The effect of fatigue on health related quality of life in stroke patients

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The Effect of Fatigue on Health Related Quality of Life in Stroke Patients: A Prospective Study

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ABSTRACT

Three main consequences of stroke are fatigue, dependency in activities of daily living (ADL), and reduced health related quality of life (HRQoL). This study hypothesized that fatigue negatively affects HRQoL in stroke patients, partially mediated by dependency in ADL. This relation was estimated over time. Fatigue surprisingly decreased dependency in ADL, and fatigue and being dependent in ADL reduced HRQoL. Dependency in ADL did not change over time, whereas HRQoL decreased. The mediation effect, however, was not significant. Therefore, the effect of fatigue on HRQoL cannot be stated to be partially mediated by dependency in ADL.

Keywords

stroke, fatigue, activities of daily living, quality of life, linear mixed models, mediation effect.

INTRODUCTION

Several studies stated that post-stroke fatigue is a common and often severe, but neglected issue, e.g. [1] and [2]. Although the course of post-stroke fatigue is unclear [3] [4], fatigue can occur until long after stroke [1]. Therefore, fatigue is important to take into account in studying a stroke population. Another consequence of stroke is reduced health related quality of life (HRQoL), which is suggested to be partly influenced by post-stroke fatigue [5]. Dependency in activities of daily living (ADL) has also been shown to be related to decreased HRQoL [6]. However, quality of life (QoL), dependency in ADL, and the relation between them may change over time [7], so it is important to study the relationship longitudinally. In addition, fatigue seemed to be an independent predictor of being dependent in ADL in stroke patients [1], although not all studies found a relation between fatigue and dependency in ADL [8].

Altogether, fatigue and being dependent in ADL seemed to have a negative effect on HRQoL, and fatigue also seemed to have a negative effect on dependency in ADL in stroke patients. In this study, it is hypothesized that fatigue has a negative effect on HRQoL in stroke patients. In addition, this effect is assumed to be partially mediated by dependency in ADL, see Figure 1. Because HRQoL, dependency in ADL, and the relation between them may change over time [7] and the course of post-stroke fatigue is unclear [3] [4], this study examines the relation between fatigue, dependency in ADL, and HRQoL over time. Regarding previous research, a negative effect of fatigue on ADL is expected. Another expectation is a negative effect of fatigue and dependency in ADL on HRQoL. It is also expected that the effects of fatigue on ADL and of fatigue and ADL on HRQoL change over time, but there is no expectation of how this will change. In studies examining fatigue, ADL, and HRQoL in stroke patients, many confounding factors were used. Using confounders reported by at least half of previous studies, this study regards age, gender, education, marital status, comorbidity, depression, and executive functioning as potential confounders. In addition, first stroke was another potential confounder, because first stroke was an inclusion criterium in nine studies and some used previous stroke as confounding factor, e.g. [1]. The hypothesized model has not been tested before, which is expected concerning previous research. Moreover, many of these studies examined the relationship at an arbitrarily selected time point [5], while fatigue, ADL, and HRQoL may change over time [3] [7]. Therefore, this study may be valuable to this field of research and hence be useful in practice in improving patients' HRQoL.

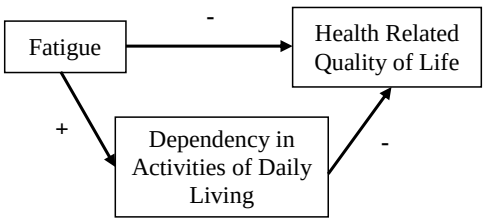

Figure 1. Conceptual model.

METHOD

Participants and Procedure

Patients were excluded if they suffered from impaired consciousness, impaired language comprehension, multiple cognitive disorders resulting from any form of dementia, an unstable physical condition with risk of death, or if they had a high emotional vulnerability. The patients were approached approximately three months after stroke (T0). They were asked to fill out a questionnaire, medical data were collected, and cognitive and executive functioning were assessed using neuropsychological tests. This procedure was repeated six

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months after stroke (T1). Twelve months after inclusion (T2) they received a short questionnaire. Participation was voluntary, and refusal to participate had no influence on the clinical treatment. The patients were informed about the design and purpose in advance of participation, and they were asked to sign informed consent.

Measures

Main variables

Fatigue was assessed using the reliable and valid Fatigue Assessment Scale (FAS), which measures general fatigue [9]. The total score ranges from 10 to 50, with a higher score indicating more fatigue. The widely used Barthel index (BI) was used to assess ADL reliably and validly [10] with a total score ranging from 0 to 100. The scores were reversed to create a measure of dependency instead of independence in ADL. HRQoL was assessed using the Stroke-Adapted Sickness Impact Profile (SA-SIP30), a reliable and valid measure [11] with a maximum total score of 30 and a higher score indicating lower HRQoL.

Potential confounders

Patients were asked about their date of birth (transformed into age at the first measurement), gender, education, marital status, whether it was their first stroke, and comorbidity. Comorbidity was defined as reported atrial fibrillation, ischemic heart disease, chronic heart failure, diabetes, hypertension, lipid dysfunction and/or peripheral vascular disease. Depressive symptoms were reliably assessed using the Beck Depression Inventory (BDI-II) [12]. A higher score indicated more depressive symptoms with a maximum of 63. The completion time of the Trail Making Test B (TMT B) [13], which involves complex visual scanning, motor speed, and attention, was used to assess executive functioning.

Statistical analysis

First, the group characteristics were described using descriptive statistics. Subsequently, the relations between different variables within each measurement were conducted using t tests, ANOVAs, and correlations. Then, linear mixed models (LMMs) were used to discover the relationship between fatigue, ADL, and HRQoL over time. One model tested the effect of fatigue on ADL, and one model tested the effect of fatigue and ADL on HRQoL. First, LMMs were computed using maximum likelihood (ML) with an unstructured covariance matrix to discover which confounders positively contributed to the model. Variables, other than the main variables, correlating significantly with the dependent variable at any time point were considered confounders and hence included in the initial model. Time was also included because of the prospective character of the study. Confounders with a nonsignificant effect were excluded in the next model. Second, the model with only significant predictors was composed with an unstructured, diagonal, and compound symmetry covariance matrix using restricted maximum likelihood (REML) to gain the most parsimonious well-fitting model. Model fit was compared using the likelihood ratio test (with the exception of comparing the diagonal and compound symmetry covariance matrix, since these are not nested), the AIC, and the BIC. Lastly, it was tested whether the effect of fatigue on HRQoL was partially mediated by ADL. If both the direct and indirect effect of fatigue on HRQoL were significant, the effect of fatigue on HRQoL would be partially mediated by ADL. The direct effect of fatigue on HRQoL was tested for significance by the LMM described previously. The Sobel test, using data from the LMMs, was computed to test whether the mediation effect of ADL was statistically significant. Significance was indicated by $p < .05$.

Table 1. *Sample Characteristics.*

	T0		T1		T2	
Variable	*N (%)*	*M (SD)*	*N*	*M (SD)*	*N*	*M (SD)*
Age	107	65.8 (12.8)				
Gender	102					
Male	69 (67.6)					
Education	89					
High	13 (14.6)					
Average	21 (23.6)					
Low	55 (61.8)					
Marital status	106					
Partner	80 (75.5)					
Comorbidity	107					
Yes	90 (84.1)					
First stroke	107					
Yes	85 (79.4)					
BDI	78	7.9 (6.8)	67	7.2 (6.5)	45	6.1 (5.9)
TMT B	100	134.2 (68.5)	78	125.8 (66.6)	45	115.5 (75.4)
FAS	81	25.3 (6.4)	74	24.0 (5.9)	49	25.2 (6.1)
BI	107	3.7 (9.4)			53	2.1 (6.8)
SA-SIP 30	69	5.9 (5.7)	65	6.7 (6.7)	48	8.1 (6.5)

RESULTS

The sample characteristics are displayed in Table 1. At the start of the study, the group of 112 participants had a mean age of 65.8 and included 69 males and 33 females (gender of 10 persons was not reported). The fatigue score showed no clear course over time ($M_{T0} = 25.3$; $M_{T1} = 24.0$; $M_{T2} = 25.2$), whereas dependency in ADL and HRQoL seemed to decrease over time ($M_{T0} = 3.7$; $M_{T2} = 2.1$; and $M_{T0} = 5.9$; $M_{T1} = 6.7$; $M_{T2} = 8.1$ respectively).

Table 2. *T-tests for Relations Between Categorical Confounders and Dependent Variables.*

	T0				T1		T2			
	BI		SA-SIP30		SA-SIP30		BI		SA-SIP30	
Variable	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*
Gender[a]	**-2.123**	**.040**	-0.331	.742	-0.724	.476	0.274	.785	-.542	.593
Education[b]	1.461	.238	2.320	.106	2.844	.067	1.162	.322	1.018	.370
Marital status[a]	**-2.376**	**.024**	**-2.160**	**.049**	**-2.748**	**.014**	-1.589	.138	-1.139	.281
Comorbidity[a]	1.163	.248	1.919	.059	0.726	.471	0.782	.458	0.601	.551
First stroke[a]	-1.557	.128	-2.016	.061	**-2.583**	**.012**	-1.420	.182	-1.764	.084

[a]Reference categories respectively: female, single, yes, and no.

[b]Values reported in the t column are *F*-values of ANOVAs for education, because it has three categories.

Table 3. *Correlations Between Continuous Confounders and Dependent Variables.*

		T0		T1	T2	
	Variable	BI	SA-SIP30	SA-SIP30	BI	SA-SIP30
	Age	.245*	.120	.407**	.222	.369**
T0	BDI	.011	.589**			
	TMT B	.310**	.437**			
T1	BDI			.610**		
	TMT B			.405**		
T2	BDI				.439**	.674**
	TMT B				.433**	.552**

Note. T0 = first measurement; T1 = second measurement; and T2 = third measurement.
*$p < .05$. **$p < .01$.

The relations between possible confounding variables and dependent variables are displayed in Table 2 and 3. Because variables correlating significantly with the dependent variable in the LMMs at any time point were considered confounders, the confounders in the initial LMM with dependency in ADL as dependent variable and fatigue as predictor were age, gender, marital status, depression, and executive functioning. Age, marital status, first stroke, depression, and executive functioning were the confounders in the initial LMM with HRQoL as dependent variable and fatigue and dependency in ADL as predictors. In the LMM with dependency in ADL as dependent variable, fatigue decreased dependency in ADL (b = -0.30, t = -2.39, p = .021) controlled for marital status (t = -3.66, $p < .001$) and depression (t = 2.82, p = .007). According to the fit indices, the compound symmetry matrix was the most parsimonious model describing the data adequately, see Table 4. Therefore, it can be assumed that the variances at the first and the last measurement are equal, and the covariance implies that the measurements are related, which corresponds with the finding that time had no fixed effect on dependency in ADL. The LMM with HRQoL as dependent variable had first stroke (t = -2.72, p = .012), depression (t = 3143, p = .003), and executive functioning (t = 2.47, p = .016) as remaining confounders. It can be concluded that HRQoL decreased over time (b = 0.99, t = 2.51, p = .020), and fatigue (b = 0.43, t = 5.69, $p < .001$) and being dependent in ADL (b = 0.23, t = 3.73, $p < .001$) both reduced HRQoL, all controlled for each other and confounders. The model with the diagonal covariance matrix was the most parsimonious well-describing model, see Table 4. This model assumes that the variances of the time points differ and that the measurements are unrelated, which corresponds with the fixed effect of time on HRQoL. Lastly, the Sobel test showed no significant mediation effect (z = -1.85, p = .064), so the effect of fatigue on HRQoL cannot be stated to be partially mediated by dependency in ADL.

Discussion

According to the results, fatigue decreased dependency in ADL controlled for marital status and depression, which is opposite to the expectation. On the other hand, it was conform the expectation that fatigue and being dependent in ADL reduced HRQoL, controlled for whether it was the first stroke, depression, executive functioning, and time, see Figure 2. However, the mediation effect was not statistically significant using the Sobel test. Time did not influence dependency in ADL, but HRQoL decreased over time. Time had such a great effect on HRQoL that the measurements appeared to be unrelated.

The negative effect of fatigue on dependency in ADL was remarkable, because previous research showed no relation [8] or a positive relation [1]. It might be possible that less functionally dependent people received less help and thus performed more activities, which resulted in more fatigue. Moreover, since the BI relies on self-report, people who thought they were not very dependent in ADL might have accepted less help, which caused them to perform more activities, resulting in fatigue. However, it has been stated that fatigue rather results from stroke itself than from increased physical activity [14]. Further research would have to discover the probability of the stated hypothesis.

Naturally, this study has several shortcomings. First, a relatively small sample was used, partly due to missing data, so generalization must be done with caution. This might explain why the mediation effect did not reach statistical significance while both direct effects did. However, LMMs deal well with missing data, which may compensate for the small sample. In addition, the effects of fatigue and ADL on HRQoL correspond with previous studies [5] [6], which indicates some generalization is possible. Another limitation is that no distinction was made between basic ADL and instrumental ADL, which has been shown to be relevant [5] and makes comparison more difficult. This study also has several strengths. One strength is that the TMT B was used as a measure of executive functioning instead of the commonly used mini mental state examination, which is not a good measure for executive functioning [15]. The greatest strength is that this study estimated the relations between fatigue, being dependent in ADL, and HRQoL over time, because they, and the relations between them, may change over time [3] [7]. Most studies examined some of these relationships at an arbitrarily selected time point, which

Table 4. *Linear Mixed Models Covariance Matrix Comparison.*

Dependent variable	Cov. matrix[a]	NPAR	-2 restricted log likelihood	AIC	BIC	LRT with UN-model Δ-2LL	*df*	*p*
BI	UN	7	678.793	684.793	692.578			
BI	DIAG	6	704.299	708.299	713.489	25.506	1	<0.001
BI	**CS**	**6**	**679.417**	**683.417**	**688.607**	**0.624**	**1**	**0.430**
SA-SIP 30	UN	10	468.118	474.118	481.302			
SA-SIP 30	**DIAG**	**9**	**468.192**	**472.192**	**476.981**	**0.074**	**1**	**0.786**
SA-SIP 30	CS	9	472.642	476.642	481.431	4.524	1	0.033

Note. Selected model in boldface. Cov. Matrix = covariance matrix; NPAR = number of parameters; and LRT = likelihood ratio test.
[a]UN = unstructured; DIAG = diagonal; and CS = compound symmetry.

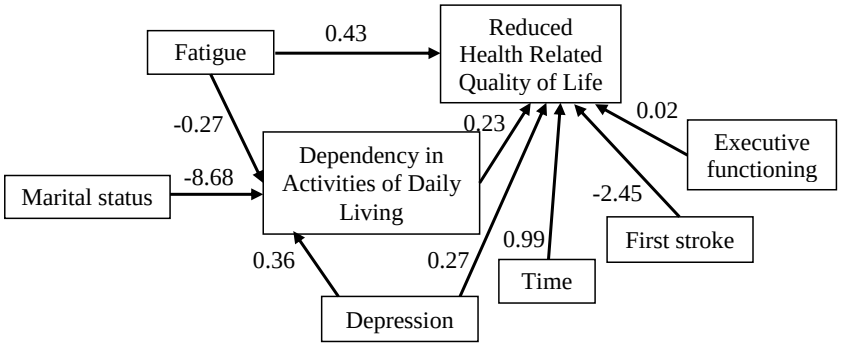

Figure 2. Model according to the final linear mixed models.
Note. Coefficients displayed are the unstandardized estimates of the linear mixed models.

complicates comparison [5]. Future research should differentiate between basic- and instrumental ADL in relation to fatigue and HRQoL in stroke patients with the possible influence of received help. This should be done longitudinally, perhaps including a mediation effect.

CONCLUSION

This study reported that fatigue reduces health related quality of life in stroke patients over time, as does being dependent in activities of daily living. Although the results indicate a negative effect of fatigue on being dependent in ADL, the relation between fatigue and dependency in activities of daily living remains uncertain. Therefore, it cannot be stated that the reduction in health related quality of life due to fatigue is partially mediated by dependency in ADL. Lastly, time does not influence dependency in ADL, but HRQoL decreases over time.

ROLE OF THE STUDENT

Elise Crompvoets chose the main topic from a by Tilburg University provided list. She subsequently formulated the specific hypotheses. A large dataset was available for the analyses. The study of literature, data analyses, drawn conclusions, and writing were performed by the student.

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