet care demands were present in a substantial proportion of the stroke patients. The risk factors identified are helpful for clinicians and health care providers to recognise patients who are at risk of perceiving unmet care demands and to optimise care to patients with chronic stroke.

Introduction

Stroke is a major cause of disablement in many western countries. The number of stroke patients in the Netherlands has been estimated at 7.5 per 1000, resulting in 118,500 patients in the Dutch population in 2000[1]. Demographic projections demonstrate a substantial increase in the number of stroke patients in the near future: 27% for the 2000 – 2020 period. In 2020, the prevalence rate will have risen to 8.6 per 1000, corresponding to 150,000 patients[1].
Since stroke is such a major cause of disablement, stroke patients are a prominent patient group in rehabilitation. After rehabilitation, 62% of stroke patients were still dependent for ADL activities and 32% were inactive in instrumental ADL activities at three years post stroke[2]. Another study found that although the majority of patients were discharged home after inpatient rehabilitation, 26% were still receiving physical therapy and 40% were receiving home care at 5 years after stroke[3]. The annual costs of stroke are estimated to exceed one billion Euros in the Netherlands, about 60% being spent on long-term care[4].
The rising numbers of stroke patients will result in growing demands on health care and social services. Since stroke often results in lifetime disability and the related costs are high, it is important that appropriate care is provided to suit the needs of these patients. Thus far, a few studies have assessed the appropriateness of health care by analysing discrepancies between health care demands and the use of care. These studies found a relatively high percentage of unmet demands in stroke patients[5-8], indicating that the health care system is not fully meeting the demands. The studies mainly analysed the unmet demands at the level of health care services and did not relate them directly to aspects of activities and participation in daily life. Rehabilitation ultimately aims at restoring a patient's autonomy and participation in society, despite persistent sequels of stroke such as impairments and disabilities. Needs assessment in rehabilitation should therefore be focusing on comprehensive assessments at the level of functioning and social participation. It was from this perspective that the Impact on Participation and Autonomy Questionnaire (IPAQ) was developed to describe the person-perceived impact of chronic conditions in the following relevant domains: mobility, self-care, family role, controlling finances, leisure time, relationships, paid work and education9. The IPAQ is a useful instrument to assess the presence of unmet demands in participation domains relevant to stroke patients. However, it is not only important to know if unmet demands are present. Knowledge about possible risk factors that are related to the occurrence of unmet demands is also relevant, to allow clinicians and health care providers to be more responsive to the demands of patients.

The first aim of the present study was, therefore, to investigate the prevalence of unmet demands concerning autonomy and participation. The second aim was to identify risk factors related to the occurrence of unmet demands in patients with stroke.

Patients and methods

Study population

The study population consisted of patients who had had a stroke three years earlier (n=168). These patients were participating in the longitudinal Functional Prognosis after Stroke study (FuPro-Stroke study) which was being conducted in four major rehabilitation centers in the Netherlands.

Patients were included at the start of their inpatient rehabilitation programme and were followed for three years. Inclusion criteria were: (1) age over 18 years; (2) having suffered a first-ever stroke and (3) a supratentorial lesion located in one hemisphere. Patients were excluded if they had a disabling comorbidity (pre-stroke Barthel Index (BI) below 18), insufficient Dutch language skills and, for the present study, were not communicative or were institutionalised at the time of assessment.

Data collection

Three years after their stroke, patients were visited at home and interviewed by an independent observer. The FuPro-Stroke study was approved by the medical ethics committee of the University Medical Centre Utrecht and the participating rehabilitation centers. All patients gave their informed consent.

Measures

Dependent variable

We used the IPAQ to study unmet demands. The IPAQ consists of eight subdomains; mobility, self-care, family role, controlling finances, leisure time, relationships, paid work and education[9]. It asks patients to what extent the participation restrictions they perceive for the different subdomains are causing them problems, and they can answer on a 3-point scale (no problem, minor problem, severe problem). For the present analysis, the score was dichotomised into problem or no problem. To determine unmet demands, we added a question to each subdomain of the IPAQ asking if the patient perceived enough support to overcome the problems they perceived in that particular domain. Unmet demands were considered to be present if a patient answered that this support was not enough. We dichotomised the overall score into absence (0) or presence (1) of perceived unmet demands in one or more domains.

Independent variables

Independent variables included sociodemographic characteristics and health characteristics. All independent variables were dichotomised.

Sociodemographic characteristics included gender, age (younger/older than 60 years), living arrangement (living together/alone), present employment status and level of education. Educational level was dichotomised into high (bachelor's or master's degree=1) or low (=0). A range of health characteristics were assessed. With respect to stroke type, we distinguished between haemorrhages and infarctions. Co-morbidity was assessed by the Cumulative Illness Rating Scale (CIRS), which is a valid and reliable instrument that addresses all relevant body systems without using specific diagnoses[10]. Co-morbidity was considered to be present if the score on one or more of the body systems (except the nervous system) was higher than 1. The Motricity Index (MI)[11] was used to determine motor function (76–100=not impaired/<76=impaired). Cognitive functioning was determined by the Mini Mental State Examination (MMSE)[12] (24–30=no cognitive problems/<24=cognitive problems). Depression was assessed by the Center for Epidemiologic Studies Depression scale (CESD)[13] (0–15=not depressed /16–60= depressed). Fatigue was assessed by the Fatigue Severity Scale (FSS)[14] (<4= not fatigued/≥4=fatigued). Functional (ADL) status was measured by the Barthel Index (BI)[15] (19–20=independent/<19=dependent). The Social Support List (SSL)[16] was used to assess social support (25–48=social support/<25=little or no social support).

Statistical analyses

The data were analysed using SPSS (version 13.0). Univariate logistic regression analyses were performed with the dichotomised score of perceived unmet demands as the dependent variable, and the sociodemographic and health characteristics as independent variables. Subsequently, variables with a significance level of $p<0.1$ were used in a backward, stepwise logistic regression analysis to identify independent factors associated with perceived unmet demands ($p<0.05$). To prevent overfitting, collinearity diagnostics were applied between the candidate variables before developing the multiple regression model. Variables were cross-tabulated, and if the agreement (Kappa statistics) was greater than 0.8, the variable with the lowest correlation coefficient, in relation to the outcome measure, was omitted from the analysis[17]. Odds ratios (derived from the regression coefficients of the logistic regression model) and 95% confidence intervals were calculated. The odds ratio approximates how much more likely it is that unmet demands are present in patients with a particular characteristic compared to patients without that characteristic. Finally, positive (PPV) and negative predicted values (NPV) of the derived multiple regression model were calculated to determine the proportion of persons with a positive test who actually perceived unmet demands (PPV) and the proportion with a negative test who did not perceive unmet demands (NPV). All tests were applied with a two-tailed analysis and 0.05 as the level of significance.

Results

In total, 147 patients completed the IPAQ questionnaire on perceived unmet demands. The main characteristics of the study population are presented in Table 1. The mean age was 58 years, and 59% of the patients were male. The majority of the patients were living together with someone (76%) and 12% of the patients had paid work. The majority had suffered an infarction (66%) and 57% reported the presence of co-morbidity. Nine percent had an impaired cognitive function, 13% showed depressive symptoms and 53% of the patients reported fatigue. Motor function was impaired in 54% of the patients and 31% were functionally dependent.

Perceived unmet demands

Table 2 shows the prevalence of unmet demands for each subdomain. Thirty-three percent of patients had at least one unmet demand. The highest numbers of perceived unmet demands were found with regard to work (27%), education (26%) and leisure time (21%).

Univariate analysis

Patients with the following characteristics were found to be more prone to perceive unmet demands: young age, unemployed, depressive symptoms, fatigue, cognitive problems and motor impairments ($p<0.1$) (Table 3).

Multivariate analysis

No collinearity was found between the candidate variables. The multivariate analyses demonstrated that four variables were independently related to perceived unmet demands, viz., motor function, age, fatigue and depression (Table 3). Depressive symptoms generated the highest odds ratio (OR) for perceived unmet demands (OR=5.28; 95%CI: 1.4-19.5). The model had a PPV of 0.79 and an NPV of 0.82.

Table 1. Study sample characteristics three years after stroke (n=147)

Patient characteristic	%
Gender (male)	59
Age (>60)	44
Living alone	24
Education (high)	21
Employment status (full- or part-time)	12
Type of stroke (infarction)	66
Comorbidity (present)	57
MI (impaired)	54
MMSE (< 24)*	9
CES-D (depressed)	13
FSS (fatigued)	53
BI (dependent)	31
SSL (social support present)	64

*N=138

MMSE=Mini Mental State Examination, MI=Motricity Index, BI=Barthel Index, CESD=Center for Epidemiologic Studies Depression scale, FSS=Fatigue Severity Scale, SSL=Social Support List

Table 2. Number of patients (n) with perceived limitations and unmet care demands in different IPAQ domains

	Perceived limitations n	Unmet care demands n
Mobility	69	13
Self-care	21	4
Family role	68	10
Controlling finances	30	4
Leisure time	42	9
Relationships	82	9
Paid work	78	21
Education	34	9

Table 3. Univariate analysis and backward multivariate analysis between the independent variables and perceived unmet demands three years after stroke

Variables	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Gender (female)	1.281	0.634 – 2.590	0.491			
Age (>=60)	0.371	0.175 – 0.787	0.010*	0.194	0.072 – 0.523	0.001
Living arrangement (living alone)	1.197	0.535 – 2.679	0.662			
Education (high)	1.058	0.452 – 2.475	0.896			
Employment status (employed)	0.241	0.053 – 1.098	0.066*			
Type of stroke (infarction)	1.468	0.687 – 3.134	0.322			
Co-morbidity (present)	1.004	0.497 – 2.027	0.992			
Motor function (impaired)	3.526	1.639 – 7.586	0.001*	5.051	1.941 – 13.146	0.001
Cognitive functioning (impaired)	3.306	1.143 – 9.563	0.027*			
Depression (present)	8.581	2.860 – 25.743	0.000*	5.282	1.429 – 19.534	0.013
Fatigue (present)	3.063	1.440 – 6.515	0.004*	3.799	1.486 – 9.711	0.005
Functional ADL status (dependent)	1.582	0.729 – 3.205	0.262			
Social support (no/limited)	1.145	0.552 – 2.373	0.716			

* p<0.1, included in the multivariate analysis

Discussion

Three years after their stroke, 33% of the patients perceived at least one unmet demand in one of the IPAQ domains. Risk factors shown to be significantly related to the presence of unmet demands were younger age, motor impairment, the presence of fatigue and depressive symptoms. The model was fairly accurate in distinguishing between patients perceiving unmet demands and those not perceiving unmet demands.

The high percentage of perceived unmet demands suggests that the current provision of health care and social services does not fully meet the needs of stroke patients. It could be questioned whether patients' demands and their expectations with respect to support are reasonable. Comparable studies[8,18] found that stroke patients with unmet demands were less healthy than stroke patients who were receiving enough support. This finding seems to indicate that patients' perceived unmet demands are relevant in identifying deficits in care and support. More insights into possible deficits would be gained if the professional perspectives could be studied as well. Patients' and professionals' perspectives could be combined to ensure that professionals are more responsive to patients' demands.

The percentage of perceived unmet demands found in studies among stroke patients ranges from 17% to 88%[5-8]. This large variation in percentages may be caused by differences in patient characteristics, definitions and assessment methods, as well as differences in the time between the stroke and the moment of evaluation. Unmet demands in other diseases also vary widely. Studies on chronic diseases such as cancer, dementia, rheumatoid arthritis and HIV have found percentages ranging from 18% to 89%[18-22].

In the present study, stroke patients perceived unmet demands especially in the domains of work (27%) and education (26%). Only 4% of this relatively young population were in full-time employment and 10% were working part-time at three years post stroke (compared to 40% and 6% before the stroke). These results suggest that care and support in relation to the possibilities to return to work deserve more attention. Kersten et al.[5] found that almost one-third of their young stroke population reported unmet needs for intellectual fulfilment. It is especially in a young population that meeting the demands concerning work and education will have a significant impact on people's ability to get back to work, and hence to optimise their life satisfaction[23].

In agreement with the studies by Kersten[5] and Low[6], we found that motor impairment was related to the presence of unmet demands. Young age was also a significant factor, which might be explained by the fact that most perceived unmet demands concerned work and education, which are relevant aspects for young stroke patients. Kersten et al[5] also found a relation between age and unmet demands related to intellectual fulfilment. Another explanation might be that young stroke patients are more aware of the available health care service options and might therefore be more disappointed and report more unmet demands[6,20]. Fatigue was a significant factor, which had not been evaluated in previously published studies on unmet demands. Staub[24] found that fatigue is very disabling in stroke patients, but is often underestimated. As a result, care and support to handle fatigue is frequently not provided, resulting in unmet demands being perceived. We also found evidence in other studies[8] that depression influences the presence of unmet demands. Fatigue and depression are both impairing symptoms after stroke, but often go unrecognized. The role of these 'invisible' factors in the perception of unmet demands needs more attention in health care and in future research.

Some remarks need to be made. Firstly, we developed an instrument to assess unmet care demands based on the IPAQ. Although the IPAQ has been found to be valid, the instrument has not been validated in the form in which we used it. We nevertheless used the instrument, since, in our opinion, its face validity suggests that the adapted IPAQ is a useful instrument to assess unmet care demands on relevant aspects of autonomy and participation. However, validity and reliability should be established in future research. Secondly, the study population was too small to assess risk factors of perceived unmet demands for each of the individual IPAQ domains. Other studies are needed to identify risk factors in different domains, stroke populations and time frames. In addition, future studies should focus on the role of depressive symptoms and mood on perceiving unmet demands. We were unable to separate perceiving unmet demands from experiencing the same because of depressive feelings. There is an urgent need for prognostic studies to identify predictors to identify those patients who will not receive the appropriate care and are therefore likely to perceive unmet demands in the near future. In addition, longitudinal studies are required to determine if the occurrence of perceived unmet demands is a dynamic process, as has been suggested[8], and to determine the effect of unmet care demands on outcome in terms of participation and autonomy. These insights will be important in clinical practice to provide optimal care to patients with chronic stroke who suffer lifelong disabilities.

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9

General Discussion

Ingrid G.L. van de Port

In this chapter I discuss the main conclusions of the research project reported on in this thesis, and address its strengths and considerations. In the light of our results I also present some implications for improving the quality of long-term health care, as well as some suggestions for future research among patients with chronic stroke.

Main Conclusions

Mobility outcome

Decreased mobility is one of the major concerns for patients surviving a stroke. A particularly serious problem in patients with chronic stroke is the deterioration of walking ability, resulting in a loss of activities of daily living (ADL) independency and social isolation. Our study showed that age, functional status, sitting balance and time between stroke and measurement to inpatient rehabilitation were important factors related to mobility outcome in the rehabilitation population (Chapter 2). The model we derived predicted 48% of the variance, while cross-validation resulted in an explained variance of 47%.

Regaining mobility is a primary goal of patients with stroke during rehabilitation. Previous studies have suggested that rehabilitation is able to improve mobility-related outcomes[1-4]. Although it remains unclear if these rehabilitation-induced gains can be sustained in the chronic phase after stroke[5,6], it is widely accepted that major changes in functional outcomes no longer appear in this chronic phase. We agree with previous researchers[5] that mean group changes in chronic stroke are small and might not be different from those in a healthy aging population. However, a number of patients individually showed significant changes in their mobility status during the chronic phase after stroke. We found that 21% of the chronic stroke victims showed a significant decline in mobility status between one and three years after their stroke (Chapter 3). Depressive symptoms, fatigue, cognitive problems and inactivity in terms of extended ADLs were important determinants of decline in mobility status. The accuracy of the model we derived was good, as was indicated by a probability of 80% to correctly classify the patients.

While physical therapists spend most of their time on restoring independent gait during rehabilitation, less time is spend on helping patients to regain the ability to walk in their own community[7]. Nevertheless, 75% of patients regard the ability to ‘get out and about’ in the community as either essential or very important[8], underpinning the importance of community ambulation as an outcome in stroke patients. Despite the fact that the majority of the stroke patients included in our study were able to walk,

we found that 26% of the patients were non-community walkers or limited community walkers three years after their stroke. In Chapter 4 we showed that community ambulation does not solely depend on gait speed. We found that endurance as well as balance control and the use of assistive devices are important factors disturbing the relation between gait speed and community ambulation. This finding suggests that despite lower gait speed, community walking can be achieved by improving balance control and endurance, and by teaching patients how to use walking aids.
Mobility-impaired patients are prone to inactivity and often lead a sedentary life style, which might result in a variety of problems affecting their quality of life. The relation between physical functioning and physical activity is reciprocal, since physical functioning provides an individual with the capability to engage in physical activities and physical activity helps to maintain and in some cases improve physical condition[9]. Preventing inactivity and breaking the vicious circle requires evidence-based intervention programmes. As our meta-analyses showed, walking ability can be improved by programmes to train specific functional gait related tasks (Chapter 5). The determinants that were found to be related to a poor mobility outcome (Chapter 3) are helpful to identify those patients who are at risk for deterioration of mobility status in the long term. It may be suggested that it is these patients in particular who should be enrolled in such function-oriented training programmes.

Depression and Fatigue

Depressive symptoms and fatigue were found to be significant determinants of mobility decline in chronic stroke (Chapter 3). Both symptoms are important sequels after stroke, and at three years post stroke, 19% of the patients showed depressive symptoms (Chapter 6) and 58% complained about fatigue (Chapter 7). So far, only a few studies have described the presence of depression[10-15] and fatigue[16] after stroke, and assessed factors related to them. The results have not been unequivocal, due to the use of different assessment methods and patient selection criteria. The impact of depressive symptoms and fatigue on functional outcome has also rarely been studied in chronic stroke survivors. In addition to the negative impact of depressive symptoms and fatigue on mobility, we also found that both symptoms were longitudinally related to poorer outcome in terms of instrumental activities of daily living (IADL) and health-related quality of life (HRQoL) between 6 months and 3 years after stroke (Chapter 7). Other studies also found that depression[11,17-21] and fatigue[17,22] were important factors that adversely affected HRQoL. However, few studies have used a longitudinal research design. A study by Naess et al.[17] among a young chronic stroke population found that fatigue was related to almost all domains of HRQoL, and especially to the physical aspects of HRQoL. It is important to note, however, that these relationships are probably not unidirectional, suggesting that poor physical functioning itself contributes to the vicious circle by reducing patients' level of activity and increasing their feelings of fatigue and depression. This suggestion is confirmed in Chapter 6, where we showed that at one year post stroke, inactivity in extended ADL activities and fatigue were the most important predictors of the presence of depressive symptoms at three years post stroke.

In agreement with previous research[23-25], the above results suggest that fatigue is highly associated with depressive symptoms in stroke patients. Fatigue is also identified as one of the criteria for major depressive disorder in DSM IV. However, previous studies have also suggested that fatigue and depression are independent factors, since fatigue can also occur in the absence of depression[23,26,27].

In addition to the relevance of depressive symptoms and fatigue to functional outcome, both factors were related to the perception of unmet care demands in chronic stroke patients (Chapter 8). We showed that 33% of the patients perceived at least one unmet demand relating to autonomy and participation three years after stroke. Besides depressive symptoms and fatigue, impaired motor function and younger age were also significantly related to unmet demands. It has been confirmed by other studies that depression might play a role in inpatient and outpatient utilisation of medical services[28] and unmet demands[29]. The effect of fatigue on unmet demands had never been investigated before. Although one might hypothesise that patients who are depressed and fatigued are generally less satisfied and therefore tend to have unreasonable care demands, Scholte op Reimer and colleagues showed that people with unmet demands are generally less healthy than those who have no demands[29]. Since we only studied patients who did experience limitations and perceived problems as a result of these limitations, it is my opinion that the reported unmet demands were reasonable demands.

Strengths and considerations

Design

The aim of the research underlying the present thesis was to explore long-term consequences of stroke and investigate possible determinants of functional outcome in chronic stroke patients. This was done in the context of the FuPro-Stroke study, a prospective multicentre study conducted in four rehabilitation centres across the Netherlands. During the inclusion period, from April 2000 until July 2002, we were able to include 308 stroke patients, making our study one of the largest longitudinal studies conducted on the long-term outcome of patients with chronic stroke. Patients were first assessed at admission to the rehabilitation center and thereafter at fixed points in time, namely 6, 12 and 36 months after stroke. The main benefit of assessment at fixed points in time, rather than using a relative moment (e.g. discharge), is that patients are comparable and that variation due to differences in the time elapsed since the stroke needs not be taken into account.

It is important to note that only those patients were included who received inpatient rehabilitation after hospitalisation, which might impede the generalisability of the present findings. In the Netherlands, 60-65% of the patients are discharged home after initial hospitalisation, while 25% are referred to nursing homes and 10-15% are admitted to a rehabilitation center[30,31]. In general, patients referred to inpatient rehabilitation are relatively young and are moderately disabled. Our patient population was indeed relatively young, although ages were comparable to those in other European studies on stroke rehabilitation[4,32]. Also, although aphasia was not an exclusion criteria in the present study, aphasic patients were omitted from most of the analyses since some of the measures (e.g. measures of depression and fatigue) were not applicable to aphasic patients.

Measures

An important characteristic of the FuPro-Stroke study is that we used an extensive set of measures to assess the consequences of chronic stroke in many International Classification of Functioning, Disability and Health (ICF) domains. We used valid and reliable physical examinations, screening instruments and questionnaires. This allowed us to obtain a broad overview of associations between measurements defined at the level of body functions, activities and participation. Since most patients were discharged home after inpatient rehabilitation, where they have to function in their own community again, prognosis was mainly focused on activities and participation outcome. In my opinion, measuring outcomes on these ICF levels is most relevant in this chronic patient population.

When assessing changes in the chronic phase after stroke, many outcome measures are prone to ceiling effects, impeding responsiveness. We used the Rivermead Mobility Index (RMI) to determine changes in mobility outcome, since in our opinion the RMI covers a wide range of relevant mobility-related activities (from turning in bed to running), which reduces the risk of a ceiling effect. However, the RMI also seemed prone to ceiling effects in our population. With the development of the ICF and the focus on participation outcome, we hope that new measures will be developed that validly assess

participation outcome (i.e. community ambulation). These measures will hopefully be less prone to ceiling effects, especially in studies conducted long-term after stroke.
Depression and fatigue, as measured by the Centre for Epidemiologic Studies Depression Scale (CES-D) and the Fatigue Severity Scale (FSS), were important determinants in our study. The CES-D is a well-known outcome measure in stroke research and has proved to be valid and reliable in stroke patients. Unfortunately, none of the instruments available to determine fatigue, including the FSS, have been validated in a stroke population. However, in the FuPro-Stroke study we showed that the FSS was reliable, with an internal consistency (Cronbach's α) of 0.89 and an intra-class correlation coefficient (ICC) of 0.82 in a study on inter-rater reliability (Chapter 7). It would be highly useful to further validate fatigue measures in stroke populations. A fatigue measure like the Fatigue Impact Scale (FIS) can, despite its length, be very useful in stroke populations, since it is able to distinguish between the effects of fatigue on cognitive, physical and psychosocial functioning. When we know more about the aetiology of fatigue and about factors that are related to the development of post-stroke fatigue, we might be able to conduct studies on the effect of physical or cognitive interventions on fatigue in stroke patients.

Methodological considerations

To answer our research questions we conducted cross-sectional regression analyses (Chapter 4, 8) and regression analyses with two measurements over time (Chapter 2, 3, 6). In our prognostic studies, we attempted to achieve high methodological quality by using valid measures, including an inception cohort, controlling for drop outs, checking for collinearity, including an adequate number of determinants relative to the numbers of patients or number of events[33] and recording patient characteristics[34].
Although the determinants included in the analyses as possible predictors were chosen on the basis of a systematic search of the literature and clinical experience, the final choice remains arbitrary. In all of the studies, part of the variance remained unexplained, so we may have missed some candidate determinants that are related to the variable of outcome. Determinants that might be important are personal factors, e.g. coping strategies and locus of control[16], but also environmental factors, like urbanisation. In addition, one should realise that the specificity of the outcome measures might determine which factors are included in the model.
External validity is important to increase the generalisability of prediction models. We therefore described inclusion and exclusion criteria and gave a comprehensive overview of the patient characteristics. External validity can be ensured not only by reporting on patient characteristics and interventions, but also by validating a model in an independent population. However, this has hardly been reported in the literature[34].

Although we validated one of our models by cross-validation (Chapter 2), further research will be required for external validation of our results in an independent set of stroke patients.

Besides the lack of reported validity, many previous studies have failed to prove the applicability of prognostic models. Before using the results of prognostic research in clinical practice, one needs to ensure their internal, statistical and external validity. Subsequently, one needs to check the accuracy of the model to be able to decide how successfully the investigated determinants predict outcome. Methods that can and should be used to further examine accuracy are explained variance or odds ratios, sensitivity, specificity and positive and negative predicting values. We have reported these variables where possible to indicate the value of the determinants we assessed in terms of the outcome of interest.

A major advantage of this study was that, in addition to traditional prognostic research with two measurements in time, we were also able to determine the longitudinal relationships between functions, activities and participation (Chapter 7) over more than two points in time. These longitudinal relationships have hardly been studied in the stroke population. A key benefit of this repeated measurement design is that it reflects reality far better than a traditional prognostic design[35]. This is especially relevant when studying the effects of time-dependent factors, such as depression and fatigue, which may show large fluctuations. We used the relatively new and sophisticated Random Coefficient Analysis (RCA) to analyse the data. Since the repeated measurements are correlated and clustered within the individuals, RCA corrects for within-subject dependency[35,36]. In addition, RCA allows heterogeneity across subjects (so-called between-subject variation). In a random coefficient model, the intercept, the regression coefficients or both can be considered random per subject. The regression coefficient of the RCA is therefore a 'pooled' coefficient of within- and between-subject relationships[37]. In contrast to traditional methods of longitudinal data analysis (e.g., MANOVA), RCA is able to handle missing values and therefore does not require complete datasets, and the time between observations may vary. This allows all available data collected in longitudinal studies to be optimally used.

We analysed the longitudinal relationship between fatigue and ADL, IADL and HRQoL, while correcting for other factors (Chapter 7). Such association models can be used to examine the possible confounders affecting the quasi-causal relationship between fatigue and outcome. Finally, we also focused on the disturbance by various factors of the cross-sectional relationship between gait speed and community ambulation (Chapter 4). It must be noted, however, that both studies used a distortion of the regression coefficient of 15% to decide whether a factor confounded the relationship, which is an arbitrary value.

Clinical implications and future research

It important for clinical practice to realise that since stroke patients experience lifetime disabilities, they will need care over a long period of time to cope with the consequences of their stroke.
Recently, the acute care for stroke patients has become increasingly based on the development of stroke service systems in which stroke units collaborate with rehabilitation and nursing settings to provide coherent interdisciplinary stroke care. However, after a patient is discharged home from the rehabilitation setting, there is often no structured policy for chronic care. Currently, long-term care is provided in different ways across the country and is mostly limited to about one year after stroke. As was shown by our study, about one third of the chronic stroke patients still perceive unmet care demands after 3 years (Chapter 8), underlining the fact that chronic stroke care is still less than optimal. It is not easy to decide how long-term stroke care in patients' own environment can be effectively optimised. Nevertheless, I would like to give some suggestions for improvement of chronic stroke care and to raise some issues for future research.

Monitoring
One of the major problems is that a number of stroke survivors tend to be forgotten, since they no longer have contact with health care professionals in the chronic phase. As a result, patients might develop problems in this chronic phase that are not noticed by health professionals. In my opinion, an important part of community-based expert care should therefore be based on having such patients (and possibly their relatives) monitored on a regular basis by the same expert. Monitoring gives an opportunity to identify patients' perceived problems and needs, as well as to identify risk factors for poor outcome and provide preventive care where possible. Such a stroke expert should act as a case manager and could be a stroke nurse, but also a physiotherapist or occupational therapist, as long as he or she is specially trained to provide care to chronic stroke patients. It would be a great improvement if each district had its own experts providing services at home. After a rehabilitation period, patients can be referred to this specialist in the community by their physician. In addition, general practitioners can refer stroke patients to the stroke specialist in their district.
In my opinion, one of the things such stroke specialists should be especially aware of is a patient's mobility status. A poor mobility status will have consequences for community reintegration and social functioning, which might result in decreased quality of life. Our results showed that the mobility outcome is not stable in the

chronic phase after stroke. In addition, monitoring will also enable the specialists to identify risk factors for negative outcome, such as fatigue and depression. Early identification of risk factors might reduce the negative impact of for example fatigue and depression on outcome. Currently, both factors are underestimated sequels in stroke care[38,39]. In my opinion, these factors need to be given much more attention in chronic stroke care, since their presence can change considerably over time.
Clinical decision-making is often based on observing changes over time, rather than on the outcome at a certain point in time. Monitoring patients longitudinally offers opportunities to study changes over time. So far, there have hardly been any studies that focused on change scores. Nevertheless, recent studies have shown that modelling change scores in a repeated measurements design offers the opportunity to explore the longitudinal relationship between time-dependent changes in functions such as depression and fatigue (but also motor function, speed and endurance) on the one hand, and observed changes in extended daily activities such as community walking and participation on the other[35].
However, merely monitoring patients will not be enough. The role of stroke specialists should go beyond monitoring, since they have an opportunity to intervene in the problems that they might monitor. For example, when a patient's mobility declines, their stroke specialist might be able to prevent further decline by providing correct information about available options, but also by teaching them to use assistive walking devices and helping them to overcome fear. A recent controlled trial showed that a simple home-based intervention by a trained occupational therapist, which focused on the provision of information, aids and overcoming fear, was successful in increasing outdoor mobility in both the short and long term[40]. Another very important aspect would be to help patients cope with 'invisible' problems like fatigue. For instance, it would be relevant to provide information about fatigue, since patients and their relatives are often unaware of the impact of fatigue on daily life. The Dutch stroke patient association, Samen Verder, has developed a brochure about coping with fatigue after stroke.
Since stroke specialists will have frequent contact with patients, they also have an opportunity to give them lifestyle advice. One thing that seems very important is to stimulate an active lifestyle in patients with chronic stroke, especially since inactivity was found to be significantly related to mobility decline (Chapter 3) and depression (Chapter 6). Previous research among healthy older adults has also shown that a physically active lifestyle reduces the decline in mobility status[41]. Patterns of inactivity may contribute to a spiral of deconditioning and functional loss[42].

Interventions

Merely monitoring patients is not enough, since proper care interventions for chronic stroke patients should be provided as well. Recently published studies found that it is possible for community-living stroke survivors to make significant progress in physical ability[43-47]. In addition, our review showed that gait-oriented training, consisting of functional strength and cardio-respiratory fitness exercises, is effective to improve gait speed and endurance (Chapter 5). However, debate is currently focusing on whether the critical variable for therapeutic efficacy is task-specificity or the intensity of the effort involved in therapeutic activities (in terms of volume, level of participation and intensity)[48]. These aspects need further investigation.

Besides favourable effects on functional outcome, exercise may also reduce post-stroke depressive symptoms. Whereas a dose-response relationship between cardiovascular fitness training and depression in the general population has already been found[49], the effect of exercise interventions on depression and fatigue in a stroke population has hardly been studied. A recent study showed that a progressive, structured physical exercise programme appeared to improve depressive symptoms and quality of life in the subacute recovery phase in stroke patients[50]. Possible explanations for the effects of exercise therapy on depression and quality of life remain unclear, however.

Despite the known interactions between physical and mental health, treatments for post-stroke disability and aspects like post-stroke depression have generally been administered separately[50]. Standard treatment for post-stroke depression currently involves antidepressant medication and psychotherapy. The frequency of anti-depressant treatment seems to increase from 19% at one month to 44% at two years after stroke in depressed patients[11]. Whereas it is known that treatment with anti-depressant medication may have measurable effects on mood, effects on functioning and quality of life are less clear[51,52]. In other words, a combination of antidepressant medication and physical exercise might be more effective in improving quality of life[51]. The effects of exercise on depression and fatigue, and the possible mechanisms behind such effects, would in my opinion constitute an interesting topic for future research.

It is clear, that more research is needed to define the optimal content of an exercise programme that could produce the greatest effects on chronic stroke patients in terms of physical and psychosocial functioning. Future studies should specifically focus on the effect of such exercise programmes on patients identified as being at risk for functional status deterioration. In addition, more longitudinal studies are needed to investigate the clinical relevance of these gains and the opportunities for sustaining gains over a longer period of time[43,47]. Another aspect that needs to be studied is the cost-efficiency of group- and home-based studies. If these programmes are found to be

as effective as individual therapy, which is mainly offered in (inpatient) rehabilitation settings, the costs of chronic stroke care could be reduced.
In addition to the effects of physical exercise interventions, I think future studies should focus on the effects of psychosocial interventions like training courses on self-management and coping strategies. One might hypothesise that improving self-management and coping strategies is important especially in the case of depression and fatigue. The first part of the FuPro-Stroke study found that locus of control is an important factor related to fatigue. Aspects like improving autonomy, self-management and empowerment are becoming ever more popular in the rehabilitation of patients with stroke. The importance of these aspects is also underlined by the fact that personal factors have been included in the ICF model. Future intervention studies are needed to determine the effects of these psychosocial interventions.

Mechanisms of improvement

Interpreting the gains achieved by physical exercise programmes requires more knowledge about the mechanisms underlying such improvements. This involves key questions such as what do patients actually learn when they show functional improvement?[6,53] At this moment, there is no clear evidence that regaining left-right symmetry is a necessary prerequisite for performing functional tasks such as sitting, standing or walking. Consequently, evidence for the effectiveness of therapies aimed at restoring symmetry in weight distribution is weak. For example, a recent study suggested that recovery of joint kinematics in hemiplegic stroke patients to a normal pattern is not required for functional recovery of walking ability[54]. These findings are in agreement with a number of electroneurophysiological studies in which the EMG activity of the paretic muscles was recorded. All studies showed significant improvements in standing balance[3,55] and walking ability[56-58] without significant improvements in the timing of activation patterns in the paretic leg. These findings suggest that task-related improvements are poorly related to physiological gains on the paretic side but rather to biohavioral adaptations on the non-paretic side[59]. For example, Den Otter et al. showed that treadmill walking with body support improved without reorganisation of the temporal muscle activation of the paretic leg[57]. In the same vein, closer associations have been found with compensatory adaptive changes on the non-paretic side, such as increased anticipatory activation of the muscles of the non-paretic leg[3,55]. In other words, there is growing evidence that functional improvements are closely related to the use of compensatory movement strategies that allow patients to adapt to existing impairments[56]. In contrast, a recent study found that it is possible to detect some common timing abnormalities in lower extremity muscle activity despite large

differences between individual patients[60]. More longitudinal kinematic and neurophysiologic studies are therefore needed to improve our understanding of the underlying mechanisms of functional improvement as a function of time[6].
Another compensatory strategy might be through the cardiorespiratory system. Energy costs of walking are substantially higher in people suffering the consequences of stroke than in healthy individuals[61,62]. These high energy demands are frequently associated with less efficient motor control in hemiplegics compared to the use of compensatory and adaptive movement strategies to perform functional tasks such as walking[63,64]. The lower walking speeds observed in patients with hemiparesis (30 m/min) consume approximately the same amount of oxygen (10 ml/kg/min)[65] as healthy people require when walking approximately twice as fast (i.e., 60 m/min)[66]. In addition, it has been shown that oxygen uptake per unit of distance is significantly higher in these patients, which makes hemiplegic gait less efficient. However, few studies have investigated energy expenditure after stroke. Obviously, improving aerobic capacity as a reflection of physical condition is an important factor in restoring walking competency. One might, therefore, speculate that exercise programmes result in more efficient energy expenditure while walking, as a result of improved endurance, but possibly also through improved balance control and a reduced fear of falling. It would be very interesting to investigate the effects on functional outcome of improving cardiorespiratory factors by means of exercise programmes. In addition, very sophisticated portable gas analysing systems are currently available to analyse energy expenditure[67]. These systems can be used to examine the mechanisms that are related to efficiency of gait in stroke patients and hence to improve functional outcomes.

In my opinion the findings of this thesis emphasise the fact that stroke patients have to cope with lifelong disabilities and that the individual status of a patient with stroke is often not stable over time. I therefore think that the implementation of these findings will lead to a change in chronic stroke care. At this moment health care policies are mainly focussed on the acute and subacute phase, whereas in my opinion expert care should pay much more attention to the chronic consequences of stroke to complete the continuum of care for these patients. The content of such chronic stroke care should be supported by the results of future studies.

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Summary

Summary

This thesis is based on the findings of the FuPro-Stroke study (the Stroke section of the Functional Prognostification and disability study on neurological disorders), which was part of the larger FuPro research programme investigating the functional prognosis of four neurological diseases (multiple sclerosis, traumatic brain injury, amyotrophic lateral sclerosis and stroke). The FuPro-Stroke study is a multicentre, prospective cohort study among patients with stroke, who were included during inpatient rehabilitation. Whereas the other researcher involved in the FuPro-Stroke study, Vera Schepers, has focused on clinimetrics and determinants of the outcome during the first year after stroke, the aim of the research reported on in the present thesis was to investigate the long-term prognosis of chronic stroke outcome up to 3 years after onset.

Chapter 1 is a general introduction about relevant outcomes in patients with chronic stroke and the importance of prospective studies in this population. It discusses the epidemiological consequences of stroke as well as the problems of treatment and research. It particularly emphasises the need for long-term follow-up studies to improve our understanding of the time course of recovery, as well as the need to identify prognostic factors related to long-term functional change after stroke. Identification of risk factors can help to provide adequate health services and prepare patients and relatives for their future lives.

A poor mobility status is a key concern in chronic stroke patients, especially since it may lead to ADL dependence and affect social reintegration. Chapter 2 reports on mobility outcome in 217 patients with stroke, as measured by the Rivermead Mobility Index (RMI). The aim was to develop a prognostic model to predict mobility outcome one year post stroke. We included the following independent variables, measured at admission to inpatient rehabilitation: patient and stroke characteristics, functional status, urinary incontinence, sitting balance and motor and cognitive function. A multivariate linear regression analysis was performed on a 'model-developing' set (n=174). Total RMI score at one-year post stroke was predicted by functional status, sitting balance, time between stroke onset and measurement, and age. The resulting model predicted 48% of the variance. Subsequently, the model was validated in a cross-validation set (n=43), resulting in a similar adjusted R^2.

Chapter 3 discusses a study of factors related to a significant deterioration in mobility status between one and three years post stroke. Mobility was again assessed by the

RMI, with a decline being defined as a deterioration of two or more RMI points. Complete datasets were available for 202 patients with stroke, and a significant mobility decline was found in 43 patients (21%). This study showed that inactivity in terms of instrumental activities of daily living (IADL), the presence of cognitive problems, fatigue and depressive symptoms at one year post stroke were the main characteristics of individuals who suffered a significant deterioration in mobility. The discriminating power of the regression model was good, as was shown by the area under the receiver operating characteristic (ROC) curve, which was 0.79. Early recognition of prognostic factors in patients at risk may guide clinicians in applying intervention regimes aimed to prevent deterioration of mobility status in chronic stroke.

Since community ambulation is an important outcome for chronic stroke patients, chapter 4 discusses patients' community ambulation and the strength of the association with gait speed at three years after stroke. Community ambulation was determined by a self-administered questionnaire consisting of four categories, based on whether the patient could walk outdoors (1) only with physical assistance or supervision, (2) e.g. as far as the car or mailbox in front of the house without physical assistance or supervision, (3) in the immediate environment (e.g. down the road, around the block) without physical assistance or supervision; (4) to stores, friends or activities in the vicinity without physical assistance or supervision. Twenty-six percent of the 72 patients were non-community walkers or limited community walkers. Community ambulation was closely related to gait speed (area under the curve 0.85); the optimal cut-off point for community ambulation was 0.66 m/s. Balance, motor function, endurance and the use of an assistive walking device were confounders, since they reduced the regression coefficient of gait speed by more than 15%. For clinical practice, this finding suggests that assessing gait speed alone may underestimate patients' ability to walk in their own community. Moreover, compensation strategies like good control of standing balance, physical endurance and the use of a walking device may lead to community walking despite a low gait speed.

Chapter 5 presents a systematic review of the effectiveness of training programmes focusing on lower limb strengthening, cardio-respiratory fitness or gait-oriented tasks, in terms of the outcome of gait, gait-related activities and health-related quality of life (HRQoL) after stroke. Databases (Pubmed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, DARE, PEDro, EMBASE, DocOnLine and CINAHL) were systematically searched for randomised controlled trials (RCTs) by two independent researchers. The following inclusion criteria were applied: (1) participants had to be people who had suffered a stroke and were older than 18 years; (2) one of the outcomes had to focus on gait-related activities; (3) the studies had to evaluate the effectiveness of therapy programmes focusing on lower limb strengthening, cardio-respiratory fitness or gait-oriented training; (4) the publication had to be in English, German or Dutch. Studies were collected up to November 2005, and their methodological quality was assessed using the PEDro scale. Twenty-one RCTs were included, 5 of which focused on lower limb strengthening, 2 on cardio-respiratory fitness training (e.g., cycling exercises) and 14 on gait-oriented training. The majority of the studies were of high quality. Meta-analysis showed a significant medium effect of gait-oriented training interventions on both gait speed and walking distance, whereas a small, non-significant effect size was found on balance. Cardio-respiratory fitness programmes had a non-significant medium effect size on gait speed. No significant effects were found for programmes targeting lower limb strengthening. Strong evidence was found for the benefits of cardio-respiratory training for stair-climbing performance. While functional mobility was positively affected, no evidence was found that activities of daily living (ADL), instrumental activities of daily living (IADL) or HRQoL were significantly affected by gait-oriented training. We suggested that gait-oriented training was effective to improve walking competency after stroke.

Depression is a well-known sequel after stroke, which has a negative impact on outcome. Since it is as yet unclear what determinants predict depression, the study reported on in chapter 6 aimed to identify factors that were significantly related to depression in patients with chronic stroke. Depression was evaluated in 165 first-ever stroke patients by the Centre for Epidemiologic Studies Depression Scale (CES-D) at three years post stroke. Scores were dichotomised into depressive symptoms (CES-D ≥ 16) and no depressive symptoms (CES-D<16). At three years post stroke, 19% of the patients showed depressive symptoms. Univariate analysis showed significant associations between post-stroke depression and type of stroke, fatigue, motor function of the leg and arm, ADL and IADL. Multivariate logistic regression analysis allowed us to conclude that depression was best predicted by one-year IADL activity and fatigue. The model showed good sensitivity (63%) and specificity (85%) in identifying those patients who suffer from depression.

Fatigue is also a common but insufficiently investigated consequence of stroke. The effects of fatigue on outcome in chronic stroke are still unknown. Chapter 7 presents an innovative regression model to investigate the longitudinal association of post-stroke fatigue with the longitudinal change scores for ADL, IADL and HRQoL. Subsequently, it was established whether this relationship was confounded by other determinants.

Fatigue was assessed with the Fatigue Severity Scale (FSS) in 223 patients. It was shown that fatigue is a major problem in patients with stroke, since 68%, 74% and 58% experienced fatigue (FSS ≥ 4) at 6, 12 and 36 months post stroke, respectively. Random coefficient analysis was used to analyse the impact of fatigue on ADL, IADL and HRQoL. Fatigue was significantly related to IADL and HRQoL, but not to ADL. Depression and motor impairment confounded the association between fatigue and IADL, since including these factors in the regression analyses resulted in a reduction of the regression coefficient for fatigue by more than 15%. Although depression also biased the relation between fatigue and HRQoL, fatigue remained an independent covariate which was significantly associated with HRQoL.

Since the number of stroke patients is rising and it is a chronic disease, it is important that appropriate care is provided to suit the needs of all these patients. Chapter 8 therefore reports on a study of the frequency of unmet care demands. Perceived unmet care demands were determined in relation to problems of participation and autonomy, as measured by the Impact on Participation and Autonomy Questionnaire (IPAQ). Of the 147 patients who were assessed, 33% perceived at least one unmet demand in one of the IPAQ domains three years post stroke. In addition, socio-demographic and health characteristics were analysed as potential risk factors for the prevalence of unmet demands, using multivariate regression analysis. Younger age, motor impairment, fatigue and depressive symptoms were significantly related to the presence of unmet demands. In view of the findings of this study, we emphasise that clinicians should be aware of unmet demands, since these indicate that our health care system is as yet not fully meeting the demands of patients with chronic stroke.

Chapter 9 offers a general discussion, reflecting on the main conclusions, strengths and limitations of the FuPro-Stroke II study. It also presents possible implications for clinical practice and future research on patients with chronic stroke, in the light of our results. The focus of care and research should be on improving our understanding of the course of functional recovery by monitoring patients over time, introducing innovative intervention strategies and exploring the underlying mechanisms of functional improvement after stroke. This may help us understand the heterogeneous outcomes of patients with stroke better.

Nederlandse samenvatting

Samenvatting

Dit proefschrift is gebaseerd op de FuPro-CVA studie (Prognose van functionele uitkomst op lange termijn bij patiënten met een cerebrovasculaire aandoening) die deel uitmaakt van het grote landelijke FuPro onderzoeksprogramma. In dit onderzoeksprogramma werd aandacht besteed aan de functionele prognose van vier neurologische aandoeningen, te weten Multiple Sclerose (MS), traumatisch hersenletsel, Amyotrofische Lateraal Sclerose (ALS) en cerebrovasculaire aandoening (CVA). De FuPro-CVA studie is een prospectieve studie uitgevoerd bij CVA patiënten die klinisch revalideerden in vier revalidatiecentra in Nederland. Er zijn twee proefschriften geschreven over de resultaten van het Fupro-CVA onderzoek. De bevindingen omtrent klinimetrie en determinanten tijdens het eerste jaar na CVA zijn beschreven in het proefschrift van Vera Schepers (revalidatiearts en mede-onderzoekster). In dit proefschrift is de lange termijn prognose van CVA patiënten tot 3 jaar na de aandoening beschreven.

In hoofdstuk 1, de inleiding, zijn belangrijke uitkomstmaten voor chronische CVA patiënten beschreven en wordt het belang van prospectieve studies benadrukt. In de Westerse wereld is CVA een van de belangrijkste oorzaken van blijvende beperkingen en het aantal patiënten blijft toenemen, ook in Nederland. Ondanks het feit dat een groot deel van de patiënten gebaat is bij revalidatie, houden velen levenslange beperkingen die vaak complex en divers zijn en kunnen zorgen voor problemen op verschillende gebieden van het functioneren. Wetenschappelijke onderzoeken waarin deze patiënten lange tijd vervolgd worden zijn dan ook nodig om meer inzicht te krijgen in het beloop en om de mogelijkheid te hebben (voorspellende) factoren te identificeren die gerelateerd zijn aan het functioneren. Inzicht hebben in belangrijke risicofactoren kan helpen bij het geven van de juiste zorg en het voorbereiden van de patiënten en hun naasten op de toekomst.

Veel CVA patiënten houden problemen met de loopvaardigheid. Gezien het feit dat dit gevolgen zal hebben voor het zelfstandig dagelijks en het sociaal functioneren is een slechte mobiliteit een belangrijke beperking. Hoofdstuk 2 beschrijft voorspellende factoren welke gerelateerd zijn aan mobiliteit. Bij 217 patiënten werd 1 jaar na de beroerte de Rivermead Mobility Index (RMI) afgenomen. Bij opname in het revalidatiecentrum was een groot aantal determinanten gemeten, waaronder patiënt- en CVA kenmerken, activiteiten van dagelijks leven (ADL), urine incontinentie, zitbalans, motorische en cognitieve functies. Deze determinanten werden gerelateerd aan RMI uitkomst middels een multivariate lineaire regressie analyse welke werd uitgevoerd in een ‘model-developing’ set van 174 patiënten. De RMI uitkomst werd het best voorspeld door functionele status, zitbalans, tijd tussen CVA en de eerste meting, en leeftijd bij opname. Het model was in staat 48% van de variantie te verklaren. Vervolgens werd het model getoetst in een ‘cross-validation’ set van 43 patiënten. In deze cross validatie set kon een vergelijkbaar deel van de variantie verklaard worden (47%).

In hoofdstuk 3 worden de determinanten beschreven die significant gerelateerd zijn aan een achteruitgang in mobiliteit tussen 1 en 3 jaar na de beroerte. Mobiliteit werd weer gemeten met de RMI en achteruitgang werd gedefinieerd als een afname van 2 of meer punten op de RMI. Eenentwintig procent van de patiënten liet een achteruitgang zien in mobiliteit tussen 1 en 3 jaar. Inactiviteit in instrumentele activiteiten van het dagelijks leven (IADL), cognitieve problemen, depressie en vermoeidheid waren factoren die voorspellend bleken voor het identificeren van de patiënten die het risico liepen op achteruitgang in mobiliteit. Het model had een goed discriminerend vermogen wat bleek uit een oppervlakte onder de ROC (receiver operating characteristic) curve van 0.79. Het herkennen van prognostische factoren bij risicopatiënten kan clinici helpen tijdig tot actie over te gaan om een achteruitgang in mobiliteit bij chronische CVA patiënten te voorkomen.

De mogelijkheid om zelfstandig te kunnen lopen in de (woon)omgeving is van groot belang. In hoofdstuk 4 wordt dan ook beschreven hoe de patiënten 3 jaar na hun beroerte in staat zijn zelfstandig te lopen in hun (woon)omgeving en wat de relatie is met loopsnelheid. De mogelijkheid om te lopen in de (woon)omgeving werd vastgesteld aan de hand van een vragenlijst bestaande uit 4 categorieën, gebaseerd op of de patiënt buiten kan lopen 1) alleen met fysieke ondersteuning of supervisie, 2) tot bijvoorbeeld de auto of brievenbus voor het huis zonder fysieke ondersteuning of supervisie, 3) in de directe omgeving (bijvoorbeeld een blokje rond) zonder fysieke ondersteuning of supervisie, 4) naar winkels, vrienden of activiteiten in de buurt zonder fysieke ondersteuning of supervisie. Van de 72 patiënten bleek 26% niet of slechts beperkt zelfstandig te kunnen lopen in de (woon)omgeving. Loopsnelheid was sterk gerelateerd aan het wel of niet zelfstandig kunnen lopen (gebied onder de ROC curve 0.85); het optimale afkappunt voor het kunnen lopen in de (woon)omgeving was 0.66m/s. Ook werd onderzocht of de relatie tussen loopsnelheid en het kunnen lopen in de (woon)omgeving verstoord werd door andere variabelen. Balans, motorisch functioneren, uithoudingsvermogen en het gebruik van loophulpmiddelen verstoorden deze relatie. Aangenomen werd dat de variabele verstorend was wanneer toevoeging van de variabele in de regressieanalyse resulteerde in een verandering van de regressiecoëfficiënt van loopsnelheid van meer dan 15%. Voor de praktijk geldt dat bij puur uitgaan van loopsnelheid, de mogelijkheid van de patiënt om zelfstandig te lopen in de (woon)omgeving onderschat kan worden. Vanwege compensatie door goede balans, uithoudingsvermogen en het gebruik van loophulpmiddelen is het voor patiënten mogelijk zelfstandig te lopen in hun (woon)omgeving ondanks een lage loopsnelheid.

Hoofdstuk 5 beschrijft de resultaten van een systematisch review over het effect van trainingsprogramma's op het verbeteren van loopvaardigheid, loopgerelateerde activiteiten en gezondheidsgerelateerde kwaliteit van leven. De trainingsprogramma's focussen op krachttraining (onderste extremiteiten), conditietraining, of loopgerelateerde activiteiten(bijvoorbeeld balans, (snel) lopen, traplopen). In verschillende databases (Pubmed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, DARE, PEDro, EMBASE, DocOnLine and CINAHL) werd door twee onderzoekers systematisch gezocht naar gerandomiseerde gecontroleerde onderzoeken (RCTs). De volgende inclusiecriteria werden gebruikt: 1) deelnemers waren patiënten met een CVA, ouder dan 18 jaar, 2) een van de uitkomstmaten was gefocust op loopgerelateerde activiteiten, 3) de studies evalueerden het effect van therapie programma's gericht op krachttraining, conditietraining en/of loopgerelateerde training, 4) de studie was gepubliceerd in het Engels, Duits of Nederlands. Studies werden geïncludeerd tot November 2005 en de methodologische kwaliteit werd beoordeeld aan de hand van de PEDro schaal. In totaal werden er 21 RCT's geïncludeerd, waarvan 5 gericht waren op krachttraining, 2 op conditietraining en 14 op loopgerelateerde training. De meerderheid van de studies was van hoge methodologische kwaliteit. Meta-analyse van geïncludeerde studies laten zien dat er een significant middelmatig effect was van loopgerelateerde training op zowel loopsnelheid als loopafstand, en een klein, niet significant effect op balans. Conditietrainingsprogramma's hadden een niet significant middelmatig effect op loopsnelheid. Er werden geen significante effecten gevonden voor krachttrainingsprogramma's. Er werd een sterk bewijs gevonden dat conditietraining een gunstige invloed had op traplopen. Loopgerelateerde training zorgde voor een positief effect op functionele mobiliteit, maar er was geen bewijs voor een gunstige invloed op ADL, IADL of gezondheidsgerelateerde kwaliteit van leven. Loopgerelateerde training bleek effectief om loopvaardigheid na een beroerte te verbeteren.

Een deel van de CVA patiënten heeft te maken met depressieve symptomen die een negatieve invloed kunnen hebben op het functioneren. Momenteel bestaat er onduidelijkheid rondom voorspellers voor depressie. Hoofdstuk 6 beschrijft de determinanten die in het huidige onderzoek significant gerelateerd waren aan depressie 3 jaar na CVA. Bij 165 patiënten werd de Centre for Epidemiologic Studies Depression Scale (CES-D) afgenomen. De score van de CES-D werd gedichotomiseerd (CES-D ≥ 16 = depressieve symptomen, CES-D<16 = geen depressieve symptomen). Drie jaar na CVA bleek 19% van de patiënten depressieve symptomen te vertonen. Uit de univariate regressie analyse bleek dat er significante relaties bestonden tussen depressie en type CVA, vermoeidheid, motorisch functioneren, ADL en IADL. Multivariate regressieanalyse liet zien dat depressieve symptomen 3 jaar na CVA het best voorspeld konden worden door IADL en vermoeidheid 1 jaar na CVA. Uit het model blijkt een goede sensitiviteit (63%) en specificiteit (85%).

Vermoeidheid is een veelvoorkomend, maar vaak onderschat probleem bij CVA patiënten. Er is dan ook weinig onderzoek naar gedaan en het effect van vermoeidheid op functionele uitkomst is onbekend. Hoofdstuk 7 beschrijft de longitudinale relatie tussen vermoeidheid en ADL, IADL en gezondheidsgerelateerde kwaliteit van leven bij CVA patiënten. Ook werd onderzocht of deze relatie wordt verstoord door andere factoren. Bij 223 patiënten werd de Fatigue Severity Scale (FSS) afgenomen om de impact van vermoeidheid vast te stellen op 6, 12 en 36 maanden na de beroerte. Op deze tijdsmomenten was er bij respectievelijk 68%, 74% en 58% van de patiënten sprake van vermoeidheid (FSS ≥ 4) waaruit blijkt dat vermoeidheid inderdaad een probleem is bij veel chronische CVA patiënten. Random Coëfficiënt Analyse (RCA) werd gebruikt om de impact van vermoeidheid op ADL, IADL en gezondheidsgerelateerde kwaliteit van leven te analyseren. Vermoeidheid bleek significant gerelateerd te zijn aan IADL en gezondheidsgerelateerde kwaliteit van leven, maar niet aan ADL. De relatie tussen vermoeidheid en IADL werd verstoord door depressie en motorische functie. Toevoeging van deze variabelen zorgde voor een verandering van de regressiecoëfficiënt van vermoeidheid van meer dan 15%. Depressie verstoorde ook de relatie tussen vermoeidheid en gezondheidsgerelateerde kwaliteit van leven. Echter, vermoeidheid bleef wel significant gerelateerd aan gezondheidsgerelateerde kwaliteit van leven.

Gezien het groeiend aantal CVA patiënten is het van groot belang dat de zorg rondom deze chronisch zieken goed is ingericht. In hoofdstuk 8 wordt de frequentie van het optreden van onvervulde zorgbehoefte op het gebied van autonomie en participatie beschreven. Deze zorgbehoefte werden vastgesteld aan de hand van de Impact on Participation and Autonomy Questionnaire (IPAQ). Van de 147 patiënten die 3 jaar na CVA onderzocht werden, was er bij 33% sprake van een onvervulde zorgbehoefte op een van de domeinen gemeten met de IPAQ. Sociodemografische en gezondheidskarakteristieken werden gemeten en meegenomen in een multivariate logistische regressieanalyse als mogelijke determinanten voor de aanwezigheid van onvervulde zorgbehoefte. Jonge leeftijd, motorische beperkingen, vermoeidheid en depressie waren significant gerelateerd aan het optreden van onvervulde zorgbehoefte. Clinici moeten zich realiseren dat er onvervulde zorgbehoefte bestaan bij chronische CVA patiënten, wat erop duidt dat de zorg rondom deze patiënten nog niet optimaal geregeld is.

Hoofdstuk 9 bevat een algemene discussie waarin de belangrijkste conclusies, pluspunten en beperkingen van de FuPro-CVA studie beschreven worden. Naar aanleiding van de bevindingen worden ook implicaties voor de zorg en ideeën voor toekomstig onderzoek gegeven. De aandacht in de zorg en in wetenschappelijk onderzoek zal moeten liggen op het ontwikkelen van patiëntenprofielen door het systematisch monitoren van patiënten in de tijd, het introduceren van innovatieve interventies binnen de revalidatie en het beter leren begrijpen van de onderliggende mechanismen die verantwoordelijk zijn voor herstel. Op deze manier zal er meer inzicht verkregen kunnen worden in het lange termijn functioneren van CVA patiënten en zal er de mogelijkheid ontstaan problemen vroeg te identificeren en vervolgens passend in te kunnen grijpen.

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List of publications

(other publications than articles in this thesis)

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- I.G.L. van de Port, Functionele prognose van dagbesteding en mobiliteit. Reader basis-cursus CVA, 2005. ISBN: 90 373 0861 9,

Curriculum Vitae

Ingrid van de Port werd op 3 december 1976 geboren in Roermond. In 1995 behaalde ze haar VWO diploma aan de Stedelijke Scholengemeenschap te Roermond, waarna ze ook in 1995 startte aan de studie Gezondheidswetenschappen aan de Universiteit Maastricht. Ingrid koos als afstudeerrichting bewegingswetenschappen.

Na een onderzoeksstage bij de School of Exercise and Sports Science in Sydney behaalde ze in 2000 haar diploma. Aansluitend werkte ze als onderzoeksassistente bij de vakgroep bewegingswetenschappen aan de Universiteit Maastricht. In 2001 werd ze aangesteld in revalidatiecentrum De Hoogstraat waar ze tot eind 2002 als onderzoeksassistente betrokken was bij het FuPro-CVA onderzoek van Vera Schepers. Gedurende deze periode werd een aanvullende subsidie verkregen van ZonMw voor verlenging van het FuPro-CVA onderzoek. Eind 2002 startte de auteur dan ook haar eigen promotie-onderzoek, FuPro-CVA II, naar de lange termijn gevolgen van CVA.

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