Functional Prognosis of Long-term Outcome after **Traumatic Brain Injury**

A prospective Follow-up Study

Agnes Willemse-van Son

The research described in this thesis, was a collaboration of the Department Rehabilitation Medicine of the Erasmus MC in Rotterdam and the Rijndam Rehabilitation Centre in Rotterdam.

This project has been performed as part of the 'Long term prognosis of functional outcome in neurological disorders', supervised by the department of Rehabilitation Medicine of the VU Medical Centre, Amsterdam and supported by the Netherlands Organisation for Health Research and Development (project: 1435.0020).
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The printing and distribution of this thesis was financially sponsored by Allergan BV, Pfizer BV, and Ipsen Farmaceutica BV. Their support is gratefully acknowledged.

ISBN 978-90-8559-474-1

Cover photography: Marleen van Son ©
The illustrations represent the actual experiences of patients with traumatic brain injury. These experiences were characteristically shared with us over many cups of coffee.

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Layout and printing: Optima Grafische Communicatie, Rotterdam, The Netherlands

Functional Prognosis of Long-term Outcome after Traumatic Brain Injury: A Prospective Cohort Study

Functionele prognose van lange termijn herstel
na een traumatisch hersenletsel:
Een prospectieve cohort studie

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.

de openbare verdediging zal plaatsvinden op
woensdag 28 januari 2009 om 15.45 uur

door

Agnes Hendrika Petronella Willemse-van Son
geboren te 's-Hertogenbosch

PROMOTIECOMMISSIE

Promotoren:	Prof.dr. H.J. Stam
Overige leden:	Prof.dr. C.M.F. Dirven
	Prof.dr. E.W. Steyerberg
	Prof.dr. G.J. Lankhorst
Copromotor:	Dr. G.M. Ribbers

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List of publications

Willemse-van Son AHP. Functionele prognostiek. In: Traumatisch hersenletsel. Nijmegen: PAOG-Heyendael UMC St Radboud; 2006; p. 73-80. ISBN 90-373-0114-2

Willemse-van Son AHP, Ribbers GM, Verhagen AP, Stam HJ. Prognostic factors of long-term functioning and productivity after traumatic brain injury: a systematic review of prospective cohort studies. Clin Rehabil 2007; 21, 1024-1037.

Willemse-van Son AHP, Ribbers GM, Hop WCJ, Duijn CM, Stam HJ. Association between Apolipoprotein ε4 long-term functional outcome after traumatic brain injury. JNNP; 2008, 79, 426-420. Online first: 2007, October 30.

Willemse-van Son AHP, Ribbers GM, Stam HJ, van den Bos GAM. Is there equity in health care utilisation after traumatic brain injury? Accepted in Journal of Rehabilitation Medicine.

Willemse-van Son AHP, van den Bos GAM, Ribbers GM, Stam HJ. A risk profile for patients with long-term unmet needs after a traumatic brain injury. Submitted.

Willemse-van Son AHP, Ribbers GM, Hop WCJ, Stam HJ. Community integration following moderate to severe traumatic brain injury. Submitted.

Chapter 1

Introduction

TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) has been termed a 'silent' epidemic because the consequences for patients, relatives, and society are substantial, but the incidence and sequential costs are not well known to the general public.[1] Not only are patients and relatives insufficiently aware of the sequelae, knowledge on TBI is also lacking among most professional caregivers.[2] Reported incidence rates vary depending on the definitions and inclusion criteria used.[3] In the USA, approximately 1.4 million people sustain a TBI on a yearly basis and about 235,000 are hospitalised. In Europe the average reported incidence is approximately 235/100,000 population with 66,000 deaths per year.[4,5] For the Netherlands, the incidence rate was estimated at 79 per 100,000 inhabitants,[6] and 88 per 100,000 inhabitants are annually admitted to hospital with a TBI or head injury.[7] TBI is often caused by falls, traffic accidents, and assaults.[8] Other causes include injuries during sports and recreational activities, and work-related accidents. Males are 1.5 times more likely to sustain TBI than females, and the highest risk was found for the age groups 0-4 years and 15-19 years.[9] Outcome after TBI can range from complete recovery to death, with many survivors having long-term disabilities.[10] At 3-7 years post-injury, about 45 to 67% of the TBI patients still suffer from situational, cognitive, and emotional or behavioural problems.[6] Many patients do not return to their previous jobs or are unable to engage in social events. Because of this patients feel less productive and experience a lower quality of life.

As most TBI victims are relatively young and have a normal life expectancy, the total costs for society are high; moreover, because mortality after TBI is decreasing[11] these costs may rise even further in the future. It was estimated that the annual average cost per case of TBI is 2,324 euros in Europe, and 3,170 euros in the Netherlands.[4] This estimation was based only on the cost of hospitalisation, and does not take into account costs for rehabilitation or due to loss of work days. The total direct health costs related to TBI in Europe in 2004 were estimated at 2.9 billion euros, and for the Netherlands at 110 million euros. Non-medical costs (e.g. transportation, social services, adaptations of accommodations, etc.) and indirect costs (costs due to loss of productivity) were not taken into account.[4]

PROGNOSIS

Information about prognosis after TBI is important to patients, relatives, and clinicians. Information about what the future may bring may help patients and relatives in the adaptation process and will enhance efficacy of the rehabilitation process. Reliable guidelines on prognosis help clinicians to distinguish which patients are at risk for an adverse outcome and which treatment is needed at what moment in time. Most studies

have only focused on short-term outcome (6-12 months post-injury), on outcome measures that poorly differentiate between actual levels of functioning and participation, and only use gross outcomes such as mortality, morbidity, and global outcome, assessed with the Glasgow Outcome Scale (GOS)[12] or its extended version.[13] These studies have been helpful in developing prediction rules for estimating survival, and for the development of secondary injuries, recovery from the vegetative state, or discharge planning.[14-17] However, for long-term health care planning, insight in the course of activity limitations and participation restrictions and their determinants is essential.

The International Classification of Functioning, Disability and Health (ICF)[18] of the World Health Organization is widely used as a structuring framework for outcome research. In the ICF model (Figure 1) the level of functioning is determined by (a) body functions and structures, and (b) activities and participation in interaction with the contextual factors such as environment and personal characteristics. In line with the ICF model, functional outcome or recovery after TBI is a multilayered concept that is determined by a variety of biological, sociodemographic, and environmental factors. Determinants regarding health condition, body function and body structure may encompass: clinical characteristics of the injury (i.e. GCS score, CT pattern, presence of hypoxia, presence of hypothermia, presence of hypotension), co-morbidity, and genetic characteristics (Apolipoprotein ε4). Activity and participation variables concern: (post-acute) independence in activities of daily life, motor functioning, cognitive functioning, disability, participation restrictions, community integration, and depression. Length of stay in the acute hospital, destination after discharge from hospital, and social support are examples of environmental determinants. Finally, personal factors are: age, gender, living situation, education level, work status, ethnicity, and locus of control.

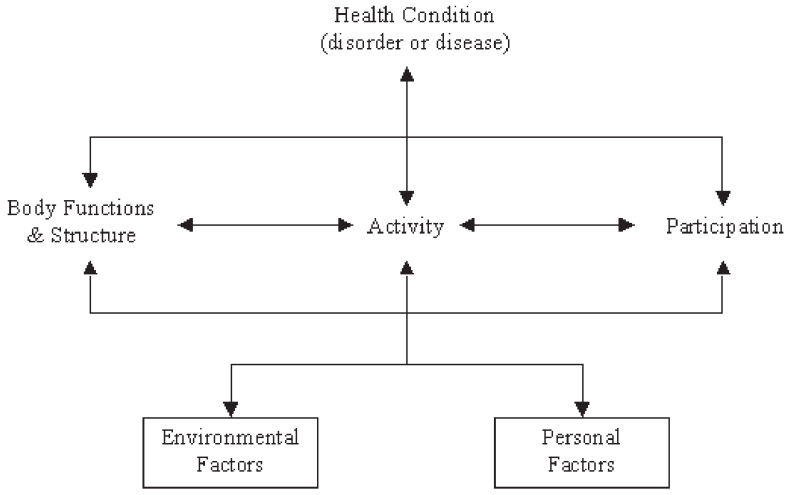

Figure 1. The International Classification of Functioning, Disability and Health (ICF)

AIM OF THIS STUDY

This thesis was performed as part of the 'Long-term prognosis of functional outcome in neurological disorders' project (FuPro), supervised by the department of Rehabilitation Medicine of the VU Medical Centre, Amsterdam and supported by the Netherlands Organisation for Health Research and Development (ZonMw project: 1435.0020). The scope of the FuPro project was to investigate long-term outcome and its determinants for four neurological disorders: multiple sclerosis, stroke, motor neuron diseases, and TBI. The following research questions are addressed:

1. What is the course of functional outcome after moderate to severe TBI, defined as activities and participation, in the first three years post-injury?
2. What are the determinants of activities and participation 3 years after moderate to severe TBI?
3. To what extent is the utilisation of healthcare and health-related community services determined by health-related needs 3 to 5 years after moderate to severe TBI?
4. What is the prevalence of patient-reported unmet needs concerning autonomy and participation 3 to 5 years after moderate to severe TBI and what risk factors are related to the occurrence of unmet needs?

OUTLINE OF THIS THESIS

Chapter 2 describes a systematic review of the literature of prospective studies on prognostic factors of long-term functioning and productivity after traumatic brain injury. Findings of this review were considered for the selection of variables for the prognostic models. Chapter 3 describes the prognostic value of one determinant (carrying the Apolipoprotein ε4 allele) on three outcome measures: 1) global functional outcome, 2) activity limitations and participation restrictions, and 3) community integration. These outcome measures were assessed at 3, 6, 12, 18, 24, and 36 months after TBI. The effect of Apolipoprotein ε4, time, and the interaction of time and Apolipoprotein ε4 were tested. The analyses were adjusted for the effect of age, gender and GCS. In Chapter 4 we evaluated the course of community integration up to 3 years post-injury and compared it with the level of pre-injury community integration. In addition, we studied which variables were the major determinants of community integration 3 years post-injury. In Chapter 5 we determined whether there was equity in long-term health care utilisation of TBI patients for 5 types of care: rehabilitation care, general practitioner, other medical care, supportive care, and overall high or low use of care. The relative contribution of predisposing, enabling and health-related factors on healthcare utilisation was determined in order to evaluate if there was equity or inequity. In Chapter 6 we

quantified the proportion of TBI patients that perceived unmet needs for participation and autonomy. Further, we determined a risk profile for patients who were more likely to have unmet needs on the long term. In Chapter 7 all findings are summarised and discussed. Finally, we present some clinical implications of our work and recommendations for future research.

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Chapter 2

Prognostic factors of long-term functioning and productivity after traumatic brain injury: A systematic review of prospective cohort studies

Willemse-van Son AHP, Ribbers GM, Verhagen AP, Stam HJ

Clinical Rehabilitation, 2007; 21: 1024-1037

ABSTRACT

Objective: To systematically review prospective cohort studies that investigated prognostic factors associated with long-term activity limitations or participation restrictions and productivity after a traumatic brain injury.

Data sources: PubMed and Psychinfo were searched from 1995 to April 2005, and references were checked.

Review methods: Publications were selected if the study assessed prognostic factors for activity limitations or participation restrictions at least one year post-injury; outcome was measured with another or additional measure besides the Glasgow Outcome Scale; the design was a prospective cohort study of adult traumatic brain injury patients; the article was a full-text article written in English, French, German or Dutch. Two reviewers independently assessed methodological quality. A study was considered as 'high quality' if it satisfied at least half of the maximum available quality score.

Results: Thirty-five articles reporting on 14 cohorts were included. Due to heterogeneity in prognostic factors and outcome measures, a best-evidence synthesis was performed. All cohorts were of high quality. Strong evidence for predicting disability was found for older age, pre-injury unemployment, pre-injury substance abuse, and more disability at rehabilitation discharge. Strong prognostic factors for being non-productive were pre-injury unemployment, longer posttraumatic amnesia, more disability at rehabilitation admission, and pre-injury substance abuse.

Conclusion: Older age, pre-injury unemployment, pre-injury substance abuse, and more disability at rehabilitation discharge are important predictors of long-term disability. Pre-injury unemployment, longer posttraumatic amnesia, more disability at rehabilitation admission, and pre-injury substance abuse are important predictors of being non-productive.

INTRODUCTION

Traumatic brain injury affects approximately 1.4 million people in the United states each year and about 235,000 are hospitalised.[1] In Europe approximately 1.6 million traumatic brain injury patients are admitted to hospital on a yearly basis. Although reported incidence rates vary per country, the incidence rate for the European population is 235/100,000 with 66,000 deaths per year.[2, 3] Direct health costs related to traumatic brain injury in Europe are estimated at 2.9 billion euros. Non-medical costs (e.g. due to loss of productivity and intangible costs due to reduced quality of life) are not taken into account in this estimation.[4]

The outcome after traumatic brain injury can vary from complete recovery to death, with many patients having long-term disabilities. Especially after severe injury, serious cognitive, behavioural, emotional and sensorimotor impairments can occur.[5] These impairments can have major consequences for activity patterns, social participation, and quality of life issues.

Reliable guidelines for prediction of long-term outcome and optimal clinical management in patients at risk for activity limitations or participation restrictions are lacking. Prediction models for patients at risk of developing these long-term restrictions are essential to optimize the use of limited health care and social resources for patients and their relatives.

Although several studies have investigated the long-term prognosis of traumatic brain injury, to our knowledge no systematic reviews have been published on prognostic factors of long-term outcome. Therefore, this study aims to summarize the literature on prognostic factors associated with activity limitations, participation restrictions and productivity at least one year post-injury. We systematically investigated the influence of socio-demographic factors, pre-morbid co-morbidity, injury characteristics, neuropsychological factors, treatment factors, and post-acute functioning and their relation to long-term outcome and productivity.

METHOD

Search strategy

We searched PubMed and Psychinfo from 1995 to April 2005. Additionally, references of identified publications were checked.

The search strategy was developed and tested for PubMed and adapted for Psychinfo. To describe the population the MeSH term 'craniocerebral trauma' was used. To describe the design the following key terms were used: 'predictive value of tests' (MeSH term)

and prognos* and predict*. To select the adult population the MeSH terms 'adult' and 'middle aged' were used. The search strategy is available from the last author.

One reviewer (A.W.v.S.) conducted the search. Two reviewers (A.W.v.S. and G.M.R.) independently screened titles and abstracts to identify relevant articles. Full papers were retrieved when abstracts were absent or provided insufficient information to enable selection.

Selection criteria

An article was included if all following criteria were met: (1) the study investigated factors associated with functional outcome after traumatic brain injury; (2) traumatic brain injury was defined as 'an alteration in brain function as a result of an acute external violent force to the head'; (3) outcome was described as activity limitations or participation restrictions, as defined in the International Classification of Functioning, Disability and Health[6]; (4) another or an additional measure besides the Glasgow Outcome Scale[7] or its extended version[8] was used to measure outcome; (5) time post-injury was at least one year; (6) the study population consisted of traumatic brain injury patients or a separately analysed subgroup of traumatic brain injury patients ; (7) the majority (at least 80%) of the patients in the studies was 18 to 65 years old; (8) the article was written in English, French, German or Dutch; (9) the article was a full-text article; (10) the study design was a prospective cohort study.

A study was excluded if: (1) the study population suffered from additional serious neurological, oncological or systemic impairments; (2) the study population included animals.

Two reviewers (A.W.v.S. and G.M.R.) assessed all criteria independently in the full-text articles. In case of disagreement, consensus was sought. If disagreements were not resolved a third reviewer (A.P.V.) made the final decision.

Methodological quality

We assessed the methodological quality of the cohorts with a modified version of an established criteria list for prospective cohort studies.[9] The criteria list was modified in concordance with the framework for assessing validity in prognostic studies.[10]

The criteria list consisted of 16 items (Table 1), with each having a 'yes/no/don't know option'. The item was scored positive (yes), if it fulfilled the criterion. If a criterion was not fulfilled, the item was scored negative (no). If there was insufficient information, the item was scored unclear (don't know). The total sum of positive items was calculated as the quality score (maximum 16 points). A study that scored at least eight points was considered as high quality. We calculated one quality score for each cohort, based on the information of all publications of that cohort.

Table 1. Criteria list for the quality assessment of studies on prognosis of patients with traumatic brain injury

Criteria	Score
Study population	
a) Inception cohort	+/ - / ?
b) Description of source population	+/ - / ?
c) Description of relevant inclusion and exclusion criteria	+/ - / ?
Follow-up	
d) Time since injury/follow-up at least 12 months	+/ - / ?
e) Drop-outs/loss to follow-up < 20%	+/ - / ?
f) Information completers versus loss to follow-up/drop-outs	+/ - / ?
g) Prospective data collection	+/ - / ?
Treatment	
h) Treatment in cohort is fully described/standardised	+/ - / ?
Prognostic factors	
i) Clinically relevant potential prognostic factors	+/ - / ?
j) Standardised or valid measurements	+/ - / ?
k) Data presentation of most important prognostic factors	+/ - / ?
Outcome	
l) Clinically relevant outcome measures	+/ - / ?
m) Standardised or valid measurements	+/ - / ?
n) Data presentation of most important outcome measures	+/ - / ?
Analysis	
o) Appropriate univariate crude estimates	+/ - / ?
p) Appropriate multivariate analysis techniques	+/ - / ?

Two reviewers independently scored the quality (A.W.v.S.; G.M.R.). In case of disagreement, consensus was sought. If consensus could not be reached, a third reviewer (A.P.V.) made the final decision. Inter-observer agreement was derived with Kappa statistics because of dichotomous values.

Data extraction

Data on study cohort, inclusion and exclusion criteria, number of participants, time post-injury, loss to follow-up, outcome measurements, prognostic factors, and results on associations were extracted, using a standardised form.

One reviewer (A.W.v.S.) extracted the data and one reviewer (G.M.R.) checked an unselected sub sample.

Analysis

A best-evidence synthesis was performed, in which four levels of evidence[9] (Table 2) were defined to determine the strength of association of prognostic factors with disability and being non-productive at least one year post onset. Disability was defined as all

Table 2. Levels of evidence for prognostic factors

Levels of evidence	
Strong	Consistent (≥ 80%) findings in at least 2 high-quality cohorts
Moderate	One high-quality cohort and consistent (≥ 80%) findings in one or more low-quality cohorts
Limited	Findings of one cohort or consistent (≥ 80%) findings in one or more low-quality cohorts
Inconclusive	Inconsistent findings irrespective of study quality

measures that described activity limitations or participation restrictions. Although being non-productive was a component of disability, we evaluated it separately. Being non-productive was defined as 'all measures that describe not returning to work, not returning to school, unemployment or otherwise not being productive'.

Significant relative risk ratios (RRs), odds ratios (ORs), or significant associations ($p < 0.05$) that were provided by the studies, were used to determine the levels of evidence. If a multivariate analysis was performed in the studies, than these results were used to establish levels of evidence. Otherwise, presented results from univariate analysis were used.

RESULTS

Selection of studies

In total, 501 non-duplicate citations were found of which 183 full text articles were retrieved. Agreement was reached in 83% (151 of 183 papers), and consensus was sought and found for 32 articles. Finally the two reviewers selected 35 articles (Figure 1). Six cohorts published more than one paper on the same cohort, resulting in a total of 14 cohorts.

Methodological quality

The overall inter-observer agreement of the methodological quality assessment was K=0.46, representing moderate agreement. Disagreement occurred mainly because of reading errors and difference in interpretation of the criteria list and was easily resolved. For 11 items disagreement persisted and a third reviewer (A.P.V.) made the final decision. The final results of the methodological assessment are presented in Table 3.

The cohorts were ranked by their quality score, in which a higher score indicated a higher quality. The names were abstracted from the city, region or database where the cohort was recruited. All cohorts scored at least eight points and were all considered high quality. Methodological quality of individual papers within the cohorts varied due to differences in the presentations of methods and analysis.

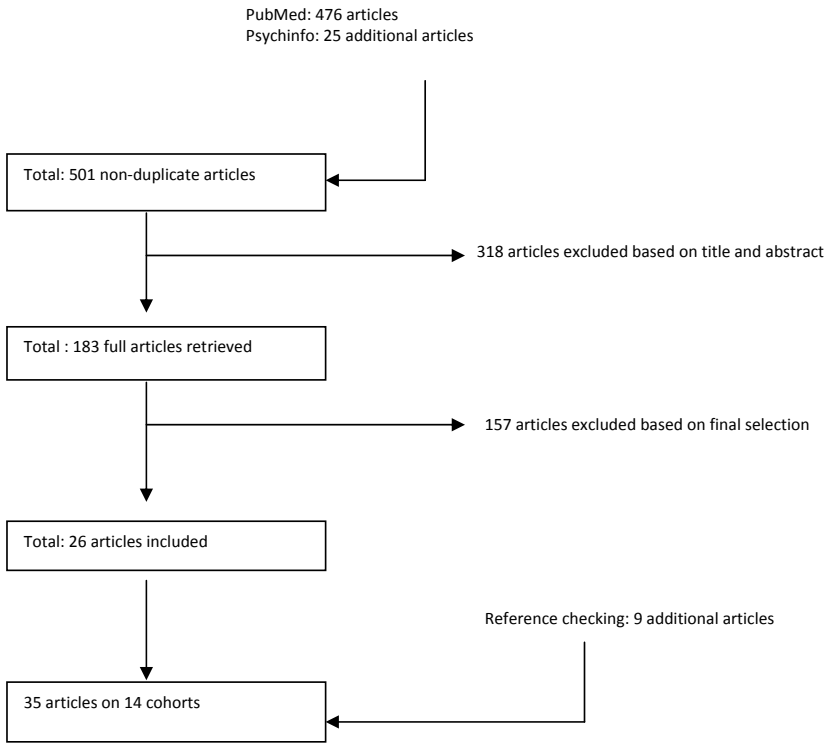

Figure 1. Flowchart showing the selection of the studies

Table 3. Results of the methodological assessment

Cohort name	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	Quality score	Range of individual papers
Traumatic Brain Injury Model Systems[13-26]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	16	9 – 14
Colorado[12, 27]	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	15	14 – 15
Groningen[28-30]	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	14	11 – 14
Houston[31]	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	14	-
Melbourne[32]	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1	14	-
Toronto[33]	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	14	-
Seattle[34, 35]	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0	13	12, 12
Westmead[36]	1	1	0	1	0	1	1	0	1	1	1	1	1	1	1	1	13	-
Rome[37]	1	0	1	1	0	0	1	0	1	1	1	1	1	1	1	1	12	-
Columbus[38-40]	1	0	0	1	0	1	1	0	1	1	1	1	1	1	1	1	12	11 – 12
Alabama [41]	1	1	1	1	0	0	1	0	1	1	1	1	1	1	0	1	12	
Veruno[11, 42, 43]	1	1	0	1	0	0	1	0	1	1	1	1	1	1	0	1	11	9 – 11
Montreal[44]	1	0	0	1	0	0	1	0	1	1	1	1	1	0	1	1	10	-
Magdeburg[45]	1	0	0	1	0	0	1	1	1	1	0	1	1	1	1	0	10	-

Table 4. Study characteristics

Cohort recruitment	Case definition and number enrolled in cohort	Follow-up period	% lost to follow-up
Acute care cohorts			
Colorado, USA[12, 27]	ICD-9 codes 800.0 – 801.9, 803.0 – 804.9, 850.0 – 854.1 (n=2,771[12]; n= 1059 complete cases[27])	1 year[12]; 12 – 18 months[27]	42.6%[12]; 41.9%[27]
Groningen, The Netherlands[28-30]	PTA 1 day – 60 days[28] / GCS 9-14 and PTA 1 hour – 28 days[29, 30] (n=60[28]; n=70[29]; n=67[30])	1 year and 2 – 5 years[28]; 1 year[29, 30]	5% (1 year); 15% (2 – 5 years)[28]; 4%[29]
Toronto, Canada[33]	Responsive within one month (n=92)	1 and 4 years	37% (1 year); 50% (4 years)
Seattle, USA[34, 35]	Loss of consciousness or PTA > 1 hour, or other objective evidence (n=448[34]; n=466 complete cases[35])	1 year	9%[35]
Alabama, USA[41]	Acute care length ≥ 3 days (n=116 complete cases)	1 and 2 years	37% (2 years)
Magdeburg, Germany[45]	GCS 3 – 12, and intracranial injury on computed tomography (n=34 complete cases)	3 – 8 years	Unclear
Acute care and inpatient rehabilitation cohorts			
Traumatic Brain Injury Model Systems Database, USA[13-26]	Receipt of acute care and inpatient rehabilitation in Model Systems (n=301 complete cases)[15]; (n=292 complete cases)[14]; (n= 71 complete cases)[16]; (n=2362)[13]; (n=538)[17]; (n=293 complete cases)[18]; (n=132 complete cases)[20]; (n=99 complete cases)[19]; (n=59 complete cases)[21]; (n=423 complete cases)[22]; (n=1839)[23]; (n=637)[24]; (n=633)[25]; (n=586)[26]	1 and 5 years[14, 15]; 4 months – 10 years[16]; 1 year[13, 20-24, 26]; 1, 2, 3, 4, and 5 years[17]; 1 – 4 years[18]; 1 – 3 years[19]; 1, 2 and 3 or 4 years[25]	1 year: 58%[14, 15]; 54.4%[13]; 16.2%[17]; 39%[22]; 48%[26] 5 years: 54%[15], 46%[14]; 77.7%[17]
Melbourne, Australia[32]	Working at time of injury (n=517, sub sample used n=74 complete cases)	2 years	50.9%
Columbus, USA[38-40]	Admitted to brain injury unit (n=351)[38]; (n=340)[39]; (n=357)[40]	1 year[38, 39]; 1 and 2 years[40]	1 year: 42%[38, 39]; 22%[40]; 2 years: 26.6%[40]
Inpatient rehabilitation cohorts			
Westmead, Australia[36]	Admitted to brain injury rehabilitation (n=110)	6 months and 2 years	50% (2 years)
Rome, Italy[37]	GCS ≤ 8, spontaneous eye opening after more than 1 week, PTA ≥ 4 weeks (n= 37)	3, 6, and 12 months	Unclear
Veruno, Italy[11, 42, 43]	Severe injury (n=143 complete cases)[42]; (n=21)[11]; (n=27)[43]	> 1 year[42]; 6 months and 1 year[11]; 1 year[43]	Unclear
Montreal[44]	No vegetative state (n=35 complete cases)	1.5 years	Unclear
Outpatient rehabilitation cohort			
Houston, USA[31]	Followed-up > 3 months post-discharge (n=76 complete cases)	22.5 months	Unclear

ICD-9, International Classification of Disease Ninth Revision; GCS, Glasgow Coma Scale; PTA, posttraumatic amnesia

Table 5. Outcome measures used and prognostic factors related to them

Cohort	Outcome measure: significant prognostic factors and non-significant factors
Acute care cohorts	
Colorado[12]	Worse cognitive alertness behaviour: moderate injuries, higher injury severity score, age < 65, female, member of ethnic minority (R^2=3.9%) Worse handicap and social integration: violence related injury, severe injury, moderate injuries, higher injury severity score, age ≥ 65, females, members of ethnic minority, not working at time of injury, single, received government funding (R^2= 22.5%)
Colorado[27]	More independence: admission in a long-term care facility (nursing home), severe injuries, moderate injuries, age ≥ 65 years, female, members of minorities, not working at injury, government funding. *Not significant*: inpatient rehabilitation, outpatient services. Worse handicap and social integration: receiving inpatient rehabilitation, admission in a long-term care facility (nursing home), receiving outpatient services, severe injuries, moderate injuries, female, members of minorities, not working at injury, government funding. *Not significant*: Age Worse cognitive symptoms: receiving inpatient rehabilitation, admission in a long-term care facility (nursing home), receiving outpatient services, severe injuries, female, age ≥ 65 years, members of minorities, not working at injury, government funding. *Not significant*: moderate injuries Worse health status: receiving inpatient rehabilitation, admission in a long-term care facility (nursing home), receiving outpatient services, severe injuries, female, members of minorities, not working at injury, government funding.
Groningen[29]	Higher % return to work: fewer symptoms 3 months, shorter posttraumatic amnesia, fewer cognitive problems 1 year (R^2=42%). *Not significant*: age, sex, level of education
Toronto[33]	More psychosocial distress: female, lower GCS, longer length of coma, longer length of stay, more days to recall (R^2 = 29%) Higher % return to productivity: lower GCS, longer length of coma, more days to recall (R^2 = 34%)
Seattle[34]	Higher % return to work: shorter time to follow commands, stable pre-injury employment, younger age, working after 1 month (regression tree analysis)
Alabama[41]	Improved quality of life 1 – 2 years: Path model (R^2 = 49%): direct pathways: higher employment stability, better FIM at 24 months, less impairments, non-white race. Indirect pathways: presence of self blame, strong family support, ability to pay for services, better FIM at 12 months, less rehabilitation
Acute care and inpatient rehabilitation cohorts	
TBIMS[14]	Improvement and deterioration of independence 1 – 5 years: Expression and comprehension improvement: lower Year 1 FIM-cognitive, lower Wechsler Adult Intelligence Scale-Block Design Social interaction improvement: lower Year 1 FIM-cognitive
TBIMS[16]	Positive driving status: better neuropsychological functioning, no awareness problems, better ability to drive safely (perceived by patient and significant other) (R^2 = 53%) Estimated miles driven post-injury: years post-injury, DRS at discharge, neuropsychological functioning, significant others' perceived safe driving ability, patients' perceived safe driving ability (R^2 = 33%) Driving safety: Years post-injury, DRS at discharge, neuropsychological functioning, significant others' perceived safe driving ability, patients' perceived safe driving ability (R^2 = 30%)

Cohort	Outcome measure: significant prognostic factors and non-significant factors
TBIMS[18]	Productivity: Patients that completed at least 1 neuropsychological test at rehabilitation and not injured in assault were more productive then patients that did not compete 1 neuropsychological test not tested in rehabilitation and injured in assault
TBIMS[19]	Higher % employment: more years of education, pre-injury productive, lower (better) DRS score at admission rehabilitation, lower (better) DRS score at discharge rehabilitation (R^2 = 26%)
TBIMS[21]	Higher community integration self report: younger age, higher REY Auditory Verbal Learning Test, worse TMT-A, better TMT-B (R^2 = 38%) Higher community integration significant other report: younger age, higher REY Auditory Verbal Learning Test, worse TMT-A, better TMT-B (R^2 = 29%) Higher home integration: younger age, higher REY Auditory Verbal Learning Test, worse TMT-A, better TMT-B (R^2 = 20%) Social integration: younger age, higher REY Auditory Verbal Learning Test, worse TMT-A, better TMT-B (R^2 = 21%)
TBIMS[22]	Higher FIM motor: higher FIM motor at discharge rehabilitation (R^2 = 49%). *Not significant*: aetiology, age, GCS-score, length of unconsciousness, gender, marital status, rehabilitation discharge FIM cognitive, race, education level, productive activity, acute payer, rehabilitation payer, blood alcohol level, alcohol use (1 year). Higher FIM cognitive: higher FIM motor and cognitive at discharge rehabilitation (R^2 = 32%). *Not significant*: aetiology, age, GCS-score, length of unconsciousness, gender, marital status, race, education level, productive activity, acute payer, rehabilitation payer, blood alcohol level, alcohol use (1 year) Higher home integration: higher level of education (R^2 = 12%). *Not significant*: aetiology, age, GCS-score, length of unconsciousness, gender, marital status, rehabilitation discharge FIM motor, rehabilitation discharge FIM cognitive, race, productive activity, acute payer, rehabilitation payer, blood alcohol level, alcohol use (1 year). Higher social integration: younger age, white race, higher education level (R^2 = 17%). *Not significant*: aetiology, GCS-score, length of unconsciousness, gender, marital status, rehabilitation discharge FIM motor, rehabilitation discharge FIM cognitive, productive activity, acute payer, rehabilitation payer, blood alcohol level, alcohol use (1 year). Higher productivity: higher productivity before injury (R^2= 23%). *Not significant*: aetiology, age, GCS-score, length of unconsciousness, gender, marital status, FIM motor, rehabilitation discharge FIM cognitive, race, education level, acute payer, rehabilitation payer, blood alcohol level, alcohol use (1 year). Higher community integration: younger age, higher education level, white race, higher productivity before injury (R^2 = 22%). *Not significant*: aetiology, GCS-score, length of unconsciousness, gender, marital status, rehabilitation discharge FIM motor, rehabilitation discharge FIM cognitive, acute payer, rehabilitation payer, blood alcohol level, alcohol use (1 year).
TBIMS[25]	More productivity: younger age, length of coma, length of acute care stay, length of rehabilitation stay, rehabilitation admission DRS (R^2 = 34%). Social integration: *not significant*: age, length of coma, length of acute care stay, length of rehabilitation stay, rehabilitation admission DRS. Home integration: *not significant*: age, length of coma, length of acute care stay, length of rehabilitation stay, rehabilitation admission DRS.

Cohort	Outcome measure: significant prognostic factors and non-significant factors
TBIMS[26]	Better FIM motor: not injured by falls, younger age, gender, type of funding, better FIM motor at rehabilitation discharge, better FIM cognitive at rehabilitation discharge (R^2 = 39%) Better FIM cognitive: not injured by falls, younger age, higher FIM cognitive at rehabilitation discharge, higher Rancho Los Amigos Levels of Cognitive Functioning Scale at discharge rehabilitation, marital status at follow up (R^2 = 23%) *Not significant*: GCS-score Higher home integration: younger age, type of funding, better Rancho Los Amigos Levels of Cognitive Functioning Scale at rehabilitation discharge, better DRS at rehabilitation discharge, living alone (R^2 = 17%) Higher social integration: white race, shorter posttraumatic amnesia, younger age, better DRS at rehabilitation discharge, higher family income, no drug use (R^2 = 24%) *Not significant*: aetiology Higher productivity: white race, no violence related injury, younger age, better DRS at rehabilitation discharge, higher family income, alcohol use, (R^2 = 25%) Higher community integration: white race, younger age, better DRS at rehabilitation discharge, higher family income, alcohol use, no drug abuse (R^2 = 28) *Not significant*: posttraumatic amnesia
Melbourne[32]	Employment status: Age, initial GCS score, total DRS score at admission rehabilitation
Columbus[38]	Higher life satisfaction: pre-injury employment, higher FIM motor score at discharge rehabilitation, no substance abuse history (R^2 = 14%) Higher productivity: younger age, pre-injury employment, higher FIM cognitive at discharge rehabilitation, no history of substance abuse (R^2 = 16%)
Columbus[40]	Higher life satisfaction: not depressed at 2 years, socially integrated at 2 years, employed at 2 years, no history of substance abuse (R^2 = 30%) Improvement of satisfaction with life 1 – 2 years post-injury: not married at 2 years, not depressed at 2 years (R^2 = 8%)
Inpatient rehabilitation cohorts	
Westmead[36]	Employment: younger age (R^2 = 19%), pre-injury employed (R^2 = 18%), employed at 6 months (R^2 = 24%), less psychological distress at 6 months (R^2 = 26%)
Veruno[42]	Functional independence: Epilepsy patients had lower Functional independence scores than no epilepsy patients, controlled for GCS at time of injury, duration of coma, severity of computed tomography scan, age Disability: Epilepsy patients had higher disability scores than no epilepsy patients, controlled for GCS at time of injury, duration of coma, severity of computed tomography scan, age
Outpatient rehabilitation cohort	
Houston[31]	Higher % employment: Pre-injury substance use (OR=0.12, 0.02-0.62))

OR, odds ratio; OR > 1 has a protective effect

TBIMS, Traumatic Brain Injury Model Systems database; FIM, Functional Independence Measure; GCS, Glasgow Coma Scale; DRS, Disability Rating Scale; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B

The most important methodological shortcomings concerned the following items: no description of source population, no description of relevant inclusion and exclusion criteria, unclear information on percentage of drop-outs or loss to follow-up of more than 20%, no information of completers versus loss to follow-up, and no description of what treatment was given, or there was no treatment.

Study characteristics

Table 4 presents the main characteristics of the cohorts ordered into source populations and ranked by cohort and quality scores. The sample size ranged from n = 21[11] and n = 2,771[12] per individual study. Seven cohorts enrolled over 100 cases and two cohorts (Colorado, Traumatic Brain Injury Model Systems) enrolled over 1000 cases. In one cohort (Traumatic Brain Injury Model Systems) the sample sizes in the individual studies ranged from 59 to 2363 cases[13-26]. The longest follow-up period was up to 10 years (Traumatic Brain Injury Model Systems). The loss to follow-up after one year between the individual studies ranged from 4% (Groningen) to 58% (Traumatic Brain Injury Model Systems). Three cohorts (Groningen, Traumatic Brain Injury Model Systems, Seattle) reported a loss to follow-up of below 20%.

Table 5 presents a summary of the results from the multivariate analysis performed by the individual studies. Results are presented for the longest follow-up period only. Over 100 prognostic factors were examined: socio-demographic and injury-related factors, neuropsychological tests, pre-morbid co-morbidity, and post-acute determinants. Twenty different outcome measures were used on handicap, disability, psychosocial distress, social integration, return to work, quality of life and independence. The heterogeneity of the prognostic factors and outcome measures precluded statistical pooling and necessitated a qualitative summary of the results.

Overall levels of evidence

We established the levels of evidence for determinants of disability (Table 6) with the results of the multivariate analysis that was performed in the individual studies. To establish the levels of evidence for being non-productive (Table 7), we used the results of the univariate or multivariate analysis that was performed by the studies. Frequently it was unclear which prognostic factors were actually tested and often only significant results were presented. Therefore, it was not always clear whether factors absent in the results were found to be not significant, or whether they were not tested. Therefore we used only negative results when they were reported as non-significant in the paper.

In the 35 selected articles, 51 determinants of disability (multivariate results) and 82 determinants of productivity (univariate and multivariate results) were registered. Only prognostic factors examined in more than one cohort are presented. Several publications of one cohort reported contradictory results.[12, 19, 21, 22, 26, 27] Differences in size and inclu-

Table 6. Levels of evidence for prognostic factors and their associations with disability

Prognostic factor	Cohorts assessed	Positive findings	Negative findings	Level of evidence
Older age	7	7/7 (100%)	0/7 (0%)	Strong
Female gender	3	2/3 (66.7%)	1/3 (33.3%)	Inconclusive
Unemployment at time of injury	4	4/4 (100%)	0/4 (0%)	Strong
Lower (worse) Glasgow Coma Scale score	3	2/3 (66.7%)	1/3 (33.3%)	Inconclusive
Pre-injury substance abuse	3	3/3 (100%)	0/3 (0%)	Strong
Higher (worse) Disability Rating Scale score at discharge rehabilitation	2	2/2 (100%)	0/2 (0%)	Strong

Positive findings were considered ORs > 2 or < 0.5, or significant associations (P < 0.05)

Table 7. Levels of evidence for prognostic factors and their associations with being non-productive

Prognostic factor	Cohorts assessed	Positive findings	Negative findings	Level of evidence
Older age	7	4/7 (57.1%)	3/7 (42.9%)	Inconclusive
Female gender	4	0/4 (0%)	4/4 (100%)	Strong no
Unemployment at time of injury	5	4/5 (80%)	1/5 (20%)	Strong
Lower education level	2	0/2 (0%)	2/2 (100%)	Strong no
Fewer years of education	4	2/4 (50%)	2/4 (50%)	Inconclusive
Lower (worse) Glasgow Coma Scale score	6	2/6 (33.3%)	4/6 (66.7%)	Inconclusive
Longer posttraumatic amnesia	3	3/3 (100%)	0/3 (0%)	Strong
Violence-related aetiology	3	1/3 (33.3%)	2/3 (66.7%)	Inconclusive
Longer loss of consciousness/ coma	3	2/3 (66.7%)	1/3 (33.3%)	Inconclusive
Pre-injury substance abuse	2	2/2 (100%)	0/2 (0%)	Strong
Longer length of stay in acute care/ hospital	2	1/2 (50%)	1/2 (50%)	Inconclusive
Lower Functional Independence Measure cognitive score at discharge rehabilitation	2	1/2 (50%)	1/2 (50%)	Inconclusive
Higher (worse) Disability Rating Scale score at admission rehabilitation	2	2/2 (100%)	0/2 (0%)	Strong

Positive findings were considered RRs or ORs > 2 or < 0.5, or significant associations (P < 0.05)

sion criteria within the individual papers might explain these contradictory results. If there was a clear majority in favour of or against a determinant, the results were reported in concordance with the majority. If evidence was conflicting within one cohort, it was left out of the analysis.

Disability

Older age, pre-injury unemployment, pre-injury substance abuse, and more severe disability at rehabilitation discharge (measured with the Disability Rating Scale) were strong predictors for disability. For female gender and lower Glasgow coma scores the evidence was inconclusive. Limited evidence was found for: non-white race, violence-related aetiology, longer length of coma, and fewer years of education. Only one cohort found significant results for these predictors.

Productivity

Pre-injury unemployment, longer posttraumatic amnesia, more severe disability at rehabilitation admission (measured with Disability Rating Scale), and pre-injury substance abuse were strong predictors of being non-productive. Female gender and a lower education level were not predictors. Inconclusive evidence was found for older age, fewer years of education, lower Glasgow coma scores (more severe injury), violence-related aetiology, longer loss of unconsciousness, longer length of stay in acute hospital, and lower cognitive functioning at rehabilitation discharge (measured with Functional Independence Measure[46-48]).

Using the results of multivariate analysis for being non-productive did not alter the conclusions considerably, except for lower Glasgow coma scores. The Glasgow coma score became a predictor. The prognostic value of fewer years of education and longer posttraumatic amnesia changed from inconclusive to limited. There was limited evidence that violence-related aetiology was not associated with being non-productive. Length of stay in an acute hospital was not tested with a multivariate analysis in the studies.

DISCUSSION

This systematic review has summarized the results of 35 papers on 14 cohorts concerning the prognostic value of various factors on long-term activity limitations and participation restrictions after traumatic brain injury. All cohorts were of good quality. Due to heterogeneity of prognostic factors and outcome measures, we performed a qualitative analysis.

Older age, pre-injury unemployment, substance abuse, and more severe disability at rehabilitation discharge were strong predictors for ongoing disability. Inconclusive evidence was found for female gender, and lower Glasgow coma scores.

Pre-injury unemployment, longer posttraumatic amnesia, substance abuse, and more disability at rehabilitation admission, were strong predictors for being non-productive. Female gender and lower education level were not predictors for being non-productive. Inconclusive evidence was found for older age, fewer years of education, lower Glas-

gow coma scores, violence-related aetiology, longer loss of consciousness, longer length of stay in acute hospital, and less independence at rehabilitation discharge.

Although these profiles are best evidence for prognosis of restrictions in activities and participation one year after traumatic brain injury, they seem to be of limited value. Most factors are not modifiable by prevention or treatment. Hence, it is not possible to change the course and prevent a future worse outcome. Further, the identified prognostic factors are of limited value in planning adequate and cost-effective long-term care. Which patients are at risk of losing their jobs or of developing marital or parental difficulties? Who is at risk of developing substance abuse or will depend heavily on the caregiver? These are examples of unanswered questions that are of paramount importance in clinical practice. As long as these issues are not dealt with, traumatic brain injury patients as well as their caregivers should be followed-up over long periods of time.

Limitations of the review

For pragmatic reasons, we searched PubMed and Psychinfo from 1995 to April 2005. It is therefore possible, that relevant publications before that time were not included in this review.

In the literature, different definitions for traumatic brain injury and methods for diagnosis are used. We chose to define traumatic brain injury as 'an alteration in brain function as a result of an acute external violent force to the head'. We chose this rather broad definition of traumatic brain injury, in order to include as many as possible relevant studies.

Publication bias might have occurred in this systematic review. Six cohorts published more than one paper, which might have resulted in publication bias. Studies with significant results are more easily published than studies without significant results, and were therefore easier to find.[49] Further, studies published in additional languages were not included in the review.

Cohorts with multiple publications may have received higher methodological quality scores because the information was retrieved from all available articles originating from the same cohort. Lacking information in one article could be completed with information from the other articles, resulting in a higher quality score for cohorts with more than one paper. Nevertheless, this strategy was used to prevent exclusion of valuable information on additional determinants due to incomplete descriptions in an individual paper.

Levels of evidence for determinants of being non-productive were established with results of univariate or multivariate analysis performed in the individual studies. The use of results from univariate analysis might have biased conclusions because these results were not adjusted for confounding. This pragmatic choice was made because it provided additional information on some determinants for productivity. Using only results of multivariate analysis on productivity did not alter the conclusions, except for lower Glasgow coma scores. Further investigation on this factor is needed in the future.

Recommendations for future research

In the reviewed studies, activity limitations and participation restrictions were assessed with many different outcome measures. Therefore comparisons between the studies were complicated. International consensus in the assessment of activity limitations and participation restrictions would improve comparability of studies.

In general, it is important that additional, large prospective cohort studies be performed to strengthen the conclusions on prognostic factors. If possible, these studies should also include modifiable prognostic factors, in order to develop future clinical interventions.

Clinical messages

1. Older patients with pre-injury unemployment, pre-injury substance abuse, or more disability at rehabilitation discharge, should be considered at risk for long-term disability.
2. Patients with pre-injury unemployment, longer posttraumatic amnesia, pre-injury substance abuse, or more disability at rehabilitation admission, should be considered at risk for being non-productive.

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Chapter 3

Association between Apolipoprotein ε4 and long-term outcome after traumatic brain injury

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Journal of Neurology, Neurosurgery, and Psychiatry, 2008;79:426-430

ABSTRACT

Objective: To investigate the effect of carrying the APOE-ε4 allele on global functional outcome, on activity limitations and participation restrictions, and on community integration at 3, 6, 12, 18, 24, and 36 months after traumatic brain injury.

Method: The Glasgow Outcome Scale (GOS), the Sickness Impact Profile-68 (SIP-68), and the Community Integration Questionnaire (CIQ) were assessed in 79 moderate and severe traumatic brain injury patients at 3, 6, 12, 18, 24, and 36 months post-injury. Repeated measures analyses of variance were performed with APOE-ε4 status and time of measurement as independent variables and the GOS, SIP-68, and CIQ as dependent variables. Analyses were adjusted for baseline age, gender, and the Glasgow Coma Score.

Results: Patients with the APOE-ε4 allele had a significantly better global functional outcome on the GOS than patients without the APOE-ε4 allele. No significant associations were found between APOE-ε4 status and the SIP-68 and CIQ.

Discussion: In contrast to other studies, we found that carrying the APOE-ε4 allele had a protective influence on outcome. Multiple mechanisms, and in some cases competitive mechanisms, may explain the variable relation between the APOE-ε4 allele and outcome after traumatic brain injury.

INTRODUCTION

Traumatic brain injury (TBI) affects each year approximately 1.4 million people in the USA and 1.6 million TBI patients are admitted to hospital in Europe.[1,2] Outcome after TBI can vary from complete recovery to death, with many patients having long-term disabilities. Differences in outcome after TBI are only partly explained by socio-demographic factors and injury severity. Studies have found that the polymorphic Apolipoprotein E gene might also be a contributing factor for predicting outcome after TBI.[3,4]

The Apolipoprotein E gene is located on chromosome 19 and has three alleles (APOE-ε2, APOE-ε3, APOE-ε4), which encode three isophorms (APOE-E2, APOE-E3, APOE-E4). Apolipoprotein is important for lipid metabolism and the maintenance of the structural integrity of microtubules.[5] Presence of the ε4 allele has been associated with a higher mortality,[6] longer duration of unconsciousness,[4] longer hospital stay,[7] more cognitive impairments,[4,8,9] and a higher risk of late posttraumatic seizures,[10] and unfavourable outcome.[3,7,11] However, not all studies could replicate these results.[10,12-14]

Most studies that investigated the relation between the APOE-ε4 allele and outcome have covered only a short follow-up period of six months post-injury. Furthermore, most studies focussed mainly on neuropsychological functioning or global functional outcome, measured with the Glasgow Outcome Scale (GOS)[15] or its extended version.[16] Only a few studies have studied activity limitations and participation restrictions as described by the International Classification of Functioning, Disability and Health.[17]

Therefore the current study investigated the effect of carrying the APOE-ε4 allele on global functional outcome, on activity limitations and participation restrictions, and on community integration. As the APOE-ε4 status may relate to short-term outcome but not to long-term outcome, the second aim was to investigate whether the relation between APOE-ε4 status and outcome changes over time, measured at 3, 6, 12, 18, 24, and 36 months post-injury.

METHODS

Participants

In the Rotterdam TBI study, 108 TBI patients were consecutively enrolled from March 1999 to April 2004 in the Erasmus Medical Centre in Rotterdam. Further, 11 TBI patients were enrolled from April 2003 to February 2004 in Medical Centre Haaglanden (The Hague) and University Medical Centre Utrecht. All centres serve as treatment centres for all moderate and severe TBI patients within their regions. Patients were treated conform the European Brain Injury Consortium guidelines.[18]

Inclusion criteria were: (1) survival until discharge from hospital; (2) age at injury between 16 and 67 years; (3) admittance in hospital for moderate or severe TBI (Glasgow Coma Scale (GCS)[19] score of respectively 9-13 or 3-8). Exclusion criteria were: (1) insufficient knowledge of Dutch or English language; (2) serious co-morbidity that might interfere with assessing TBI-related disability.

All participants gave informed consent and the Medical Ethics Committee of Erasmus MC approved the study.

Procedure

The following baseline characteristics were collected during hospital admittance: age in years, gender, cause of injury, CT pattern, the lowest GCS score in the first 24 hours after injury, education level (junior secondary education or lower versus higher education), pre-injury employment status (employed, not employed), and length of stay in hospital. From February 2000 to September 2006, DNA samples were obtained with buccal swabs, at one of the follow-up measurements. Participants had to abstain drinking coffee before tissue collection. The samples were stored in a freezer until they were analysed for genotyping.

Participants were prospectively followed-up at 3, 6, 12, 18, 24, and 36 months post-injury. Two study psychologists, who were blinded for the genotype, collected the data in a structured interview at the participant's home or institution of admittance. If it was impossible to interview the patient, a significant other or professional caregiver was interviewed instead.

Outcome measures

Global functional outcome was measured with the GOS,[15] which assesses the state of consciousness, home independence, independence in community activities, return to work, social and leisure activities, and interpersonal relationships. The GOS compares present performance with pre-injury performance. The scores range from 1 (dead) to 5 (good recovery). The GOS was assessed with a structured interview, which showed good inter-observer reliability (weighted kappa=0.89)[20] and validity.[21]

Activity limitations and participation restrictions were assessed with the Sickness Impact Profile-68 (SIP-68),[22] which has 68 statements on behaviour, feelings, and functions. Respondents are asked if these statements apply to their current situation (yes/no) and whether they are health related. The SIP-68 score is calculated by summing all positively scored items (range 0-68). A higher score indicates more participation restrictions. The SIP-68 has excellent test-retest reliability (ICC=0.97).[23]

Community integration was determined with the Community Integration Questionnaire (CIQ),[24] which assesses home integration, social integration, and productivity. It contains 15 questions on how activities are usually performed (alone, with another

person, by someone else) and how frequently activities are done. The score ranges from 0 to 29, with a higher score indicating better community integration. The reliability of the CIQ is sufficient.[25]

Statistical analysis

Descriptive statistics were performed with SPSS 12.0.1. Baseline characteristics were compared for the groups with and without APOE-ε4 with the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. To test for the effect of carrying APOE-ε4 on outcome, the data were analysed with SAS 8.2. Repeated measures analysis of variance (ANOVA) was performed using the procedure PROC MIXED. An advantage of this procedure is that it does not require complete datasets, because it adjusts for missing values by replacing them for the most optimal estimate. First, APOE-ε4 status (present, absent), time (3, 6, 12, 18, 24, and 36 months post-injury), and interaction between time and APOE-ε4 status (APOE*time) were entered as independent variables and the GOS, SIP-68, or CIQ as dependent variables. Later, age, gender, and the GCS were added to adjust for socio-demographic factors and initial severity

RESULTS

From the 119 patients, 79 patients were genotyped. Seven patients refused to give DNA. Twelve patients were lost to follow-up before the assessment could occur. Twenty-one patients were not assessed because the follow-up measurement fell outside the period of DNA assessment (February 2000 to September 2006) or because patients accidentally drank coffee before the assessment. Baseline characteristics (age, gender, education level, pre-injury employment status, GCS, cause of injury, CT pattern, and length of stay in hospital) did not differ significantly between patients assessed for DNA and patients not assessed for DNA.

The genotype frequencies were: ε2/ε3, 7 (9%); ε2/ε4, 1 (1%), ε3/ε3, 55 (70%); ε3/ε4, 14 (18%); ε4/ε4, 2 (2%). Hence, 17 patients (22%) possessed at least one APOE-ε4 allele. Genotype and allele proportions were in Hardy Weinberg equilibrium (p=0.54).

Baseline characteristics are presented in Table 1. Patients with and without the APOE-ε4 allele did not differ significantly for the presented characteristics.

Baseline characteristics were checked for interrelations. Older patients (Spearman's rho=0.28, p=0.017) and patients with a lower GCS (Spearman's rho=-0.42, p<0.001) had longer admission times in hospital. More lower educated patients than higher educated patients were unemployed (Chi-square=9.83, p=0.002) and lower

Table 1. Baseline characteristics of patients with and without the APOE-ε4 allele, and the total group

	Without APOE-ε4 n=62	**With APOE-ε4 n=17**	**Total group**
Age in years: mean (SD)	33.6 (12.9)	33.2 (11.4)	33.5 (12.6)
Gender (male): n (%)	45 (73%)	12 (71%)	57 (72%)
Employed at injury: n (%)	48 (80%)	15 (94%)	63 (83%)
Higher education: n (%)	33 (53%)	11 (65%)	44 (56%)
GCS: mean (SD)	6.9 (3.0)	6.8 (2.7)	6.9 (2.9)
Cause of injury			
Traffic accident	45 (73%)	13 (77%)	58 (73%)
Work	4 (7%)	2 (12%)	6 (8%)
Fall	8 (13%)	2 (12%)	10 (13%)
Other	5 (8%)	0 (0%)	5 (6%)
CT-scan			
No visual pathology	1 (3%)	1 (7%)	2 (4%)
Pathologies (no absent or compressed cisterns, shift or mass lesion)	30 (77%)	8 (53%)	38 (70%)
Compressed cisterns	3 (8%)	1 (7%)	4 (7%)
Shift	0 (0%)	1 (7%)	1 (2%)
Mass lesion	5 (13%)	4 (27%)	9 (17%)
Days in hospital: median (range); mean (SD)	30 (5 – 173); 39 (30.9)	41 (7 – 85); 40 (20.2)	32 (5 – 173); 39 (28.8)

educated patients had worse CTs patterns (linear by linear association=4.2, p=0.04). Further, there were no interrelations.

At three years post-injury, 76 patients of the 79 patients (96%) were followed up and 3 patients were lost to follow-up. No significant differences were found for the presented baseline characteristics between the interviewed and not-interviewed subjects.

GOS

Outcome scores on the GOS are presented in Table 2. Figure 1 shows the course of the GOS over time for the two groups. For the ANOVA analysis 433 of the 474 observations (79 patients x 6 measurements) were available. APOE-ε4 status (p=0.041), time (p<0.001), and the interaction effect of time*APOE (p=0.031) were all significantly associated with the GOS. These associations remained significant after adjusting for age, gender, and GCS. Patients with the APOE-ε4 allele had a better recovery than patients without the APOE-ε4 allele. The adjusted overall difference between mean scores was 0.26 points (95% CI: 0.02 – 0.51, p=0.037). Further, the association between the APOE-ε4 status and the GOS differed over time (interaction p=0.033). Evaluation at the separate time points showed no significant associations at 3 and 6 months post-injury, but at 18 and 36 months post-injury a significant association was present (see Figure 1). The difference was borderline significant at 12 and 24 months. At 12 to 36 months

Table 2. Outcome scores on the GOS at 3, 6, 12, 18, 24, and 36 months post-injury for patients with and without APOE-ε4 allele

Outcome	Dead n (%)	Vegetative n (%)	Severe n (%)	Moderate n (%)	Good n (%)	Total n	P-value*
3 months							
Without ε4	0 (0)	1 (2)	16 (30)	35 (65)	2 (4)	54	0.415
With ε4	0 (0)	0 (0)	7 (41)	10 (59)	0 (0)	17	
6 months							
Without ε4	0 (0)	0 (0)	13 (23)	39 (70)	4 (7)	56	0.175
With ε4	0 (0)	0 (0)	2 (14)	9 (65)	3 (21)	14	
12 months							
Without ε4	0 (0)	0 (0)	8 (15)	36 (67)	10 (18)	54	0.054
With ε4	0 (0)	0 (0)	1 (6)	9 (53)	7 (41)	17	
18 months							
Without ε4	0 (0)	0 (0)	6 (11)	38 (67)	13 (23)	57	0.011
With ε4	0 (0)	0 (0)	0 (0)	8 (47)	9 (53)	17	
24 months							
Without ε4	0 (0)	0 (0)	5 (9)	35 (64)	15 (27)	55	0.055
With ε4	0 (0)	0 (0)	0 (0)	8 (50)	8 (50)	16	
36 months							
Without ε4	0 (0)	0 (0)	6 (10)	39 (66)	14 (24)	59	0.013
With ε4	0 (0)	0 (0)	0 (0)	8 (47)	9 (53)	17	

post-injury, patients with the APOE-ε4 allele had better mean GOS scores than patients without the APOE-ε4 allele.

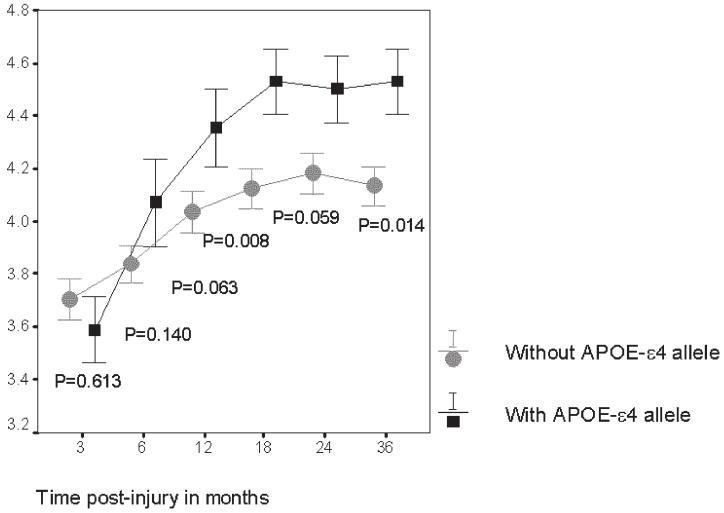

Figure 1. Course of GOS over time for the groups with and without the APOE-ε4 allele. Data shown are mean scores with standard errors. P-values are derived from ANOVA and denote differences between groups at the various time points.

SIP-68

Figure 2 presents the course on the SIP-68 over time for the two groups. For the ANOVA analysis 376 of the 474 observations were available. Although a trend was observed, no significant associations with the SIP-68 were found for APOE-ε4 status (p=0.139) and the interaction effect of time*APOE (p=0.463). Time was significantly associated with the SIP-68 (p=0.002). Also, after adjusting for age, gender and GCS, no significant associations were found with APOE.

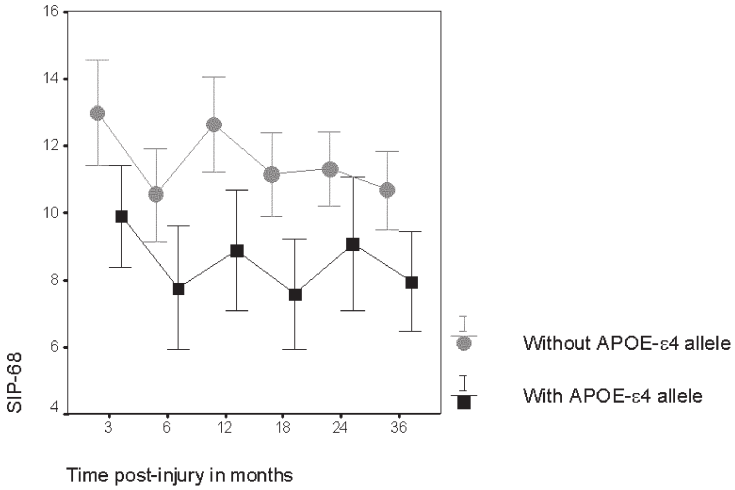

Figure 2. Course of SIP-68 over time for the groups with and without the APOE-ε4 allele. Data shown are mean scores with standard errors.

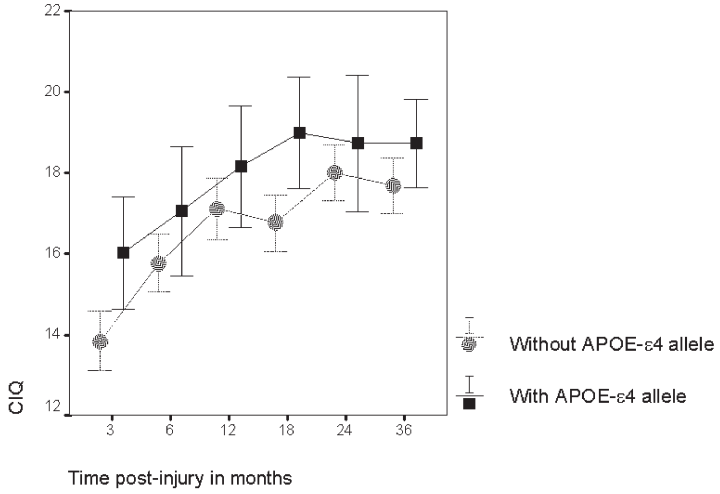

Figure 3. Course of CIQ over time for the groups with and without the APOE-ε4 allele. Data shown are mean scores with standard errors.

CIQ

Figure 3 presents the course on the CIQ over time for the two groups. For the ANOVA analysis 358 of the 474 observations were available. Although a trend was observed, no significant association with the CIQ was found for APOE-ε4 status (p=0.161) and the interaction effect of time*APOE (p=0.158). Time was significantly associated with the CIQ (p<0.001). Also, after adjusting for age, gender and GCS, no significant associations were found.

DISCUSSION

This study found that patients with the APOE-ε4 allele had a better global functional outcome, measured with the GOS, than patients without the APOE-ε4 allele, especially at 12, 18, 24, and 36 months post-injury. No significant association was found between carrying the APOE-ε4 allele and activity limitations and participation restrictions or with community integration.

It seems contradictory that several studies found a negative effect of the APOE-ε4 allele on outcome after TBI,[3,7,26] while some found no association,[10,12-14] whereas our data indicate a positive association between the APOE-ε4 allele and outcome. The major question is: has there been selection bias in our study population? Although it cannot be excluded it seems unlikely, because the baseline characteristics did not differ between the participants and non-participants. Furthermore, the series was in Hardy Weinberg equilibrium, suggesting that no major selection against the genotype has occurred.

This study has some limitations. Firstly, the sample sizes for the SIP-68 and CIQ were lower than for the GOS. Although this may have affected the results, this is not probable, while the PROC MIXED procedure corrects for missing data. Secondly, only severe and moderate TBI patients were studied. As it was procedure that all moderate and severe TBI patients were referred to the three centres, we may assume that they represent a normal population of moderate and severe TBI patients. However, it is not clear whether the results can also be generalised to mild TBI.

There are several explanations for the differences in our results and those of others. First, differences might arise because the APOE-ε4 allele induces multiple mechanisms, some with negative effects but also some with positive effects. Earlier studies hypothesised that the negative relation between APOE-ε4 and outcome could be explained by various mechanisms: decreased neurite outgrowth,[27] increased amyloid β-protein deposits,[28] and apoptosis.[29] However, several protective mechanisms induced by APOE-ε4 have also been described.

The APOE-ε4 protein was shown to activate an extracellular signal-regulated kinase cascade that results in activation of cAMP-response element binding protein and induction

of many genes including the cell-protective gene, Bcl-2.[30] Cholesterol is another potential protective mechanism. APOE-ε4 carriers are known to have elevated low-density lipoprotein and total cholesterol levels,[31] which lead to an increase in γ-glutamyltransferase, that is protective against neurotoxic effects of excitotoxic amino acids.[32]

Further, the APOE-ε4 allele might have a positive effect on neurogenesis. Studies found that the APOE-ε4 allele was associated with higher infant neurodevelopment.[33, 34] Neurogenesis not only occurs in developing nervous systems, but also in adults.[35-37] Neurogenesis was stimulated in humans trough brain diseases as focal cerebral ischemia,[38] and Huntington's disease.[39] It is possible that neurogenesis is positively influenced by the APOE-ε4 allele under circumstances of brain injury. In support of this hypothesis, we refer to a study in transgenic mice that found that APOE-ε4 positive mice, under normal housing circumstances, had increased neurogenesis compared to APOE-ε3 positive mice.[29]

A second possible explanation for discrepancies in results with studies that used the GOS,[3, 7, 26] may be found within the GOS itself. The GOS is a valuable outcome measure for determining outcome,[40, 41] but has some limitations. A limitation is that the GOS does not distinguish whether the reported changes are due to the brain injury or to co-morbidity. Particularly, figures on mortality outcome[3, 4, 7, 26] could have been overestimated as a result of co-morbidity and might have altered the relation between the APOE-ε4 allele and outcome. Another limitation is that the GOS is only assessable with patients above 16 years; several items are not applicable to children.[20] Assessment in young children would make only three of the five outcome scores possible: dead, vegetative, and good recovery. The inclusion of children[3, 26] might have influenced outcome scores and the results should therefore be interpreted cautiously.

A third possible explanation is that genetics is only one aspect of recovery. Genotype can be influenced by environmental factors, especially because polymorphisms only lead to a modest alteration of outcome.[42] Lastly, genetic association studies in general should be interpreted carefully, especially if these are based on too small samples. To exclude false-positive results it is necessary to use a significance level of $\alpha = 5 \times 10^{-8}$, in case of a large number of studied genes.[43, 44]

Finally, we found a significant association between APOE-ε4 status and the GOS, but not with the SIP-68 and CIQ. Whereas the SIP-68 and CIQ provide detailed information about limitations in functioning, the GOS only reflects how these limitations affect performance in functioning. A small limitation, which reduces performance, has a major impact on the GOS score whereas it has a much smaller impact on the SIP-68 and CIQ score. This might explain why we found different results for the different outcome measures.

Conclusion

We found a positive association between the APOE-ε4 allele and outcome at the GOS, especially on the long term. We found no association between APOE-ε4 status and outcome on the SIP-68 and CIQ. We have argued that multiple and in some cases competitive mechanisms may explain the variable relation between the APOE-ε4 allele and outcome after TBI. Further research is warranted on this subject.

Acknowledgements

We thank Jeannette Vergeer and Alejandro Arias of the Department Epidemiology and Biostatistics of the Erasmus MC for their help in DNA extraction and genotyping.

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Chapter 4

Community integration following moderate to severe traumatic brain injury

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Submitted

ABSTRACT

Objective: To evaluate the course and identify determinants of community integration up to three years following moderate to severe traumatic brain injury.
Design: Prospective cohort study.
Patients: 119 moderate to severe traumatic brain injury patients aged 16 to 67 years
Methods: The Community Integration Questionnaire was completed at 3, 6, 12, 18, 24, and 36 months post-injury. Repeated measures analysis of variance was performed to determine changes over time in the Community Integration Questionnaire and its subscales. Multivariate regression analysis was used to identify determinants of community integration 36 months post-injury.
Results: Compared to pre-injury, mean home integration, social integration, productivity, and total questionnaire scores decreased three months post-injury. Patient scores showed maximal improvement during the first year post-injury. Mean home integration, productivity, and total scores increased to a lesser extent during years 1 to 3 post-injury. Age, Barthel Index scores, and pre-injury questionnaire scores were the major determinants of community integration 36 months post-injury (R^2=52%).
Conclusion: After an initial decline, mean Community Integration Questionnaire scores gradually improve following moderate to severe traumatic brain injury. Understanding the course and determinants of community integration is needed to determine functional prognosis following traumatic brain injury.

INTRODUCTION

Outcome following traumatic brain injury (TBI) can vary from complete recovery to death, with many survivors having long-term disabilities [1]. Information regarding the course and prognosis following TBI is necessary to determine which patients are at risk for unfavourable outcomes, and to optimise the use of limited health care and social resources. For TBI patients and their families, early prognostic information is important for coping and anticipating long-term consequences. To date, most studies on TBI patients have focused on short-term outcomes. Although a recent review addressed prognostic factors of long-term activity limitations and participation restrictions [2], the clinical and sociodemographic determinants of such restrictions are unknown.

Participation, or involvement in a life situation [3], is an important outcome following TBI. However, measuring participation is a challenge. Participation is a multilayered concept encompassing such domains as mobility, domestic life, interpersonal interactions and relationships, as well as community, social and civic life. The Community Integration Questionnaire (CIQ) [4] has been used to assess participation in TBI patients [5].

Several clinical and sociodemographic factors may be related to community integration. Clinical determinants of poor community integration following TBI include a more severe injury, poorer functional performance and disability, extended post-traumatic amnesia [6,7], prolonged acute hospital stay [6], loss of emotional control [7], poor cognition [6,8], poor physical condition [6], poor pre-morbid functioning [8], and severe limitations to activity [6,7]. Furthermore, patients injured by a violent mechanism have lower levels of community integration [9], whereas patients injured by motor vehicle accidents have higher community integration levels [10].

Relevant sociodemographic determinants of community integration are male gender, living with others, emotional distress [5], being member of a minority race [11-13], lower educational level [9,12], and unemployment at the time of injury [9,12]. Some studies show that older age is a risk factor for poor community integration [6,12], whereas one study reported that younger patients were at higher risk for poor community integration [7].

Most studies of community integration following TBI used a limited follow-up of one year [8-12,14]. Two studies have used longer follow-up periods but had retrospective designs [6,7]. Only one study had a follow-up of 3 to 4 years and used a prospective design; however, the sample size was small [15]. It is also unclear whether outcome following TBI stabilizes one year post-injury or whether community participation levels change over time. Hammond et al [16] found that, although the majority of patients remained stable during years 1 to 5 post-injury, some made dramatic gains, whereas a minority declined. In contrast, a study by Sander et al. [15] showed no changes in community integration between the first and third or fourth year. The present study was conducted to 1) evaluate

the course of participation after moderate to severe TBI until 36 months post-injury, and 2) identify determinants of community integration at 36 months post-injury.

METHODS

Procedure

The study consecutively enrolled 119 TBI patients between January 1999 and April 2004 at three Dutch level-one trauma centres: Erasmus Medical Centre, Rotterdam (January 1999 to April 2004); Medical Centre Haaglanden, The Hague (January 2003 to February 2004); and University Medical Centre Utrecht, Utrecht (April 2003 to February 2004) [17]. All study sites were regional TBI treatment centres and for all moderate and severe TBI patients within their regions. Patients were treated in accordance with the European Brain Injury Consortium guidelines [18].

Upon admission, acute TBI patients or family members received verbal and written information about the study and were asked if they were willing to participate. When possible, patients gave informed consent. Otherwise, a family member gave informed consent and patients were asked to give consent at a later time. The Medical Ethics Committee of Erasmus MC approved this study.

Baseline measurements were collected at hospital admission and patients were followed prospectively at 3, 6, 12, 18, 24, and 36 months post-injury. Two study psychologists collected data using structured interviews at the patients' homes or at the nursing or rehabilitation facility where the patient resided. If a patient interview was not possible, a family member or professional caregiver was interviewed.

Patients

Inclusion criteria were: (1) admission to a hospital for moderate (Glasgow Coma Scale (GCS) [19] of 9 to 13) or severe (GCS of 3 to 8) TBI due to a blunt or penetrating trauma; (2) aged 16 to 67 years; and (3) survival until discharge from hospital. Exclusion criteria were: (1) insufficient knowledge of the Dutch or English language to participate in the study; or (2) serious pre-traumatic neurological, oncological, or systemic impairments (e.g. spinal cord injury, psychiatric disorder, cancer) that may interfere with TBI-related disability assessment.

Measures

Community integration

Community integration was assessed using the CIQ, which is designed specifically to assess issues affecting TBI patients [4, 20]. The survey consists of 15 questions about how

certain activities are usually performed (alone, with another person, or by someone else), and how frequently these activities are performed. Total scores vary from 0 to 29, with higher scores indicating better community integration. The CIQ addresses three domains: home integration (range 0 to 10), social integration (range 0 to 12), and productivity (0 to 7). The reliability and validity of the CIQ has been well established [4, 21-24]. The CIQ was designed to assess community integration in non-institutionalised patients; therefore, the CIQ was not assessed at times that patients were admitted in a nursing or rehabilitation facility following hospital discharge.

Independent variables

Potential sociodemographic and clinical determinants were identified by reviewing the published literature. Sociodemographic characteristics assessed included age in years, sex, pre-injury residence (alone versus with others), nationality (Dutch versus other nationality), pre-injury education level (secondary versus post-secondary education), and pre-injury work status (employed versus not employed). Pre-injury community integration levels were assessed retrospectively. Clinical characteristics assessed included lowest GCS score within 24 hours of injury, cause of injury (motor vehicle accident versus other cause), length of stay in hospital (in days), discharge destination following hospital discharge (home versus institution), and computed tomography (CT) results (normal versus abnormal). Presence or absence of hypoxia ($PaO_2 \leq 8$; $SaO_2 \leq 90\%$), hypotension (systolic blood pressure ≤ 90 mm Hg), and hypothermia (≤ 35°C) at admission was noted; a clinical diagnosis was also considered sufficient evidence of these conditions.

Post-acute functional measures included the Barthel Index (BI) [25] and the Functional Independence Measure plus Functional Assessment Measure (FIM+FAM) [26]. The BI and FIM+FAM scores at time of hospital discharge were used if available. Otherwise, three month post-injury scores were used. The BI, which has good reliability and validity [27], consists of 10 items on activities of daily living (e.g. bowel and bladder status, grooming, dressing, and bathing) each with two or four response categories (0 to 3 points). Total scores range from 0 (severely restricted) to 20 (no restrictions). The FIM+FAM, which has good reliability and validity [28-31], consists of 30 items that are evaluated on a seven-point scale (completely independent to totally dependent). The FIM+FAM evaluates motor and cognitive functioning with respect to self-care, sphincter control, transfers, locomotion, communication, psychosocial adjustment, and cognitive functioning. Total scores range from 30 (totally dependent) to 210 (totally independent).

Statistical analysis

Descriptive analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 12.0.1. Baseline characteristics for participants and non-participants

were compared using the Mann-Whitney U test for continuous variables and chi-square test for categorical variables.

To determine if the course changed over time for home integration, social integration, productivity, and total CIQ, a repeated measures analysis of variance (ANOVA) was performed using the PROC MIXED procedure in SAS 8.2. The advantage of this procedure is that it does not require complete follow-up data. For all patients, time was included as a categorical variable in the model to test changes over time.

To identify possible predictors of total CIQ score at 36 months, we first tested all independent variables for univariate relationships using SPSS 12.0.1. Univariate relationships between community integration and independent variables were tested with Spearman correlations for continuous variables and with t-tests for dichotomous variables. Because of the small sample size and relatively large number of independent variables, we selected variables only with $P < 0.10$ for the multivariate analysis. P=.05 (two-sided) was chosen as the level of significance.

RESULTS

Population

Table 1 presents baseline characteristics, post-acute functional level, and pre-injury CIQ for the study participants (n=119). The mean age was 34 years; the male to female ratio was 3:1; most patients were of Dutch nationality; most patients lived with a partner or parent; mean GCS score was 7.1; and 94% had an abnormal CT scan. During the post-acute stage, the mean BI score was 16 and the mean FIM+FAM score was 167. The mean pre-injury CIQ score was 19.3.

CIQ measurements were available for 91 patients pre-injury, 52 patients at 3 months, 65 patients at 6 months, 82 patients at 12 months, 85 patients at 18 months, 84 patients at 24 months, and 94 patients at 36 months. At the 36-month follow-up, 25 measurements were unavailable because 3 patients had died, 16 were lost to follow-up, 4 were residing in an institution, and 2 were not assessed due to logistical problems. Patients that completed 36-monhts follow-up had a higher education level (p=.020), were more likely to be employed prior to injury (p=.017), and were more likely to have an episode of hypoxia (p=.017), than the patients that did not complete the final follow-up (n=25). There were no other significant differences between participants and non-participants.

Community integration

Figure 1 shows the course of home integration, social integration, productivity, and total CIQ from pre-injury to 36 months post-injury. Time was significantly associated with

Table 1. Characteristics of moderate and severe traumatic brain injury patients (n=119)

Patient characteristic	
Age in years: mean (SD)	34 (13.2)
Sex: men:women (n:n)	86:33
Dutch nationality: n (%)	111 (93)
Lived alone pre-injury: n (%)	17 (14)
Low pre-injury education level: n (%) *	58 (50)
Employed pre-injury: n (%) *	93 (80)
Pre-injury home integration: mean (SD)*	4.9 (3.3)
Pre-injury social integration: mean (SD)*	8.9 (2.1)
Pre-injury productivity: mean (SD)*	5.7 (1.3)
Pre-injury total CIQ: mean (SD)*	19.3 (4.3)
Motor vehicle accident cause of injury: n (%) *	85 (73)
GCS score: mean (SD)	7.1 (3.0)
Length of hospital stay in days: median (range)	32 (4-173)
Discharge from hospital to institution: n (%)	62 (52)
Abnormal CT pattern: n (%)	97 (94)
Hypoxia present: n (%) *	32 (32)
Hypotension present: n (%) *	12 (12)
Hypothermia present: n (%) *	16 (21)
FIM+FAM: mean (SD)*	167 (39.1)
Barthel Index: mean (SD)*	16 (5.9)

*Data missing for: living status (n=1), education level (n=4), pre-injury work status (n=3), pre-injury home integration (n=27), pre-injury social integration (n=28), pre-injury productivity (n=27), pre-injury total CIQ (n=28), cause of injury (n=2), CT pattern (n=16), presence of hypoxia (n=20), presence of hypotension (n=21), presence of hypothermia (n=44), FIM+FAM (n=8), Barthel Index (n=6).

home integration (p<.001), social integration (p<.001), productivity (p<.001), and total CIQ (p<.001).

Regarding home integration, 558 out of a potential 833 scores (119 patients x 7 time points) were available for ANOVA. Compared to pre-injury, the mean home integration score decreased at three months post-injury (decrease 1.30 points, SE=0.33, p<.001). At six months post-injury, home integration scores improved but the mean level remained below the mean pre-injury level (p=.019). At 12 months, mean home integration scores attained pre-injury levels; a modest increase beyond pre-injury levels occurred during the subsequent 24 months (p=.014).

For social integration, 555 scores were available for ANOVA. Compared to pre-injury, the mean social integration score decreased three months post-injury (decrease 1.00 points, SE=0.23, p<.001). The mean social integration score stabilised at the three-month level, experienced a small increase at 24 months post-injury, but remained low compared to pre-injury levels at the 36-month follow-up (difference 0.69 points, SE=0.21, p=.002).

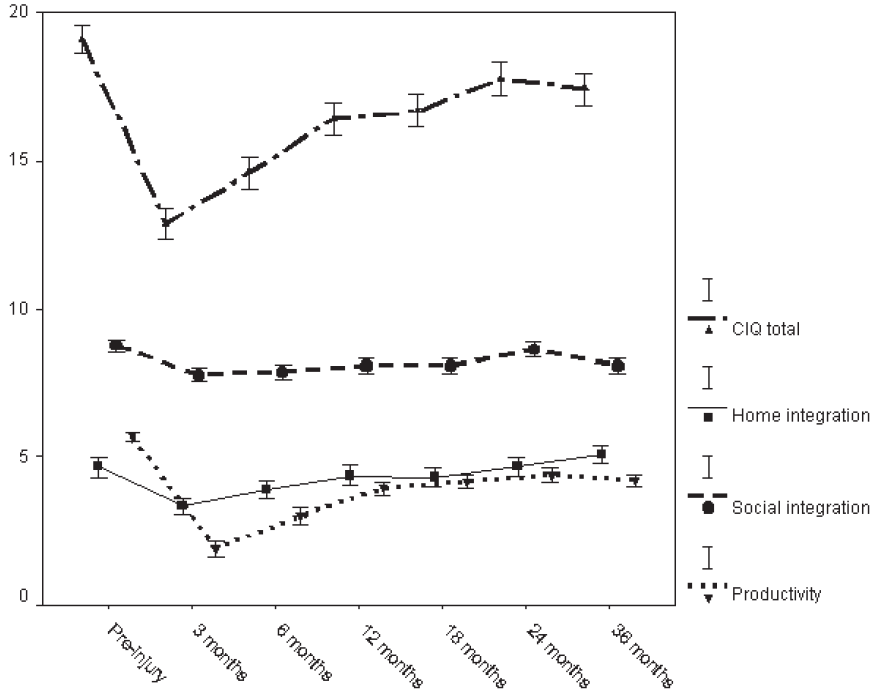

Figure 1. The course of total CIQ, home integration, social integration, and productivity scores from pre-injury to 36 months post-injury. Data are presented as means (+/- SEM), as calculated by ANOVA.

For productivity, 558 scores were available for ANOVA. Compared to pre-injury, the mean productivity score decreased three months post-injury (decrease 3.69 points, SE=0.28, p<.001). Subsequently, mean productivity level increased at 6 and 12 months post-injury, stabilised, then experienced a small increase at 24 months post-injury. At 36 months post-injury, the mean productivity level remained significantly low compared to the mean pre-injury level (difference 1.45 points, SE=0.20, p<.001).

For total CIQ, 553 scores were available for ANOVA. Compared to the mean pre-injury level, the mean community integration score decreased three months post-injury (decrease 6.20 points, SE=0.50, p<.001). Subsequently, mean community integration scores significantly increased at 6 and 12 months, then stabilised. Increased mean levels of community integration were noted at 24 months and remained stable at 36 months.

Determinants of community integration

Table 2 presents univariate results between independent variables and 36-month post-injury CIQ scores. The following patients had lower community integration scores 36 months post-injury: males, older patients, those living with others pre-injury, those with longer hospital stays, those with abnormal CT scans, those with low post-acute BI scores (more dependence), those with low post-acute FIM+FAM scores (more dependence),

Table 2. Univariate linear regression analyses for CIQ at 36 months post-injury (n=94)

Predictive variable	**Univariate analysis**	
		p-value
Sociodemographic characteristics		
Age in years	-0.32	<.002
Sex		
Male	16.97 (0.68)	.012
Female	19.50 (0.71)	
Nationality		
Dutch	17.82 (0.54)	.580
Other	16.50 (3.05)	
Living status		
Alone	21.00 (1.06)	.018
With parent or partner	17.27 (0.57)	
Pre-injury education level		
Secondary	16.96 (0.78)	.167
Post-secondary	18.45 (0.73)	
Pre-injury work status		
Employed	17.84 (0.61)	.596
Unemployed	17.04 (0.93)	
CIQ pre-injury*	0.54	<.001
Clinical characteristics		
Cause of injury		
Motor vehicle accident	17.65 (0.61)	.945
Other	17.74 (1.09)	
Glasgow Coma Scale	0.054	.605
Length of hospital in days	-0.19	.062
Destination following hospital discharge		
Home	19.16 (0.61)	.009
Institution	16.45 (0.82)	
Computed Tomography		
Abnormal	17.50 (0.55)	.007
Normal	23.55 (1.56)	
Hypoxia		
Present	18.69 (1.04)	.311
Absent	17.51 (0.65)	
Hypotension		
Present	17.77 (1.78)	.923
Absent	17.94 (0.60)	
Hypothermia		
Present	17.04 (1.66)	.651
Absent	17.77 (0.704)	
Post-acute functioning		
FIM+FAM*	0.33	<.001
Barthel Index*	0.37	<.001

Results for continuous data calculated by Spearman correlation. Results for categorical data calculated as means (SEM).

*CIQ pre-injury (n=83); FIM+FAM (n=91); Barthel Index (n=91)

Table 3. Multivariate model for predicting community integration at 36 months post-injury. Results are presented as regression coefficients (β) with 95% confidence intervals (CI) and p-values.

Predictive variable	β	95% CI (β)	p-value
Intercept	4.55	-9.7; 10.07	
Age in years	-0.09	-0.16; -0.03	.005
Barthel Index	0.34	0.19; 0.49	<.001
Pre-injury CIQ	0.56	0.37; 0.75	<.001

those with low pre-injury CIQ scores, and those who were discharged to an institution. As expected, the BI and FIM+FAM scores were strongly correlated (Spearman rho=0.79, p<.001), and therefore could not be entered simultaneously into the multivariate analysis. We chose the BI score for the multivariate model because the questionnaire requires less time to administer, and therefore would be more valuable in clinical practice.

Table 3 shows the multivariate results for community integration at 36 months post-injury. Age, BI score and pre-injury CIQ score were the major determinants of community integration and explained 52% of the variance. The addition of age and BI score to the model explained more variance than the pre-injury CIQ score alone (which explained 31% of the variance). Older age, a lower BI score (more dependence), and lower pre-injury CIQ score predicted lower levels of community integration. No further model improvements were found by adding other independent variables. When the FIM+FAM was entered into the model in place of the BI, a model with similar predictive value was found; age, pre-injury CIQ score and the post-acute FIM+FAM score determined community integration (explained 53% of the variance).

DISCUSSION

In this prospective study we evaluated the course of community integration from pre-injury to 36 months post-injury for moderate to severe TBI patients. Furthermore, we identified determinants of community integration at 36 months post-injury. All CIQ subscales initially declined following injury, but slowly increased over time. Maximal improvement occurred during the first year following injury, but several domains showed small improvements between years 1 and 3 post-injury. Some increases were transient and non-sustained at 36 months.

Because there are no standardised normal values for CIQ, some researchers [32, 33] have used a non-disabled sample as a referent to interpret findings in TBI patients [4]. Others have used retrospectively collected pre-injury CIQ scores [13]. Pre-injury CIQ scores and non-disabled CIQ scores range from 17.4 to 20.5, whereas post-injury TBI patient CIQ scores range from 13.0 to 17.7 [4, 13, 20, 33]. Our findings for pre-injury and post-injury CIQ scores were consistent with these previously reported ranges. Our finding

that participation modestly increased one year following TBI contrasts with a longitudinal study by Sander et al., which showed no changes in community integration between the first and third or fourth year [15]. Differences in study populations and power may explain this difference.

Pre-injury community integration, age, and the post-acute BI score were the major determinants of community integration at 36 months post-injury in this study. Our finding that older persons had lower community integration levels is consistent with other studies [6, 11, 12, 14]. This may be partly explained by the observation that most persons reduce their activity patterns as they age. Another possibility is that older patients have a poorer recovery compared to younger patients, which leads to participation restrictions. The post-acute BI score was a significant predictor of community integration in this study. Previous research indicates that post-acute functional factors predict several aspects of community integration at one year post-injury [15, 34] but not at two or three to four years post-injury[15]. Post-acute functional measures have also predicted long-term disability and productivity level [21].

In contrast to several other researchers [8, 9, 12, 14], we found no prognostic value for pre-injury work status. However, 80% of our study participants were employed prior to injury; this percentage is much higher compared to other studies. It is possible that the effect of pre-injury employment could not be detected due to small sample variability.

Pre-injury education level and nationality were not predictive in this study, although they were found to be predictors in other studies [9, 11-13]. No prognostic value was found for the GCS score in this study of moderate to severe TBI patients. However, the GCS has predicted community integration in a study including also mild TBI patients [8]. Discharge to an institution and abnormal CT scan showed univariate relationships with community integration, whereas cause of injury, presence of hypoxia, presence of hypotension and presence of hypothermia did not.

Multivariate analysis did not show that any of these clinical characteristics were significant determinants of community integration. According to the International Classification of Functioning, Disability and Health (ICF) [3] published by the World Health Organization, activities and participation restrictions are determined by many factors. These include disease factors such as injury severity, as well as personal factors and environmental factors, which are especially useful in predicting long-term outcome. Although most clinical characteristics were predictive for short-term outcome, they may be less important than personal or environmental factors (e.g. coping style, social environment, and depression) in predicting long-term outcome. Others have concluded that injury severity may be a less important predictor than pre-morbid status and six-month post-injury cognitive status [15, 34].

Pre-injury community integration level, age, and the post-acute BI can assist clinicians in identifying which patients are at risk for poor community integration and who might

benefit from additional care or long-term facility placement. This information would also assist clinicians in providing more detailed information regarding functional prognosis. In our study sample, patients with low pre-injury community integration, older age, or low post-acute BI were at risk for long-term community integration problems.

This study has some limitations. Although the CIQ is considered sensitive for measuring differences between diagnoses, it is not yet evident whether the CIQ is sensitive to changes over time [35]. Furthermore, standardised normal values for the CIQ do not exist. Previous studies assessing the CIQ cross-sectionally presented challenges in determining whether statistically significant changes were clinically relevant. Although drawing conclusions is difficult, the decline in community integration at three months post-injury was relatively large. When we divided the differences in pre-injury scores and three-month post-injury scores, trough the range of the subscale, we found a 21.5% decrease in total CIQ (13% for home integration, 8% for social integration, and 53% for productivity). Except for social integration, these changes all seem clinically relevant. Future research on the psychometric properties for sensitivity to change and the development of normative values will provide more information about the interpretation of such results. Another limitation of the CIQ is that it can only be used in non-institutionalised patients. Therefore, patients living in an institution were not assessed for community integration and results can only be generalised to non-institutionalised patients.

Additionally, there were differences in baseline characteristics between participants and patients lost to follow-up. Loss to follow-up is a common problem in both prospective cohort studies and TBI studies and can lead to selection bias. Socioeconomically disadvantaged patients are more likely to be lost to follow-up, whereas more severely injured patients have less loss to follow-up [36]. We found a similar pattern in that non-participants had lower education levels, were less likely to be employed pre-injury, and were less likely to experience hypoxia. The loss to follow-up might have resulted in selection bias, and therefore generalisations should be done cautiously.

Finally, our sample size was relatively small; therefore, some determinants may have been undetectable. However, adding variables to the major determinants (age, BI, and pre-injury community integration) did not further improve the model.

In conclusion, TBI patients experienced significant declines in community integration following TBI, but slowly improved for most domains over time. Although maximal improvement occurred during the first year post-injury, improvements for most domains also occurred beyond one year. Lower pre-injury community integration, older age, and lower BI scores were associated with lower community integration. Eventually, these determinants may be useful additional tools to determine which patients are at risk for poor community integration and would benefit from additional care or long-term facility placement.

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Chapter 5

Is there equity in long-term healthcare utilisation after traumatic brain injury?

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Accepted in Journal of Rehabilitation Medicine

ABSTRACT

Objective: To quantify the long-term use of various types of healthcare services in traumatic brain injury (TBI) patients, and secondly to estimate the relative contribution of predisposing characteristics, enabling factors and health-related needs to determine whether there is equity in healthcare utilisation.
Design: Cross-sectional study.
Patients: 79 non-institutionalised moderate to severe TBI patients (aged 16-67 years).
Methods: Healthcare use was measured at 3-5 years post-injury. The relative contribution of predisposing characteristics, enabling factors, and health-related needs to the utilisation of various types of care was analysed with logistic regression to determine whether there was equity in healthcare utilisation.
Results: At least one healthcare service was used by 68% of the patients. Health-related needs explained most of the utilisation. However, predisposing characteristics were also related to the use of other medical care and supportive care. Patients with a high internal locus of control were more likely to be users of supportive care, and patients with a high locus of control with the physician were more likely to visit medical specialists.
Conclusion: The results suggest that most of our patients who needed care, received care. However, inequity could not be totally ruled out as predisposing characteristics also contributed to some types of healthcare utilisation.

INTRODUCTION

Approximately 1.6 million traumatic brain injury (TBI) patients are admitted to hospital on a yearly basis in Europe [1,2]. The outcome after TBI can vary from complete recovery to death, with many patients having long-term physical, cognitive and psychosocial disabilities. A Dutch follow-up study showed that the majority of mild to moderate TBI patients experienced situational, cognitive, emotional and behavioural disabilities at 3-7 years post-injury [3]. About 41% experienced related participation restrictions [4], and needed various healthcare services. Information on health care needs and health care services that are used at the long term are crucial for adequate planning of long-term care. Further, it is important to determine if health care is delivered to patients that require services.

To assure equity in healthcare utilisation, it is important to evaluate whether the limited healthcare services are used by those patients that need them the most. According to the model of Andersen, healthcare utilisation depends on: 1) predisposing characteristics, 2) enabling factors, and 3) health-related needs [5,6]. Predisposing variables reflect a person's preposition to use services. Predisposing variables comprise demographic variables (e.g. age, gender), health beliefs, and coping styles. Enabling factors determine whether healthcare services are available (e.g. income, availability of services where people live, insurance, etc.). Need factors represent the most immediate cause for health service use, reflected by perception of illness, symptoms, diagnosis, and functioning [7]. The model was designed to explain the use of services rather than to focus on important interactions that take place as people receive care, or on health outcomes [6]. The model of Andersen has been used to evaluate equity in health care utilisation in chronic diseases like stroke, rheumatoid arthritis, heart disease, and diabetes [8-11]. Equitable access to health care services is occurring when demographic and need variables account for most of the variance in utilisation; this is an indication that patients receive the care they need. Inequitable access is demonstrated when care is explained by social structures, health beliefs, or enabling factors [5,6].

A review on predictors of health care utilisation in the chronically ill, reported that health related needs were the most important predictors of health care utilisation, whereas predisposing characteristics (age, sex, and marital status) and most enabling factors (income, insurance, and social support) were not predictive [11]. In patients with myocardial infarction and in elderly patients, locus of control was also associated with health care utilisation [12,13]. Studies in TBI populations identified the following predictors of health care utilisation: severity of injury [14-16], physical and cognitive disability, psychosocial disability [14], sex, years of education, a longer length of stay in hospital, admittance to a hospital or rehabilitation centre for TBI [15], and motor deficits at discharge from inpatient rehabilitation [16]. However, these studies had some limitations for evaluating

equity in health care utilisation: only health related needs were investigated [14], TBI was diagnosed retrospectively with self-reports [15], and health care utilisation was estimated with the amount that was billed to Medicaid [16].

Therefore, the aims of this study are: 1) to quantify the use of various types of healthcare services in non-institutionalised moderate and severe TBI patients 3-5 years post-injury, and 2) to estimate the relative contribution of predisposing characteristics, enabling factors, and health-related needs in order to determine whether there is equity or inequity in healthcare utilisation. Given the principle of equity in health care – one of the basic quality indicators of the Dutch health care system – it is hypothesized that health care utilisation is mainly determined by health related needs.

METHODS

Procedure

For the present cross-sectional study a subsample of 79 patients was included from the cohort that was recruited in the Rotterdam TBI study [17]. In the Rotterdam TBI study, 119 TBI patients were consecutively enrolled from January 1999 to April 2004 in 3 medical centres: Erasmus Medical Centre in Rotterdam (entire period), University Medical Centre Utrecht (enrolment from April 2003 to February 2004), and Medical Centre Haaglanden in The Hague (enrolment from January 2003 to February 2004). The 3 centres served as treatment centres for all moderate and severe TBI patients within their region. Patients were treated in accordance with the European Brain Injury Consortium guidelines [18].

For the Rotterdam TBI study, patients were prospectively followed-up at 3, 6, 12, 18, 24, and 36 months from April 1999 to April 2007. For this study the 36 month follow-up measurements were used. All data, except for the questionnaire on health care utilisation, were collected in a structured interview at the participant's home or institution of admittance by two study psychologists. In cases where patients suffered from serious communication impairments, a significant other or professional caregiver was interviewed. The questionnaire on healthcare use was added to the structured interview at the regular follow-up measurement of 3 years in October 2003. As 39 patients were followed-up by that time, these patients were sent the health care questionnaire by mail up to 5 years post-injury. For these 39 patients, the other data were already collected in the structural interview at the regular follow-up.

Patients

Inclusion criteria of the Rotterdam TBI study were: 1) admittance in hospital for moderate or severe TBI due to blunt or penetrating trauma (Glasgow Coma Scale (GCS) [19] score of 9-13 or 3-8, respectively); 2) age at onset between 16 and 67 years; 3)

survival until discharge from hospital. Exclusion criteria were: 1) insufficient knowledge of the Dutch language to participate in the study; 2) serious pre-traumatic neurological, oncological or systemic impairment (e.g. spinal cord injury, psychiatric disorders, cancer) that might interfere with the assessment of TBI-related disability. For the present study, only non-institutionalised patients were included. All patients received verbal and written information about the study and signed an informed consent form. The Medical Ethics Committee of Erasmus MC approved the study.

Measures

Healthcare utilisation

Utilisation of health care was assessed for a wide range of 16 healthcare services. Patients were asked if they had used these healthcare services in the last year (scored as 'yes' or 'no'). We selected healthcare services that were relevant in multidisciplinary care for chronic diseases, and in particular for TBI such as a neurologist, a rehabilitation physician, a psychologist, or an activity centre. If necessary, patients were assisted by the study psychologist or a family member. Because of the small numbers, the studied healthcare services were aggregated according to care function into four categories: 1) general practitioner (GP), 2) medical specialists (neurologist/neurosurgeon, urologist, eye physician, and other medical specialists), 3) rehabilitation care (rehabilitation physician, physiotherapist, occupational therapist, speech therapist, social worker, and psychologist), and 4) supportive care (home nurse, home help, activity centre, day care, and patient organisations). The scores were dichotomised into 'use' or 'no use'. In addition, the total number of all care services was calculated. Total care use was dichotomised on the fourth quartile into 'high use' and 'low care use'.

Independent variables

Predisposing characteristics encompass: age at injury in years, gender, living situation (with or without partner), and health beliefs. Health beliefs were assessed with the Multidimensional Health Locus of Control Scales (MHLCS) [20]. The MHLCS consist of 3 separate scales: internal locus of control, locus of control with a physician, and locus of control with chance. The scales indicate how much patients believe that the health status is influenced by themselves, a physician, or by chance. A higher score indicates that the patient attributes more influence to that factor. The scores were dichotomised into high and low locus of control on the median scores of the patients.

Enabling factors encompass: work status (working vs. not working), level of education (lower or junior secondary education vs. higher education), urbanisation level (rural or urban), and social support. Received social support was measured with the Social Support Scale (SSL) [21]. Subjects are asked to fill in a 4-point scale on how often they

experienced a certain type of social support. The scores range from 34 to 136, where a higher score indicates more experienced social support. Scores were dichotomised on the median score into high or low social support.

Health-related factors encompass: clinical aspects, and aspects of functioning and disabilities as described in the International Classification of Functioning Disability and Health (ICF) [22]. The following clinical factors were assessed: TBI severity (GCS score) and co-morbidity. Co-morbidity was measured with the Cumulative Illness Rating Scale (CIRS). The CIRS is a valid and reliable instrument that rates 13 body systems on a 5-point scale (no impairment to life-threatening impairment) without using specific diagnoses [23]. The numbers of body systems that had a score of 1 or higher were accumulated to a sum score for co-morbidity. Medical symptoms of TBI were not considered as co-morbidity.

Cognitive and motor functioning was determined with the Functional Independence Measure combined with the Functional Assessment Measure (FIM+FAM) [24]. The FIM+FAM consists of 30 items with a 7-point scale (completely independent to totally dependent) on the domains self-care, sphincter control, transfers, locomotion, communication, psychosocial adjustment, and cognitive functioning. At 3 years post-injury many patients had ceiling effects on the FIM+FAM. Hence we used a relatively high cut off value of 180, which corresponds to an average item score of 6 (modified independence, needing more time or devices). Scores were dichotomised into lower than 180 (indicating limitations in functioning) and 180 and above (indicating independence in functioning).

The presence of depression was measured with the Wimbledon Self-Report Scale (WSRS) [25]. The WSRS consists of 30 questions on how often a certain feeling was felt in the past 4 weeks (most of the time, quite often, only occasionally, not at all). The items are transformed into a 2-point scale with a maximum score of 30. Scores ranging from 0 to 7 are considered as normal functioning, scores ranging from 8 to 10 are considered as borderline for mood disorders, and scores of 11 to 30 are considered as cases with a clinically significant mood disorder. The scores were dichotomised into lower or equal to 7 indicating no depression, and above 7 as depression.

Participation restrictions were assessed with the Sickness Impact Profile-68 (SIP-68) [26], which has 68 statements on behaviour, feelings, and functions. The Respondents are asked if these statements apply to their current situation (yes/no) and whether they are health related. The SIP-68 score is calculated by summing all positively scored items (range 0-68). A higher score indicates more participation restrictions. The SIP-68 has excellent test-retest reliability (ICC=0.97) [27]. The SIP-68 was originally not primarily intended to measure participation restrictions but was developed to measure functional health status. However, the version from which the SIP-68 was derived, the Sickness Impact Profile-136 (SIP-136) [28], covered a broad bandwidth of different ICF categories and among them the category activities and participation is represented most extensive [29]. Despite the limitation that the SIP-68 also measures other ICF categories, we consid-

ered it suitable for measuring participation restrictions. The SIP-68 was dichotomised on the median into restricted or not restricted in participation.

Community integration was determined with the Community Integration Questionnaire (CIQ) [30], which assesses daily activities in the home, social environment, and in work or education. It contains 15 questions on how activities are usually performed (alone, with another person, by someone else) and how frequently activities are done. The score ranges from 0 to 29, with a higher score indicating better community integration. The reliability of the CIQ is sufficient [31]. The CIQ was dichotomised on the median into high or low community integration.

Statistical analysis

Descriptive statistics were performed with SPSS 12.0.1. Four separate logistic regression analyses were performed for each of the 4 types of care and for high total use of care.

First, the association between the independent variables and the 4 types of care and total care were tested with χ^2 tests. Effect sizes were expressed with odds ratios (ORs) and 95% confidence intervals (95%CI). Because the sample was relatively small and there were many independent variables, we set the criterion for inclusion in the multivariate model at 0.10. Variables that were selected for the multivariate model were tested for interrelations with spearman's rho. If there were interrelations (spearman's rho $\geq$ 0.80) between a type of factors (pre-disposing, enabling, or need factors), than the highest contributor was selected for the multivariate model. If there were interrelations (spearman rho $\geq$ 0.80) between types of factors, multiple models were built in order to investigate the influence of the contributing factors.

Second, the selected independent variables were analysed with a backward logistic regression analyses. A p-value below 0.05 was considered significant.

RESULTS

Study population

Of the 119 TBI patients included in the Rotterdam TBI study, 4 patients were institutionalised, 3 were deceased, and 16 patients were lost at the time of follow-up. Of the 96 eligible patients, 79 (82%) patients filled in the healthcare utilisation questionnaire at 3-5 years post-injury. Seventeen patients had not returned their questionnaire. Compared with non-participants, participants had a more severe initial injury (lower GCS score) (p=0.040) and higher education levels (p=0.034). There were no significant differences for the other independent variables between participants and non-participants.

Table 1 presents the characteristics of the study participants: mean age was 35 years, there were twice as many males as females, and the majority (72%) lived with a partner

Table 1. Characteristics of all participating patients (n=79)

Patient characteristics	
Age in years, mean (SD)	35 (13.3)
Gender	
Male, n (%)	54 (68)
Female, n (%)	25 (32)
Living situation	
Without partner or parent, n (%)	22 (28)
With partner or parent, n (%)	57 (72)
Internal locus of control (n=67)	
Low (MHLCS internal ≤ 22), n (%)	32 (48)
High (MHLCS > 22), n (%)	35 (52)
Locus of control with a physician (n=67)	
Low (MHLCS physician ≤ 15), n (%)	31 (46)
High (MHLCS physician >15), n (%)	36 (54)
Locus of control with chance (n=67)	
Low (MHLCS chance ≤ 17), n (%)	32 (48)
High (MHLCS chance > 17), n (%)	35 (52)
Education (n=78)	
Low (lower or junior secondary education), n (%)	31 (40)
High (higher than junior secondary education), n (%)	47 (60)
Work status at follow-up	
Not working, n (%)	34 (43)
Working, n (%)	45 (57)
Urbanisation level	
Rural, n (%)	26 (33)
Urban, n (%)	53 (67)
Social Support	
Low (SSL ≤ 72), n (%)	34 (50)
High (SSL > 72), n (%)	34 (50)
Glasgow Coma Scale, mean (SD)	6.7 (3.0)
Co-morbidity (n=77)	
Present, n (%)	57 (74)
Absent, n (%)	20 (26)
Functioning	
Limitations (FIM+FAM < 180), n (%)	7 (9)
Independent (FIM+FAM ≥ 180), n (%)	72 (91)
Depression (n=77)	
Present (WSRS > 7), n (%)	10 (13)
Absent (WSRS ≤ 7), n (%)	67 (87)
Participation (n=78)	
Restricted (SIP-68 > 9), n (%)	40 (51)
Not restricted (SIP ≤ 9), n (%)	38 (49)
Community integration	
Low integration (CIQ ≤ 19), n (%)	44 (56)
High integration (CIQ > 19), n (%)	35 (44)

or parent. The mean GCS score was 6.7 (SD=3.0). Co-morbidity was present in 57 patients (74%). Limitations in functioning were found for 7 patients (9%) and depression was present in 10 patients (13%).

Healthcare utilisation

Figure 1 presents the long-term utilisation by the 79 patients of the different types of health care. Of these 79 patients, 26 (32%) did not use any care at all and the remainder received various types of care. Of all healthcare services, the GP was contacted most frequently (48%). Rehabilitation care was used by 38% of the patients; 42% visited medical specialists, and 16.5% had supportive care. Within rehabilitation care, most contacts were with the rehabilitation physician, followed by the physical therapist. Several supportive care services were equally received: home help, support from other TBI victims, and activity centres. Figure 2 shows the amount of different type of services that were used; high overall care use (3 or more services) was found in 24 patients (30%).

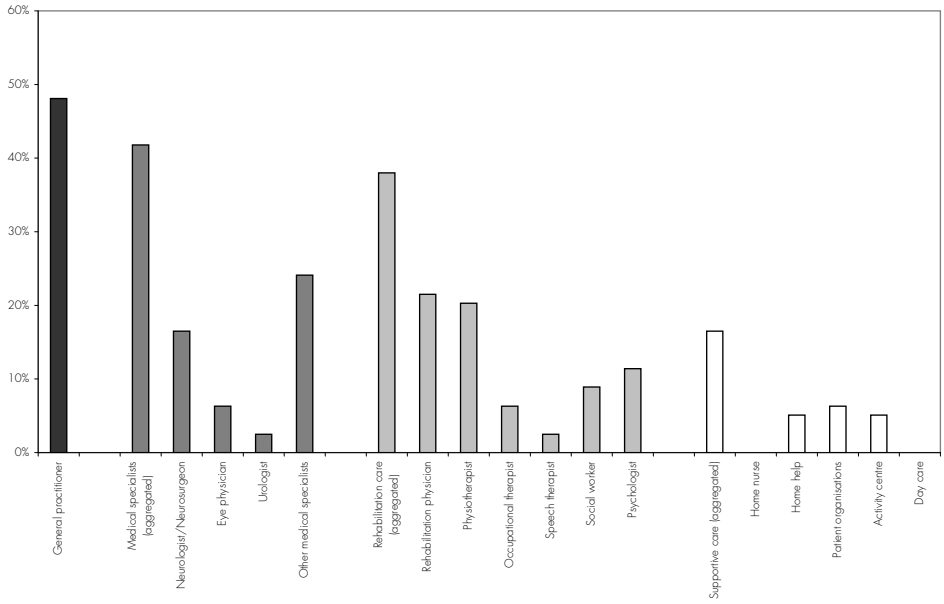

Figure 1. Long-term healthcare utilisation by the group of moderate to severe TBI patients (n=79)

General practitioner
Medical specialists
Rehabilitation care
Supportive care

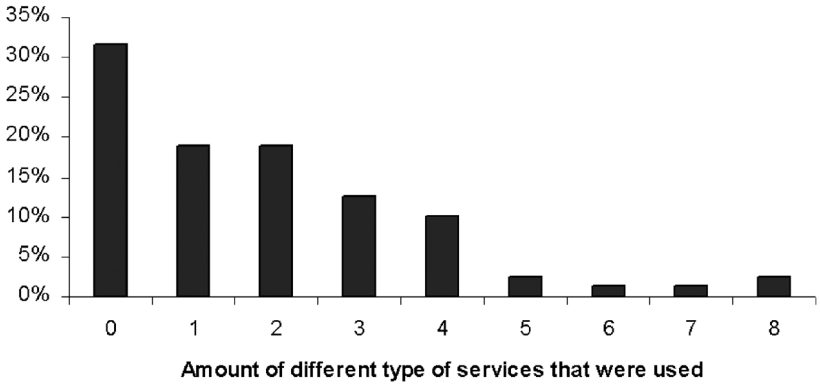

Figure 2. Amount of different type of healthcare services used at 3-5 years post-injury by the group of moderate to severe TBI patients (n=79)

Determinants of healthcare utilisation

The results of the univariate and multivariate analyses for utilisation of the 4 types of care and high overall care use are presented in Table 2. Only significant univariate results ($p < 0.10$) and significant multivariate results ($p < 0.05$) are presented.

High overall care use

In the univariate analyses, not working at follow-up, limitations in functioning, and restrictions in participation were risk factors for a high overall use of healthcare. Significant interrelations were found between limitations in functioning and respectively work (spearman's rho = 0.36) and restrictions in participation (spearman's rho = 0.31); patients with limitations in functioning were less likely to work and were more likely to have participation restrictions. Because these values were below the cut off value of 0.80, all variables were entered in the multivariate model. In the multivariate model, only restrictions in participation were significant (OR=3.273, 95%CI: 1.166-9.190, p<0.024).

General practitioner

In the univariate analyses, more co-morbidity was the only significant determinant for GP use (OR= 1.631 per impaired body system, 95%CI: 1.093-2.435, p=0.017). Therefore, no multivariate model was tested.

Medical specialists

In the univariate analyses, male gender, more co-morbidity, restrictions in participation, and a high locus of control for a physician were risk factors for utilisation of medical specialists. The spearman correlations between these variables were all not significant and therefore all variables were entered in the multivariate model. In the multivariate model, more co-morbidity (OR per extra impaired body system=1.767, 95%CI: 1.106-

Table 2. Univariate and multivariate analyses for long-term utilisation of high overall care use and all aggregated care types

Variables	Univariate analyses			Multivariate analyses		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
High overall care use						
Work status (not working)	2.451	0.919-6.536	0.070			
Functioning (limitations)	6.974	1.247-39.005	0.024			
Participation (restrictions)	3.268	1.166-9.174	0.021	3.273	1.166-9.190	0.24
General practitioner						
Co-morbidity in number of systems	1.631	1.093-2.435	0.017			
Medical specialists						
Gender (male)	2.387	0.858-6.623	0.091			
Participation (restrictions)	2.392	0.951-6.024	0.062			
Locus of control with physician (high)	2.444	0.887-6.739	0.081	3.759	1.191-11.862	0.024
Co-morbidity in number of systems	1.473	1.012-2.145	0.043	1.767	1.106-2.823	0.017
Rehabilitation care						
Functioning (limitations)	3.448	1.325-8.929	0.010			
Supportive care						
Functioning (limitations)	4.650	0.903-23.952	0.083			
Participation (restrictions)	15.873	1.945-125.000	0.001	14.373	1.611-128.212	0.017
Internal locus of control (high)	10.731	1.274-90.363	0.010	11.693	1.298-105.352	0.028
TBI-severity (GCS score)	0.762	0.582-0.997	0.048			

Only reported here are significant ($p < 0.10$) results for the univariate analyses, and significant results ($p < 0.05$) for the multivariate analyses.

2.823, p=0.017) and a high locus of control for a physician (OR=3.759, 95%CI: 1.191-11.862, p=0.024) remained significant risk factors.

Rehabilitation care

In the univariate analyses, only dependence in functioning was significant (OR=4.700, 95%CI: 0.850-25.988, p=0.098); therefore no multivariate model was tested.

Supportive care

In the univariate analyses, a more severe initial injury, dependence in functioning, restrictions in participation, and a high internal locus of control were risk factors for use of

supportive care. Interrelations were found between dependence and functioning and restrictions in participation (Spearman's rho=0.31) and between initial severity and internal locus of control (Spearman's rho=0.26); patients who were dependent in functioning were more likely to have restrictions in participation and more severely injured patients were more likely to have higher internal locus of control. Because these values were below the cut off value of 0.80, all variables were entered in the multivariate model. In the multivariate model, restrictions in participation (OR=14.373, 95%CI: 1.611-128.212, p=0.017) and a high internal locus of control (OR=11.693, 95%CI: 1.298-105.352, p=0.028) remained significant risk factors.

DISCUSSION

This study investigated which healthcare facilities were used by moderate to severe TBI patients 3-5 years post-injury. Equity or inequity was determined by analyzing which factors contributed to the use of healthcare services: i.e. predisposing characteristics, enabling factors, or health-related needs.

At least one healthcare service was used by 68% of the patients on the long term, which is similar to results of earlier studies on TBI patients [14,15]. The GP, medical specialists, and rehabilitation care were contacted most frequently. Compared to the general Dutch population, a smaller percentage of the study population had visited a GP [32]. The GP is the first contact and gatekeeper in the Dutch healthcare system and referrals are generally made by GPs; however, because our patients were already in the system they probably needed fewer referrals from the GP. A remarkable finding was that physical therapists were contacted more frequently than psychologists or social workers, despite that on the long term most TBI patients experience psychosocial problems rather than physical problems [3,33]. Perhaps rehabilitation programs focused more on regaining physical capacity than on psychosocial issues. Another explanation might be that patients have organised care themselves and were more inclined to arrange physical support than psychosocial support because they were more familiar with this type of care. Many TBI patients were using a variety of healthcare services: 49% visited at least 2 services, and 30% received 3 or more services. The utilisation of multiple services underscores the importance of good collaboration and coordination between these services.

The model of Andersen was used to evaluate equity or inequity of care [5,6]. Equity in healthcare use is demonstrated when this use is mainly determined by health-related factors and not by enabling or predisposing factors. Health-related needs (such as restrictions in participation and co-morbidity) explained most of the variance of healthcare utilisation. Hence, these results seem to suggest that most patients who needed care,

received care. However, for medical specialists and supportive care, inequity could not be ruled out as predisposing factors also contributed to healthcare utilisation.

Patients with a high locus of control with the physician were more likely to visit medical specialists than other patients, despite comparable health-related factors. Patients with a high internal locus of control were more likely to use supportive care than other patients, despite comparable health-related factors. In contrast, a study in patients after a myocardial infarct reported that a lower belief in personal control was related to more physician visits [13]. However, the differences in findings might be explained by the fact that this study used a one-dimensional health locus of control scale, in which internal and external orientations were not separate scales but opposites on the same dimension. Therefore, their results are in agreement with our findings for the use of medical specialist care but in disagreement with the use of supportive care. A study in elderly found no association between internal locus of control and hospitalisation and physician use [12]. An internal orientation might lead to different actions in health behaviour, which can explain differences in findings between studies. Usually, patients with a high internal orientation control their own health by performing healthy behaviour, while patients with an external control rely on others for their health. However, their behaviour also depends on what patients expect to be effective for their health [34]. If patients believe that a treatment will be beneficial, then internal orientated patients can choose an active problem-solving approach by seeking support to overcome health problems. An alternate explanation is that health locus of control might change as a consequence of continued health care utilisation. A study in elderly found that a continued period of hospitalisation or an increase of physician visits over time, was associated with an increase of a powerful others (physician) and an increase in a chance health locus of control orientation. However, internal health locus of control was not affected by continued health care utilisation [12].

An interesting item is whether the influence of health beliefs on care use point to inequity or whether patient preferences should be considered in healthcare utilisation. Andersen originally stated that there was inequity when health beliefs determined healthcare utilisation [5], but later reported that it also depended on the circumstances [6]. It is a matter of concern when patients refuse or do not seek health care because they have insufficient insight into their sickness or are unaware of their problems. However, it is now common knowledge that health care is more effective if patients are involved in the management of care [35, 36]. With a patient-centred approach, health beliefs and expectations of patients and professionals can be matched, and patients can be activated to take some control in disease management [37]. Particularly in chronic illness, this approach was found to result in a better satisfaction, adherence to treatment, and outcome [37]. In the future, professionals might pay more attention to the influence of health beliefs on healthcare utilisation, which might prevent some patients failing to receive the care they need because of their health beliefs.

Some caution is warranted in interpreting the results. First, because the results are based on a small study sample, some small but important associations might not have been identified. However, we assume that the sample was representative because the procedure stipulated that all moderate and severe TBI patients be referred to the 3 recruitment centres. It is not known whether the results can also be generalised to mild TBI patients.

Second, we only assessed whether the patients had contact with healthcare services, and not the frequency or intensity of the provided health care. Therefore, it was beyond the scope of this study to determine whether the quantity and quality of the delivered healthcare services were sufficient to deal with all experienced health problems.

Third, we evaluated equity in aggregated care types and not for individual services. On the individual level, TBI patients might still have unmet needs for healthcare services. On the long term, TBI patients may disappear from the healthcare system. New healthcare needs, created by altered circumstances, might therefore remain undetected. TBI research has a strong focus on short-term outcome, whereas it is a lifelong problem. Because we have not yet succeeded in identifying which patients need intensive long-term follow-up, it is recommended that TBI rehabilitation be a lifelong, well-coordinated process focusing on both the patient and their family [38].

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Chapter 6

A risk profile for patients with long-term unmet needs after a traumatic brain injury

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Submitted

ABSTRACT

Objective: To quantify long-term unmet needs concerning autonomy and participation in non-institutionalized patients with moderate to severe traumatic brain injury (TBI) and to determine a risk profile for patients with long-term unmet needs.
Design: Cross-sectional design of prospectively followed-up patients with TBI; follow-up at 3 to 5 year post-injury (n=78).
Setting: Home setting.
Participants: Moderate to severe patients with TBI (aged 16-67 years) recruited from three Dutch medical centers who were not institutionalized at follow-up.
Outcome measure: Perceived unmet needs, measured with the shortened version of the Impact on Participation and Autonomy Questionnaire.
Results: 17% of the patients reported long-term unmet needs. Most perceived unmet needs concerned work (31%), education (45%), and supporting others (46%). Patients with a risk profile of possible clinical depression (OR=9.3; 95%CI: 1.8-48.2, p=0.008) were more likely to perceive unmet needs.
Conclusions: The findings suggest that domains of complex participation might receive insufficient attention in long-term rehabilitation care. The risk profile can help care professionals to be more responsive to the long-term needs of patients with TBI, especially to patients with possible clinical depression.

INTRODUCTION

Incidence figures for traumatic brain injury (TBI) range from 180 to 250 per 100,000 per year in the USA, depending on the study methods.[1] TBI affects approximately 1.4 million people in the USA each year and about 235,000 are hospitalized.[2] In Europe about 1.6 million patients with TBI are admitted to hospital each year,[3,4] and in the Netherlands the incidence rate was estimated at 79 per 100,000 inhabitants.[5] Although spontaneous recovery may occur, many patients have lifelong disabilities for which health care services are needed. A study in moderate to severe patients with TBI 3 to 5 years post-injury showed that 65% returned to their pre-injury level of personal care, and about 40% returned to the pre-injury levels of cognitive competency, major activity, leisure and recreation. The remainder had difficulties or were completely dependent on others.[6] The Center for Disease Control and Prevention estimated that at least 5.3 million Americans have long-term or lifelong need for help to perform activities of daily living.[7] Hence, the burden on the health care system is extensive, especially because many TBI victims are young and have a normal lifespan.

Few studies have investigated health care needs in adult patients with TBI. Corrigan et al. reported that in the first year after injury 59% had at least one need, and 40% experienced at least one unmet need.[8] Services most needed were those aimed at improving cognitive skills, i.e. improving memory performance and problem solving, as well as managing stress, emotional upsets and money. Needs that were least likely to be met were improving cognitive abilities, finding employment, and managing alcohol or drug use.[8] Several variables were associated with experiencing needs at one year post-injury.[8] Patients older than 65 years, females, an Injury Severity Scale above 25, presence of skull fractures, and intoxication at time of injury were related to needs for self-care, cognitive needs, and for finding employment.[8] In addition, several measures of functioning, measured concurrently with the time that needs were expressed (such as independence in activities in daily life (ADL), drinking habits, post-concussive syndromes, presence of behavioral problems, and working status) were quite predictive.[8]

Pickelsimer et al. found comparable figures; 35% of the TBI patients experienced unmet needs one year after discharge from hospital and 51.5% had unrecognized needs.[9] Non-white males or patients with cognitive problems, problems in ADL, a poor or fair general health, a low income, who were receiving Medicaid benefits, with inadequate social support, without health insurance, or without employment reported more frequently unmet needs. About 47% experienced at average two barriers for receiving services; the highest reported barrier for not receiving services was lack of awareness, advocacy and case management. Receipt of services significantly increased satisfaction of life, whereas patients with unmet needs had a lower satisfaction of life.[9]

Rotondi et al. reported that TBI patients described their needs via stages parallel to transitions in treatments and roles.[10] They identified four distinct stages: acute care, inpatient rehabilitation, the return home (approximately until 3-4 months post discharge), and reassuming life in the community. Prominent needs during the inpatient rehabilitation were the quality of the health care provider, emotional support, and understanding the nature and consequences of injuries. In the return home phase and the life in the community phase, important needs were guidance, life planning, community integration and behavioral and emotional issues.[10] They recommended that professionals should be aware of changes needs during different phases after TBI.

Allen and Mor investigated the prevalence of unmet needs in adults with disability.[11] The prevalence of unmet need for assistance with individual ADL ranged from 4.1% for eating to 22.6% for making a transfer. For more complicated activities, instrumental ADL, the prevalence was ranging form 15.9% for cooking to 34.6% for heavy housekeeping.[11] Indicators of morbidity and impairment severity predicted an elevated risk of unmet need for help with ADL and instrument ADL, whereas sociodemographic variables were not influential for unmet needs. [11] Further, they reported that having unmet needs was associated with a higher health care utilization and depression.

In summary, several studies examined the prevalence, related determinants, and the consequences of needs and unmet needs after TBI. Although some were contradicting, several determinants have been found to be related to needs and unmet needs: sociodemographic characteristics,[8,9] clinical characteristics,[8,9,11], and the level of functioning concurrent with perceived needs, although some results were contradicting.[8,9,11] Having unmet needs was associated with a lower satisfaction of life, depression, and higher health care utilization. Unmet needs might therefore further hinder recovery after TBI.

Therefore, this study was set up to 1) quantify long-term unmet needs in non-institutionalized moderate to severe patients with TBI, and 2) to develop a risk profile for patients with long-term unmet needs. Several reports on acquired brain injury in the Netherlands suggested that only a limited amount of TBI patients is receiving adequate services after discharge and that it was by large a question of coincidence and luck whether or not you will receive it.[12-14] In combination with previous reports on unmet needs after TBI, we hypothesize that a substantial proportion of patients with participation problems will experience unmet needs for support with these problems. As unmet needs are related to impairments in body structures and functions, and to activity limitations and participation restrictions, we expected a complex risk profile of personal, clinical, and social for unmet needs.

METHODS

Procedure

For the present cross-sectional study a subsample of 78 patients was included from the cohort recruited in the Rotterdam TBI study.[15] In the Rotterdam TBI study, 119 patients with TBI were consecutively enrolled from January 1999 to April 2004 in 3 medical centres: Erasmus Medical Center in Rotterdam (entire period), University Medical Center Utrecht (enrollment from April 2003 to February 2004) and Medical Center Haaglanden in The Hague (enrollment from January 2003 to February 2004). These centers served as treatment centers for all moderate and severe patients with TBI within their regions. Patients were treated in accordance with the European Brain Injury Consortium guidelines.[16]

For the Rotterdam TBI study, patients were prospectively followed-up at 3, 6, 12, 18, 24, and 36 months from April 1999 to April 2007. For this study the 36-month follow-up measurements were used. Two study psychologists collected the data in a structured interview. In cases where patients suffered from serious communication impairments, a significant other or professional caregiver was interviewed. The questionnaire on unmet needs was added to the structured interview at the regular follow-up measurement of 3 years in October 2003. As 39 patients were already followed-up by that time, these patients were sent the unmet needs questionnaire by mail up to 5 years post-injury. For these 39 patients, the other data were previously collected in the structural interview at the regular follow-up.

Patients

Inclusion criteria of the Rotterdam TBI study were: 1) admittance in hospital for moderate or severe TBI due to blunt or penetrating trauma [Glasgow Coma Scale (GCS)[17] score of 9-13 or 3-8, respectively)]. We classified patients with a GCS of 13 as moderate TBI, according to a study that showed that patients with a GCS of 13 have similar complications, mostly due to intracranial hematomas, as patients with a GCS of 9-12[18]; 2) age at onset between 16 and 67 years; 3) survival until discharge from hospital. Exclusion criteria were: 1) insufficient knowledge of the Dutch language to participate in the study; 2) serious pre-TBI neurological, oncological or systemic impairments (e.g. spinal cord injury, psychiatric disorders, cancer) that might interfere with the assessment of TBI-related disability. All patients received verbal and written information about the study and signed an informed consent form. The Medical Ethics Committee of Erasmus MC approved the study.

For the present study, we only analyzed patients that were not institutionalized at follow-up. Of the 119 patients with TBI included in the Rotterdam TBI study, 4 patients were institutionalized, 3 were deceased, and 16 patients were lost at the time of follow-up. Of the 96 eligible patients, 78 (81%) patients filled in the unmet needs questionnaire at 3

to 5 years post-injury. Eighteen patients had not returned their questionnaire. Participants were not significantly different from the non-participants for the following characteristics: age, sex, education level, work status, living status, and TBI severity.

Measures

Unmet needs

Unmet needs were assessed with the shortened version of the Impact on Participation and Autonomy Questionnaire (IPAQ).[19, 20] The IPAQ is a valid and reliable instrument and measures participation and autonomy on nine domains (mobility, self-care, daily activities, controlling finances, leisure time, relationships, supporting others, work, and education).[21] The IPAQ asks patients (using a 3-point scale) if they experienced restrictions on the domains (no restrictions, moderate restrictions, severe restrictions) and to what extent these restrictions are experienced as a problem (no problem, minor problem, severe problem). For the present analysis, the scores were dichotomized into respectively "no restrictions" and "restrictions", and "no problem" and "problem". An extra question per domain was added to measure whether patients perceived enough support (want more support, enough support, want less support). Unmet needs were considered to be present if patients with restrictions that were perceived as problems answered that the support was not enough. Because of small numbers the overall score was dichotomized into absence (0) or presence (1) of perceived unmet needs.

Patient characteristics

Patient characteristics were categorized as shown in Table 1. The average age was 35 years (SD=13.4) and the majority of patients was men (67%). In total, 40% had junior secondary education or lower and 60% had a higher education. At follow-up, 56% was working fulltime or part-time in a competitive job. Housekeeping, going to school or college, and volunteering were classified as 'not working'. Most patients lived with a parent or partner (74%) and 26% lived alone.

TBI severity, co-morbidity and possible clinical depression were assessed as clinical factors. TBI severity was assessed with the GCS, which is the most common measure for classifying severity of TBI.[22] The majority of patients (76%) was classified as having severe TBI (GCS 3-8), the remainder was classified as moderate TBI (GCS 9-13).[18] Co-morbidity at follow-up was assessed with the Cumulative Illness Rating Scale (CIRS). The CIRS is a valid and reliable instrument that rates 13 body systems on a 5-point scale (no impairment to life-threatening impairment) without using specific diagnoses.[23] The total number of body systems that had a score of 1 or higher were accumulated to a sum score for co-morbidity. Direct symptoms of TBI (such as post-traumatic headache) were not considered as co-morbidity. Co-morbidity was present in 58 patients (76%), and 35

patients (46%) had co-morbidity on at least two body systems. The presence of clinical depression was measured with the Wimbledon Self-Report Scale (WSRS).[24] The WSRS consists of 30 questions on how often a certain feeling was felt in the past 4 weeks (most of the time, quite often, only occasionally, not at all). The items are transformed into a 2-point scale with a maximum score of 30. Scores ranging from 0 to 7 are considered as normal functioning, scores ranging from 8 to 10 are considered as borderline for mood disorders, and scores of 11 to 30 are considered as cases with a clinically significant mood disorder. The scores were dichotomized into lower or equal to 7 indicating no clinical depression, and above 7 as indicating possible clinical depression. Possible clinical depression was found in 13% of the patients.

Several measures of functioning were selected to obtain a cumulative spectrum of functioning: specific dimensions of general health (EuroQol), independence in daily activities (Functional Independence Measure), impact of the injury on possibilities for activities and participation (Sickness Impact Profile-68), and integration or participation in the community (Community Integration Questionnaire). The EuroQol (EQ-5D) is a questionnaire that was designed for evaluating health outcome in a wide range of health conditions and treatments. [25] The EQ-5D consists of 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Respondents are asked to score experienced limitations on these items (no problems, some problems, severe problems). A compiled index value for health status can be calculated for comparing with other conditions, but the individual can also be used to obtain a simple profile of functioning (this study). Because of low numbers in the severe problems category, the scores were dichotomized into no problems or problems (some or severe). At the follow-up, 7% of the patients experienced problems in self-care and 24% had mobility problems. Further, 32% had problems with usual activities, 38% experienced pain or discomfort, and 38% reported feelings of anxiety or depression.

Independence in daily activities were measured with the motor and cognitive subscale of the Functional Independence Measure (FIM).[26, 27] The FIM consists of 18 items measuring independence in basic activities of daily living on several domains: self-care, sphincter control, transfers, locomotion, communication, psychosocial adjustment, and cognitive functioning. The items are scored on a 7-point scale (completely independent to totally dependent). The FIM consists of 2 dimensions: a motor dimension (13 items, range 13-91 points) and a cognitive dimension (5 items, range 5-35 points). A higher score indicates more independence. At follow-up, the motor scale scores ranged from 58 to 91 with a median of 90, and the cognitive subscale scores ranged from 15-35 with a median of 31.

Participation restrictions were assessed with the Sickness Impact Profile-68 (SIP-68) [28], which has 68 statements on behaviour, feelings, and functions. It is developed as a general health measure, which measures the behavioural impacts of a sickness or

Table 1. Characteristics of all participating patients (n=78)

Patient characteristic (n=78)	
Age in years: median (range)	35 (16-66)
Sex	
Men, n (%)	52 (67)
Women, n (%)	26 (33)
Education (n=77)	
Low (lower or junior secondary education), n (%)	31 (40)
High (higher than junior secondary education), n (%)	46 (60)
Work status at follow-up	
Not working, n (%)	34 (44)
Working, n (%)	44 (56)
Living situation	
Without partner or parent, n (%)	20 (26)
With partner or parent, n (%)	58 (74)
Glasgow Coma Scale	
Moderate	19 (24)
Severe	59 (76)
Number of co-morbidities, median (range) (n=76)	1 (0-7)
Clinical depression (n=76)	
Absence of depression, n (%)	66 (87)
Possible depression, n (%)	10 (13)
Mobility (n=76)	
No problems, n (%)	52 (68)
Problems, n (%)	24 (32)
Self-care (n=77)	
No problems, n (%)	72 (93)
Problems, n (%)	5 (7)
Usual activities (n=77)	
No problems, n (%)	52 (68)
Problems, n (%)	25 (32)
Pain/discomfort (n=77)	
No problems, n (%)	48 (62)
Problems, n (%)	29 (38)
Anxiety/depression (n=77)	
No problems, n (%)	48 (62)
Problems, n (%)	29 (38)
FIM Motor functioning: median (range)	90 (58-91)
FIM Cognitive functioning: median (range)	31 (15-35)
Participation restrictions, SIP-68 (n=77): median (range)	9 (0-47)
Community integration, CIQ: median (range)	18.5 (6-29)
Internal locus of control, MHLCS (n=67): median (range)	22 (7-32)
Locus of control with a physician, MHLCS (n=67): median (range)	16 (6-26)
Locus of control with chance, MHLCS (n=67): median (range)	18 (6-29)
Social Support, SSL: median (range)	73 (48-96)

injury on physical functioning, emotional functioning, and social aspects of functioning. Respondents are asked if these statements apply to their current situation (yes/no) and whether they are health related. The SIP-68 score is calculated by summing all positively scored items (range 0-68). A higher score indicates more participation restrictions. The SIP-68 has excellent test-retest reliability (ICC=0.97).[29] The median score was 9 (range 0-47).

Community integration was determined with the Community Integration Questionnaire (CIQ),[30] which assesses daily activities in the home, social environment, and work or education. It contains 15 questions on how activities are usually performed (alone, with another person, by someone else) and how frequently activities are done. The score ranges from 0 to 29, with a higher score indicating better community integration. The reliability of the CIQ is sufficient.[31] The CIQ was dichotomized on the median into high or low community integration. Scores for community integration ranged from 6 to 29 with a median of 18.5. Health beliefs were assessed with the Multidimensional Health Locus of Control Scales (MHLCS).[32] The MHLCS consist of 3 independent scales with each 6 items: internal locus of control, locus of control with a physician, and locus of control with chance. All items are statements about health and factors of influence on health for which participants are asked on a 6 point Likert scale whether they 'totally agree' or 'totally disagree' with the statement. The scales indicate how much patients believe that the health status is influenced by themselves, a physician, or by chance or faith. The scales range from 6 to 36 points; a higher score indicates that the patient attributes more influence to the factor. Health beliefs were selected as a potential determinant of unmet needs, because they were shown to influence the utilization of health care services and physician visits.[33, 34] If patients attribute more influence to an internal or external factor, they are more inclined to act upon their expectations. For example, someone who attributes more influence to a physician will be more inclined to use or ask for medical services then someone who has a lower attribution towards a physician. Thus, a person's attribution may determine whether someone experiences or reports unmet needs. At follow-up, the scores for an internal locus of control ranged from 7 to 32 with a median of 22, the scores for a locus of control with the physician ranged from 6 to 26 with a median of 16, and the locus of control scores with chance ranged from 6 to 29 with a median of 18.

Received social support was measured with the Social Support Scale (SSL).[35] Subjects are asked to fill in a 4-point scale on how often they experienced a certain type of social support. The scores range from 34 to 136, where a higher score indicates greater social support. A person with high social support will probably also receive more help and support for performing daily activities than someone with a small social network. Therefore, we expect that a person with less social support will report more unmet needs. The scores for social support ranged from 48 to 96 with a median of 72.

Statistical analysis

Descriptive statistics were performed with SPSS 12.0.1. Univariate and multivariate analyses were used to test what variables were risk factors for unmet needs. Only those patients with one or more problems in daily life as a consequence of restrictions were analyzed. First, the association between the independent variables and unmet needs were tested with univariate logistic regression analysis. Effect sizes were expressed with odds ratios (ORs) and 95% confidence intervals (95%CI). The sample size was relatively small and the number of independent variables relatively large. Therefore, the criterion for inclusion in the multivariate model was set on p=0.10. Second, we used a backward logistic regression analysis to test the multivariate model. The variables selected for the multivariate model were tested for multicolinearity with the variance intolerance factor. A variance intolerance factor larger than 10 indicated multicolinearity. In case of interrelations, only the highest contributing variable to unmet needs was entered into the multivariate model. A p-value below 0.05 was considered significant. Third, the percentage of correct predictions of the proportion of patients with unmet needs and the proportion of patients without unmet needs were calculated. [36]

RESULTS

Unmet needs

Of the 78 patients, 13 patients (17%) reported one or more unmet needs: 3 patients experienced 1 unmet need, 5 patients had 2 unmet needs, 1 patient reported 3 unmet needs, 1 patient had 4 unmet needs, 2 patients perceived 5 unmet needs, and 1 patient experienced 9 unmet needs. Table 2 presents the frequencies of patients who reported restrictions, problems, and unmet needs for the 9 domains. In total, 55 patients had restrictions on one or more domains, and 45 patients experienced these restrictions

Table 2. Number of reported unmet needs per domain

Domain	Experienced restrictions n	Perceived problems n	Reported unmet needs n
Mobility	16	16	4
Self-care	4	4	1
Daily activities	21	16	3
Controlling finances	15	5	1
Leisure time	22	19	3
Relationships	24	20	4
Supporting others	22	13	6
Work	36	26	8
Education	26	20	9

as a problem. From the 45 patients that experienced restrictions that were a problem, 13 (29%) patients experienced unmet needs and 32 reported no unmet needs. Most restrictions were reported on the domain of work and the least restrictions were reported on the domain of self-care. If restrictions in mobility or self-care were present, all patients experienced these restrictions as a problem in daily life. If restrictions in controlling finances were present, 33% of the patients experienced this as a problem. Most frequently reported unmet needs concerned work (31%), education (45%), and supporting others (46%).

Risk profile for unmet needs

Only those patients with one or more problems in daily life as a consequence of restrictions were analyzed, 45 patients were analyzed in the regression analysis. Table 3

Table 3. Data on univariate analyses between the independent variables and perceived unmet needs 3 to 5 years post-injury

Variables	**Univariate analyses ****		
	OR	**95% CI**	**p**
Age in years	1.0	1.0-1.1	0.612
Sex (men)	1.4	0.3-5.4	0.670
Education (lower)	1.4	0.4-5.2	0.599
Work status (working)	2.3	0.6-8.8	0.245
Living situation (alone)	0.7	0.2-2.9	0.585
Glasgow Coma Scale (severe)	1.1	0.2-5.1	0.892
Number of co-morbidities	1.3	0.8-2.1	0.237
Possible clinical depression	9.3	1.8-48.2	0.008*
Mobility (problems)	1.5	0.4-5.7	0.559
Self-care (problems)	5.0	0.7-34.7	0.104
Usual activities (problems)	8.3	1.6-44.6	0.013*
Pain/discomfort (problems)	2.1	0.5-7.9	0.298
Anxiety/depression (problems)	2.3	0.6-9.1	0.247
FIM Motor functioning	0.9	0.8-1.0	0.028*
FIM Cognitive functioning	0.8	0.7-0.9	0.004*
Community integration, CIQ	0.9	0.8-1.0	0.089*
Participation restrictions, SIP-68	1.1	1.0-1.2	0.003*
Internal locus of control, MHLCS	1.0	0.9-1.1	0.880
Locus of control with physician, MHLCS	1.0	0.9-1.2	0.757
Locus of control with chance, MHLCS	1.0	0.9-1.1	0.745
Social support, SSL	1.0	1.0-1.1	0.835

*Variables with p≤0.10 were selected for the multivariate model

**Available data for univariate analysis: mobility (n=43), self-care (n=44), usual activities (n=44), pain/discomfort (n=44), education level (n=44), possible clinical depression (n=43), internal locus of control (n=37), locus of control with physician (n=37), locus of control with chance (n=37), social support (n=38), and co-morbidity (n=44)

presents the results of the univariate analyses. For some determinants there were missing data (mobility, self-care, usual activities, pain/discomfort, education level, possible clinical depression, internal locus of control, locus of control with physician, locus of control with chance, social support, and co-morbidity) (Table 3). Patients with problems with usual activities, who were more dependent in motor functioning or in cognitive functioning, who had more participation restrictions, with lower community integration, or with possible clinical depression, were more likely to have unmet needs at follow-up.

The variance intolerance factors were all below 10 (range 1.3 to 4.6), indicating no severe multicolinearity; therefore all variables were entered in the multivariate backward regression analysis. For the multivariate analysis 43 complete cases were available. In the backward regression analysis, only possible clinical depression remained as a significant predictor (OR=9.3 95% CI: 1.8-48.2, p=0.008) for unmet needs. Patients with possible clinical depression were more likely to have unmet needs. The multivariate model correctly predicted 50% of the patients with unmet needs and 90% of the patients without unmet needs.

DISCUSSION

In the present study we quantified the proportion of patients that perceived long-term unmet needs after moderate to severe TBI, and developed a risk profile for patients with perceived unmet needs. Of the 78 patients, 13 (17%) had one or more unmet needs. Unmet needs were most frequently reported on domains with respect to complex participation in the community: work, education, and supporting others. Further, we found that patients with a risk profile of possible clinical depression were more likely to perceive unmet needs than patients without these problems.

The proportion of patients with unmet needs suggests that the available health care services are not sufficient for all health care needs after TBI. In this respect, an important question is whether the reported unmet needs reflect actual health care problems or whether they are the result of too high expectations. It should be noted that all patients that reported unmet needs, also reported restrictions causing problems in daily life. Furthermore, earlier studies reported that a relation between experiencing health care needs and somatic and psychosocial functioning. Health care needs were present in patients with a poorer general health, behavioral problems, or dependence in daily activities.[8, 9] In addition, studies that also assessed professionally defined needs found that patients tend to underestimate their needs.[9, 37] These finding support the notion that the reported health care needs reflect actual health care problems. Due to sickness insight, or lack of awareness of possible care facilities, patients do not recognize all their health care needs. Thus, we recommend that future studies should integrate the patient's

and professional's perspectives to improve the recognition of health care needs and the provision of adequate health care.

In our cohort, more patients had contacts with physical therapists than with psychologists or social workers (data not presented). Apparently, an important focus in long-term TBI rehabilitation care is on improving mobility and physical functioning and less attention going to psychosocial care. The current findings also indicate that more care is provided in the area of physical functioning and less to issues that require psychosocial care. In agreement with our findings, earlier studies also reported that more needs were perceived for complex participation problems.[8,9,38] This is surprising, because most studies found complex participation to be more restricted than physical functioning.[5,6,39]

There are several explanations why health services for complex participation seem to fall short. First, the timing for the provision of care may not be quite right. During inpatient rehabilitation the focus is mainly on regaining mobility, self-care, structuring daytime activities, and family education.[40] In outpatient rehabilitation complex restrictions are addressed, but for most patients it is not yet evident whether their restrictions will remain. For example, many patients had an unstable employment status after TBI,[41,42] and 25% of the patients who were employed at 1 year post-injury were no longer employed at 2 years post-injury.[41] Because reliable long-term predictions for individual patients are difficult, for some patients the provision of care comes too early. During the outpatient rehabilitation, most patients are still recovering and trying to accept their changed circumstances. Others have already disappeared from the rehabilitation care system by the time they actually perceive needs, and therefore have difficulty in finding appropriate care. A better fine-tuning would enhance the provision of care and enable professionals to be more responsive toward the needs of patients. Another problem might be that the complexity of the long-term participation restrictions requires individual treatment programs that have a multidisciplinary approach that focuses on these long-term problems. Unfortunately, there are only a few intensive neurorehabilitation programs in the Netherlands.[43,44]

We found that patients with a risk profile of possible clinical depression were more likely to report unmet needs. Previous studies reported several other type of factors to be related with unmet needs: sociodemographic variables (race, income, insurance, employment,[9] age,[8] sex,[8,9]), clinical characteristics (general health,[9] injury severity, skull fractures, intoxication at time of injury,[8] morbidity, and impairment severity[11]), and measurements of functioning at follow-up (cognitive problems, ADL problems,[9] independence in ADL, drinking habits, post-concussive syndromes, behavioral problems, and working status[11]). We found similar variables to be related with unmet needs in the univariate analysis: problems with usual activities, dependence in motor functioning, dependence in cognitive functioning, more participation restrictions, lower community integration, and possible clinical depression. Although only possible clinical depression

was in the risk profile after the multivariate analysis, all patients with unmet needs had restrictions in participation and autonomy. Therefore, possible clinical depression is an additional characteristic, which can help to identify patients with unmet needs besides their participation restrictions.

Several studies in TBI as well as other patients found similar relations between unmet needs and depression. Hibbard et al. found that TBI patients with late onset depression or chronic depression had more unmet needs and a lower quality of life than the group without depression or resolved depression.[45] Hwang et al. reported that veterans with cancer with higher psychological distress reported more unmet needs in the emotional/social, economic, and medical domains.[46] In contrast to these studies, Blazer et al. investigated the reverse relation in the elderly; they found that perceived unmet basic needs were predictive for future depressive symptoms.[47] It is not clear whether depression is a consequence of unmet needs or that unmet needs are perceived due to depressive symptoms. In TBI patients, both depression and unmet care needs were found to be related with a lower satisfaction with life.[9, 48] The prolonged dissatisfaction with life can eventually lead to requests for extra care to overcome the restrictions and regain a better quality of life. Therefore, professionals should be alert on patients with restrictions in participation in combination with possible clinical depression, as these might receive insufficient care or support.

Some limitations of the current study need to be addressed. First, because the present study only investigated patients' perceived needs some needs might have been undetected. By integrating the patient's perspective with the professional's perspective, more insight can be gained in the long-term health care problems and the provision of care might be improved. Second, because the results were based on a small study sample, small but important associations may not have been identified. Further, our sample size was small in relation to a relatively large number of determinants that were studied. As a consequence the parameters might be overestimated. The alternative was to consider only a limited amount of possible risk factors and possibly loosing relevant information. In order to limit the amount of variables in the multivariate model, we only selected variables with a p-value equal or below 0.10 in the univariate analysis. Nevertheless, the small sample should be considered as a limitation. Third, unmet needs were only assessed at one time point; longitudinal studies on health care needs and utilization can reveal when specific health care needs emerge and which needs remain unmet over time. This will eventually result in a better fine-tuning of care provision and care utilization.

Conclusions

A proportion of moderate to severe patients with TBI perceived long-term unmet needs. Patients with a risk profile of possible clinical depression were more likely to perceive long-term unmet needs. Because some domains might receive insufficient attention,

professionals should be aware of the long-term problems and needs of patients in order to provide adequate care. We recommend that future studies should preferably be longitudinal so that more insight can be provided into the onset and course of needs so that future unmet needs can be prevented or adequately addressed. In addition, future studies should integrate the patient's and professional's perspectives to improve the recognition of health care needs and the provision of adequate health care.

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Chapter 7

Discussion

The rationale for conducting the studies presented in this thesis is that long-term healthcare for patients with acquired brain injury, and traumatic brain injury (TBI) in particular, has many flaws and pitfalls. In 1990, TBI was depicted as a 'silent' epidemic with long-term consequences that are largely unknown and affect many more victims than known to healthcare policymakers and even professionals.[1] Since that time, the consequences of TBI have received increasing attention in research, indicating an alarming prevalence of late consequences (even in cases of mild brain injuries), and a lack of well-coordinated, lifelong care programs for individual patients and their caregivers.[2-7] Although studies on prognosis and its determinants have been performed, these generally had a limited follow-up time of 6 months to 1 year and used outcome measures that were seldom targeted at levels of activity and participation and healthcare utilisation.

Therefore, the aim of this thesis was fourfold. First, we identified long-term prognostic determinants of activities and participation after moderate to severe TBI. Second, the course of activities and participation in the first 3 years following moderate to severe TBI was investigated. Third, the use of healthcare facilities and its determinants 3-5 years after TBI were studied. Fourth, we determined the prevalence of unmet needs concerning autonomy and participation at 3-5 years post-injury and developed a risk profile.

In this chapter, we summarize the main findings and discuss the strengths and limitations of this study. In addition, we present the clinical implications of our findings and our recommendations for future research.

MAIN FINDINGS

1) Prognostic determinants of activity and participation 3 years post-injury

To select potential determinants of long-term activity limitations and participation restrictions, we systematically reviewed the literature on the subject (Chapter 2). After reviewing 35 papers[8-42] covering 14 cohorts, we concluded that heterogeneous measures were used for a broad variety of determinants of outcome after TBI, including socio-demographic factors, pre-morbid co-morbidity, injury characteristics, neuro-psychological factors, treatment factors, and post-acute functioning. In a best- evidence synthesis strong evidence for predicting long-term disability was found for: older age, pre-injury unemployment, substance abuse, and more severe disability at rehabilitation discharge (measured with the Disability Rating Scale[43]). Strong predictors of non-productivity were: pre-injury unemployment, longer posttraumatic amnesia, substance abuse, and more disability at rehabilitation admission (measured with the Disability Rating Scale). Gender and education level were not predictors of non-productivity. For the following items it remains inconclusive whether or not they predict long-term disability or non-productivity: years of education, Glasgow Coma Scale[44] (GCS) scores, aetiology, length of conscious-

ness, length of stay in the acute hospital, and independence at rehabilitation discharge (measured with the Functional Independence Measure[45]).

Outcome after TBI is only partly explained by the determinants discussed. Genetic polymorphism is considered to play a role in explaining variances in individual susceptibility to the long-term consequences of TBI. The potential association of APOE polymorphisms with head injury was postulated 12 years ago.[46] However, the effect of the APOE genotype on outcome after TBI remains controversial. Presence of the ε4 allele has been associated with a higher mortality,[47] longer duration of unconsciousness,[48] longer hospital stay,[49] more cognitive impairments,[48,50,51] a higher risk of late posttraumatic seizures,[52] and unfavourable outcome after TBI.[46,49,53] However, other studies found no association between carrying the APOE-ε4 allele and outcome.[52,54-56] In Chapter 3, we found no significant association between carrying the APOE-ε4 allele and activity limitations and participation restrictions (Sickness Impact Profile-68[57,58]) or with community integration (Community Integration Questionnaire[59,60]) at 3, 6, 12, 18, 24, and 36 months. The APOE-ε4 allele was associated with global functional outcome after TBI, measured with the Glasgow Outcome Scale[61]. Instead of being a risk factor for an adverse outcome, we found a protective effect of the APOE- ε4 allele; global functional outcome was better in the 17 patients (22%) that possessed at least one APOE-ε4 allele (especially at 12, 18, 24, and 36 months post-injury) than for the 62 patients (78%) that were not carriers of the APOE-ε4 allele.

In Chapter 4 we explored the major determinants of community integration at 3 years post-injury. In addition to our systematic review (Chapter 2), we summarized the literature specifically aiming at determinants of community integration. Clinical determinants for community integration after TBI concerned: severity of injury, functional performance and disability, a longer duration of post-traumatic amnesia,[62,63] a longer acute stay in hospital,[62] loss of emotional control,[63] a worse cognition,[62,64] a worse physical status,[62] worse pre-morbid functioning,[64] more activity limitations, [62,63] and aetiology.[65,66] Sociodemographic determinants were: age, gender, living environment, emotional status,[67] being member of a minority race,[28,68,69] a lower education,[28,65] unemployment at the time of injury,[28,65] and age.[28,62,63] Evidence on determinants of community integration remained inconclusive and contradictory. Therefore, we investigated several sociodemographic and clinical characteristics, and post-acute and pre-injury functioning, in relation to the Community Integration Questionnaire (CIQ).[59,60,70] The post-acute Barthel Index[71,72] score, age at injury, and the pre-injury CIQ score together explained 52% of the variance. More post-acute limitations in functioning, a higher age, and lower pre-injury community integration were predictive for poorer community integration at 3 years post-injury.

2) The course of activities and participation in the first three years after TBI.

In Chapter 4 we evaluated the course of the CIQ from the pre-injury situation up to 3 years post-injury. For all CIQ domains (home integration, social integration, and productivity) and the CIQ total the mean scores deteriorated after injury (Figure 1). Although there was improvement, the mean CIQ levels remained below the mean pre-injury levels, except for home integration. Participation restrictions persisted on the CIQ domains social integration and productivity up to 3 years post-injury. These findings were supported by the study in Chapter 3. Of the 76 patients with 3-year follow-up scores for the GOS, 47 patients (62%) were moderately disabled, indicating that they experienced participation restrictions on the domains of return to work, social and leisure activities, or interpersonal relationships. Similar findings were reported in Chapter 6: of the 78 patients, 55 (71%) experienced restrictions in one or more domains on the IPAQ, and most restrictions were experienced on the domains of daily activities, leisure time, relationships, supporting others, work and education. In conclusion, this study confirms earlier findings, that long-term participation restrictions are experienced after TBI, especially in engaging social or leisure activities, and productivity.

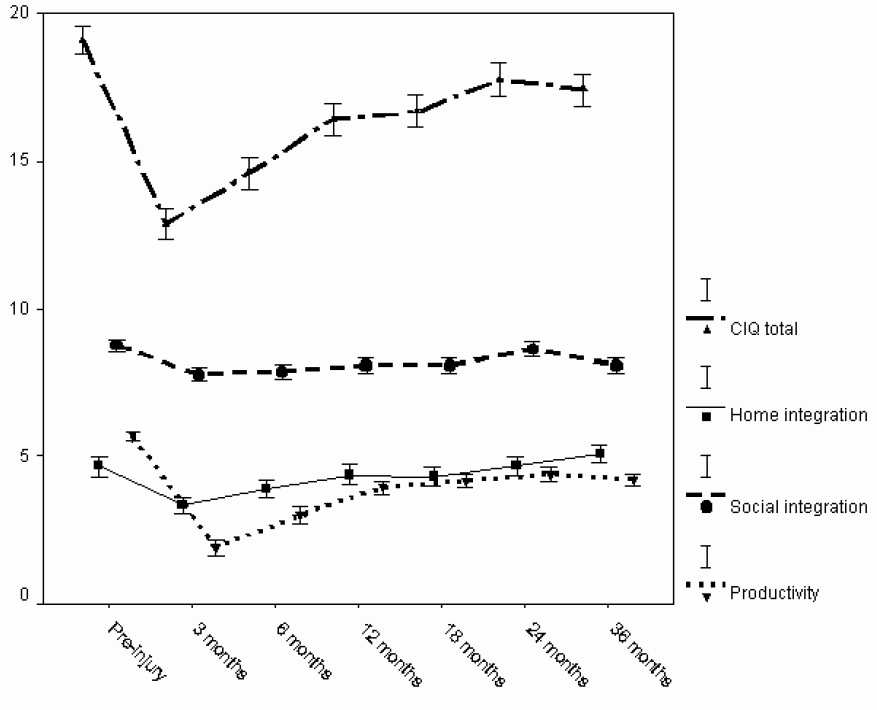

Figure 1. The course of the CIQ total, home integration, social integration, and productivity scores from the pre-injury situation up to 3 years post-injury. Data are means (+/- standard error of the mean) as calculated by ANOVA.

3) Heath care utilisation and its determinants

Due to long-term activity limitations and participation restrictions, many patients require adequate long-term treatment. In Chapter 5 we evaluated whether healthcare utilisation by moderate to severe TBI patients was equitable; for this we used the model of Andersen.[73,74] According to this model, there is equity in the utilisation of healthcare services when it is mainly determined by health-related needs or sociodemographic factors. When enabling factors or health beliefs determine healthcare utilisation this points to inequity. Healthcare utilisation in our sample appeared to be determined mainly by health-related needs like restrictions in participation and co-morbidity. However, health beliefs such as a high locus of control with the physician and a high internal locus of control, were related to utilisation of medical specialists and supportive care, respectively. Hence, for these types of care inequity could not be ruled out because patients might be more or less declined to use services, depending on their health beliefs.

Our study revealed that 3-5 years post-injury 68% of the included TBI patients used at least one healthcare service. The general practitioner was contacted most frequently (48%), followed by visits to medical specialists (42%). Furthermore, 38% used rehabilitation care, and 16.5% received supportive care. This figure is more optimistic than the previously reported 10% that received rehabilitation services after post-acute care.[2] Within rehabilitation care, physical therapists were contacted more frequently (20%) than psychologists (11%) or social workers (9%), despite the fact that on the long term most TBI patients experience psychosocial problems rather than physical problems.[2,75] The percentage of patients using supportive care (16.5%) seems low when viewing TBI as a chronic condition.

4) Unmet needs concerning autonomy and participation

We hypothesised that, although there seems to be equity for aggregated care types, on the individual level patients might still have unmet needs for services. In Chapter 6, we investigated this hypothesis by evaluating whether patients experienced unmet needs concerning autonomy and participation. At 3-5 years post-injury, 13 of the 78 patients (17%), reported unmet needs on one or more domains. The most frequently reported unmet needs concerned complex participation, such as work (31%), education (45%), and supporting others (46%). Patients with a risk profile of possible clinical depression were more likely to experience unmet needs. We suggested that the long-term care for these patients may be insufficient or not properly fine-tuned to the moment that patients actually experience these needs. In addition, we hypothesized that the actual problem of unmet needs might be even larger, because of needs that may be unrecognized by the patients themselves.[76,77]

In conclusion, the availability and use of healthcare services in our population of moderate and severe TBI patients is more positive than reported earlier.[4-6] However, the

study on unmet needs revealed some drawbacks. In total, 17% of the patients perceived unmet needs after TBI and experienced them as participation restrictions in daily life. If the perspective of the patients and the professionals had been combined, unmet needs might have been reported more frequently because patients may not perceive their needs, e.g. due to lack of insight (unrecognized needs). We recommended that TBI rehabilitation should incorporate a lifelong follow-up or monitoring of patients, so that newly developed needs or problems can be prevented or adequately addressed.

STRENGTHS AND LIMITATIONS

The major strength of this study is the longitudinal design. We studied a cohort, recruited during hospital admittance, and followed patients prospectively at 7 different time points. A longitudinal design is more reliable for answering prognostic questions, than a cross-sectional or case-cohort study.[78,79] Although conclusions about causality are not possible, prospective cohort studies have the advantage that the prognostic factor precedes the evaluated outcome (criterion of temporality). A second advantage of a longitudinal design is that it enables to explore the course over time. For example, in Chapter 3 we studied whether global outcome, participation restrictions, and community integration developed over time, and if there were differences between two groups based on differing genetic characteristics. In Chapter 4 we determined when deterioration or improvement in community integration occurred, and if the levels stabilized after a certain time point.

Besides the design of the study, an important strength is that our sample is an inception cohort.[78] In his framework for assessing quality of articles dealing with prognosis, Altman described that prognostic variables should be evaluated in a well- defined cohort of patients in the same stage of their disease, preferably an inception cohort.[80] We recruited patients early after the event, i.e. as soon as patients were discharged from intensive care to a general ward. Patients or relatives were contacted and informed about the study and asked whether they were willing to participate and give their informed consent. An inception cohort is preferably recruited in one setting, to prevent referral bias because an academic medical centre often gets referrals that include atypical or unusually sick patients that are more severely injured than the normal population.[80] We recruited patients from three different medical centres. However, we assume that our study sample represented a normal Dutch moderate to severe population, because it was standard procedure that all moderate to severe TBI patients in the region were referred to these three medical centres.

A limitation of this study is the small sample size. Due to the small sample size, we could only investigate a limited number of determinants in relation to outcome, and had

restricted possibilities for internal validation of our findings. The main reasons for the small sample included a disappointing inclusion rate, loss to follow-up, and missing intermittent data. We visited patients at their homes or in the institution of admittance in order to prevent loss to follow-up. Nevertheless, at 3 years post-injury 16 patients were lost to follow-up, 3 had died, and 4 were still admitted in an institution (total of 21%) (Chapter 4). Loss to follow-up is a common problem in cohort studies[81, 82] and especially in TBI patients.[83] In agreement with the literature,[83] we found more loss to follow-up in patients with socioeconomic disadvantages, whereas more severely injured patients were more likely to finish the follow-up measurements. Loss to follow-up can cause selection bias and (despite that our loss to follow-up did not exceed 21%), selection bias may have occurred.[84]

There were several reasons for the missing intermittent data. Some measurements were not assessed if patients were admitted to an institution. During admittance in the hospital or in an institution, we assessed only a limited set of measurements to prevent fatiguing the patient or because measurements were only suited for assessment with patients living independently, e.g. the CIQ. In other cases, patients refused to participate because they did not have enough time, were not feeling up to it, were on holiday, or because they lived temporarily outside the country. We took several steps to make optimal use of our small study sample. We used an ANOVA for repeated measurements (PROC mixed) in SAS to measure change over time (Chapters 3 and 4). This technique allows the use of incomplete datasets instead of only studying complete cases for all measurements. A disadvantage was that sometimes only one observation was used to make an estimation of the outcome.

To identify determinants of outcome at one time point (Chapters 4, 5 and 6) we used a linear or logistic regression analysis. A general rule of thumb is that approximately 10 outcome events are required per determinant.[85, 86] To prevent overfitting, we first reviewed the literature for relevant determinants and combined them with determinants of interest for own purposes. Next, we tested all potential predictors for their univariate relation with the outcome measure. All variables with a p-value below 0.10 were entered in the backward regression analyses. Ultimately, all determinants with a two-sided p-value below 0.05 remained in the models.

Although the backward regression is a common method, it has several drawbacks: the selection is unstable, it has limited power to select prognostically important covariables, and it has a biased estimation of the regression coefficients.[87] For small samples, it was proposed that a full model should be tested with a limited number of important predictors that were preferably pre-specified based on external information.[87] However, the literature on determinants of activities and participation was heterogeneous, unspecific or reported conflicting results. Therefore, it was not possible to select a limited set of predictors in advance. External or internal validation might have revealed whether our

predictive models were too optimistic. Models often perform worse in new patients than in the development sample, and regression coefficients may be overfitted.[88, 89] In reality, external validation of prognostic data is often difficult, because it requires a large independent but comparable population. Internal validation, by dividing into a derivation and a test sample, was simply not possible because of our small sample. Although other internal validation methods (like the bootstrap or jack knife procedure) could have been applied, our research aim was not to make the best prediction, but to identify the most important predictors. For this purpose, the backward regression analysis was considered suitable.

Outcome measures for assessing long-term activities and participation were chosen based on a literature review on commonly used outcome measures in TBI populations.[90] The CIQ and SIP-68 were considered to be reliable and valid instruments for measuring long-term outcome among various health conditions and diseases.[57-60, 70, 91-93] To test the inter-observer reliability within a TBI population, a selection of questionnaires was tested within our own cohort.[94] A good to excellent inter-observer reliability was found in our TBI sample for both the SIP-68 and the CIQ (ICCs of 0.87 and 0.69, respectively) at 1 year post-injury. However, sensitivity to change could not be established as these instruments were only measured once (at 1 year post-injury). However, the SIP-68 was able to detect relatively small differences in an individual over time, therefore it seemed promising.[94] For the CIQ it remained unclear whether it was sensitive to change,[83] especially because norm values were unavailable. Nevertheless, we chose the SIP-68 and CIQ because the combination covered all 9 domains of activities and participation, i.e. learning and applying knowledge; general tasks and demands; communication; mobility; self-care; domestic life; interpersonal interactions and relationships; major life areas; and community, social and civic life.[95]

Based on previous studies on TBI,[2, 96-98] and upon conversations with patients and patient support groups, we expected outcome after TBI to be poorer than in fact found in our study. Patients and relatives repeatedly reported a major impact of TBI on their lives and suggested that their quality of life (QOL) was lower than before the injury. We defined outcome objectively, as activities and participation, based on the ICF model.[95] However, QOL also encompasses an individual component besides physical, cognitive, social, and emotional functioning. Individualised QOL measurements involve personal expectations and satisfaction with characteristics of a person's life.[99, 100] It is likely that the addition of individualized QOL measurements shows a more complete picture of the consequences of TBI, which justifies the experiences of patients and relatives.

CLINICAL IMPLICATIONS

The aim of this thesis was to provide more detailed information on long-term outcome at the levels of activities and participation after moderate to severe TBI. Besides, predicting which patients will survive or will remain in a vegetative state, for those who show a better recovery more detailed information on outcome is needed. Who will return to their work and who will fail to do so? Who will develop marital problems or parental difficulties? Who will be able to engage in social and leisure activities again? TBI is a heterogeneous condition; the cause, injuries, and consequences can vary substantially among patients. It will probably remain difficult to make precise prognoses on these questions.

This thesis explored what determinants predict the level of activities and participation after moderate to severe TBI. These determinants should be considered when discussing outcome with patients and relatives and in planning long-term care. However, the major determinants were not validated either internally or externally and might give an overestimation; in addition, outcome depends on many more determinants than those addressed here. Nevertheless, if clinicians provide a global perspective of possible outcomes this may help patients and their families to cope with the new situation and anticipate the future.

This thesis covered various topics regarding outcome, prognosis, and use of health care after TBI. In the following paragraphs we suggest clinical implications for these specific topics. Our results concerning the determinant APOE-ε4 (Chapter 3) were in contrast to those reported in other studies. Therefore, it seems premature to implement findings on genetics into prognostication of outcome after TBI. The association with APOE-ε4 and outcome, and the mechanisms behind it, are not yet sufficiently understood. After publishing our results, others have also suggested a protective effect of APOE-ε4 on neuropsychological outcome.[101] On the other hand, a meta-analysis of studies on APOE-ε4 found that the APOE-ε4 allele was associated with a poor outcome at 6 months after TBI.[102] The effect of APOE-ε4 may differ over time and genetics may be only one aspect of recovery;[103] other environmental factors might diminish the possible effects APOE-ε4. Future research is needed to elucidate the potential mechanisms induced by APOE-ε4, and the relationship between genetics and outcome.

Because this thesis has shown that participation restrictions persisted even after 3 years, and that unmet needs for restrictions were experienced, several interventions aiming at improvement or stabilising participation may be considered. One possibility to counteract an adverse outcome is to focus treatment on determinants of outcome. APOE-ε4, age and pre-injury community integration are not open to intervention. Prevention or treatment of co-morbidity, limitations in functioning, participation restrictions, and depression may directly alter outcome on the long term. Although probably worthwhile

to apply interventions aimed at determinants in order to influence outcome, it should be mentioned that determinants are not *per se* causally related to outcome. Secondly, depicting outcome, even in global terms, is crucial in a patient-centred approach. When health beliefs and expectations of patients and professionals are matched, patients are stimulated to adopt an active problem-solving coping style and to take control in their own disease management.[104] This might lead to better satisfaction, increased adherence to treatment, and better outcome.[104] The results of our studies emphasise that outcome after TBI is not static and stabile after a predetermined period of time. Outcome is dynamic, changing with transition stages (e.g. discharge from hospital or post-acute rehabilitation, return to leisure activities and return to work) and contextual demands. Intensive rehabilitation programs aimed at improving or stabilising patient's participation appeared to be successful, even up to 12 months post-injury.[105-110] With long-term monitoring of TBI patients and caregivers, drawbacks can be detected in an early phase and suitable interventions applied.

RECOMMENDATIONS FOR FUTURE RESEARCH

Future studies should have a longitudinal design and should be aimed at specific outcome measures that support clinical decision-making or healthcare planning. Most prognostic variables investigated so far cannot be influenced by any therapeutical intervention. Both clinical practice and healthcare policy can benefit from studies directed towards modifiable variables. Examples of such variables include: health beliefs, coping styles, availability of personal aids, and the provision of services. TBI is a highly specialised field. It will take a combined effort of basic scientists (that study e.g. neural recovery mechanisms), clinicians involved in acute neurosurgical and intensive care medicine, and planners of sub-acute rehabilitation medicine and long-term care to achieve and guarantee optimal care for TBI patients.

In conclusion, TBI research requires a prolonged and intense collaboration between basic scientists, clinicians, and policymakers integrated with the patient's and relative's perspective.

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Summary

Outcome after traumatic brain injury (TBI) can range from complete recovery to death, with many survivors having long-term disabilities.[1] In the Netherlands, 3-7 years post-injury 45-67% of the TBI patients suffers from situational, cognitive, and emotional or behavioural problems.[2] Remarkably, 41% of the patients experiences restrictions in participation,[3] but only 10% actually receives rehabilitation services after discharge from acute care.[2] Other Dutch reports describe the following problems related to brain injury patients: 1) insufficient knowledge on TBI and its consequences for patients and their relatives; 2) a gap between healthcare needs and healthcare provision, and 3) an unsatisfactory and inflexible coordination and continuity of care. Therefore, it was often a matter of luck and coincidence whether a patient actually receives adequate healthcare services.[4-6]

This disturbing situation was the rationale for setting up the Rotterdam TBI study: i.e. to investigate the prognosis, the course and determinants of long-term activities, and participation. Another important goal was to evaluate whether healthcare utilisation was based on health-related needs or whether enabling factors or health beliefs also play a role. Finally, we aimed to quantify the prevalence of unmet needs. The Rotterdam TBI study was performed as part of the project 'Long-term prognosis of functional outcome in neurological disorders' (FuPro), supervised by the Department of Rehabilitation Medicine of the VU Medical Centre, Amsterdam and supported by the Netherlands Organisation for Health Research and Development (ZonMw: 1435.0020). The FuPro project investigated long-term outcome and its determinants of four neurological disorders: multiple sclerosis, stroke, motor neuron diseases, and TBI.

For the Rotterdam TBI study, patients were recruited from three Dutch hospitals: the Erasmus Medical Centre (Rotterdam), the Medical Centre Haaglanden and the University Medical Centre Utrecht. Eventually, 119 patients that fulfilled the inclusion criteria were included.

Chapter 1 (Introduction) describes the relevance of the Rotterdam TBI study. Until now, research on outcome and prognosis mainly focused on short-term outcome (6-12 months) and used measures that poorly differentiate between functioning and participation, whereas there is a need for reliable prognostic information on long-term activities and participation. The International Classification of Functioning, Disability and Health (ICF) is presented as an appropriate model to study activities and participation, and to select its potential determinants.

The following research questions are addressed:

1. What is the course of functional outcome after moderate to severe TBI, defined as activities and participation, in the first three years post-injury?
2. What are the determinants of activities and participation 3 years after moderate to severe TBI?
3. To what extent is the utilisation of healthcare and health-related community services determined by health-related needs 3 to 5 years after moderate to severe TBI?
4. What is the prevalence of patient-defined unmet needs concerning autonomy and participation 3 to 5 years after moderate to severe TBI, and what risk factors are related to the occurrence of unmet needs?

At the end of Chapter 1 an outline of the thesis is presented.

Chapter 2 presents a systematic literature review that was performed in preparation for the selection of potential determinants for activity limitations and participation restrictions. In total, 35 papers[7-41] covering 14 prospective cohort studies (published between 1995 and April 2005) were included and evaluated on methodological quality. Data on the results were extracted, and a best-evidence synthesis was carried out to determine the prognostic value for long-term functioning after TBI. Outcome measures were divided into two categories: 1) long-term disability, and 2) being unproductive on the long term.

There was strong evidence that the following prognostic factors predicted long-term disability: older age, pre-injury unemployment, substance abuse, and more severe disability (Disability Rating Scale)[42] at rehabilitation discharge. Inconclusive evidence was found for female gender, and lower Glasgow Coma Scale (GCS) scores[43] in predicting long-term disability.

Strong evidence was found for the following prognostic factors in predicting being unproductive on the long term: pre-injury unemployment, longer posttraumatic amnesia, substance abuse, and more disability (Disability Rating Scale) at rehabilitation admission. Female gender and a lower education level were not predictors of being unproductive on the long term. Inconclusive evidence was found for: older age, fewer years of education, lower GCS scores, violence-related aetiology, longer loss of consciousness, longer length of stay in acute hospital, and less independence at rehabilitation discharge (Functional Independence Measure[44]).

These profiles are predictive for long-term disability and non-productivity and may be used as risk profiles for an adverse outcome. Most predictors from these profiles are not modifiable by prevention or interventions. Further, functional recovery depends on multiple factors and is only partly predicted by these risk profiles.

Genetic factors may also influence outcome after TBI.[45, 46] Presence of the ε4 allele has been associated with a higher mortality,[47] longer duration of unconsciousness,[45] longer hospital stay,[48] more cognitive impairments,[45, 49, 50] and a higher risk of late posttraumatic seizures,[51] and unfavourable outcome after TBI.[46, 48, 52] However, it was not known whether

the gene Apolipoprotein (APOE-ε4) was also related to activity limitations and participation restrictions, or lower community integration and if the association changed over time.

In the study presented in **Chapter 3**, DNA samples were collected for 79 patients; 17 patients (22%) possessed at least one APOE-ε4 allele. No significant association was found between carrying the APOE-ε4 allele and activity limitations and participation restrictions (Sickness Impact Profile-68)[53] or with community integration (Community Integration Questionnaire, CIQ)[54, 55] at 3, 6, 12, 18, 24, and 36 months. Carrying the APOE-ε4 allele was associated with global functional outcome after TBI, measured with the Glasgow Outcome Scale.[56] In contrast to other studies, we found a protective effect of the APOE-ε4 allele. Patients carrying the APOE-ε4 allele had a better global functional outcome than patients without the APOE-ε4 allele, especially at 12, 18, 24, and 36 months post-injury. To explain the difference with other studies that found no association or even a negative influence of the APOE-ε4 allele, we hypothesized that multiple competitive mechanisms were induced by the APOE-ε4 allele. Further, we pointed out that caution is warranted in genetic association studies. Polymorphisms have only a small influence on outcome and other environmental factors might modify their influence.[57] Also, in case of many genes, larges samples are required to draw reliable conclusions.[58, 59]

In **Chapter 4** the course and determinants of participation in the first 3 years after TBI is described. Participation was measured with the CIQ.[54, 55] The CIQ was specially developed for assessing outcome in TBI patients because other measurements were found not to be responsive enough.[54, 55] Evaluation of the course of the CIQ and its subscales, showed a deterioration of the mean scores shortly after the injury compared to the mean pre-injury levels. Afterwards, most domains slowly improved over time. Most improvement was found in the first year after injury but, as expected, we found small increases for several domains after 1 year. Except for the subscale home integration, at 3 years post-injury the mean levels of social integration, productivity, and the total CIQ scores were still below the mean pre-injury levels. Potential determinants were identified with a literature study and tested for their relation with the CIQ at 3 years post-injury. The post-acute Barthel Index[60, 61] score, age at injury, and the pre-injury CIQ score were identified as the major determinants of community integration at 3 years post-injury (R^2=52%). We chose the post-acute Barthel Index score in preference to the post-acute FIM+FAM[62, 63] score, because this was quicker to assess in clinical practice. However, an alternative set of determinants including age at injury, the pre-injury CIQ score, and the post-acute FIM+FAM score proved to be just as adequate in predicting community integration at 3 years post-injury (R^2=53%). Although uncertainties remain for the prognosis, these major determinants can be used to inform patients and relatives, and to distinguish patients at risk for poor community integration.

As a result of these limitations in long-term activity and restrictions in participation, many patients require healthcare and community services. Using the model developed

by Andersen[64,65] the study in **Chapter 5** evaluates healthcare utilisation. According to this model, the utilisation of healthcare services is justified and equitable if it is determined by health-related needs and socio-demographic factors. When enabling factors or individual health beliefs contribute to healthcare utilisation, this indicates an unjustified utilisation or inequity. In total, 16 healthcare and social services, divided into 4 types of care (general practitioner, medical specialists, rehabilitation care, and supportive care) were evaluated in 79 patients. We analysed which type of variables (health-related needs, socio-demographic factors, enabling factors, or health beliefs) contribute to healthcare utilisation. After 3-5 years, 26 patients (32%) no longer used any healthcare services. The general practicioner was contacted most frequently (48%), 42% visited medical specialists, 38% used rehabilitation care, and 16.5% had supportive care. Health-related needs, like participation restrictions and co-morbidity, contributed to all four healthcare types. This suggests that most patients that need care, do actually receive care. However, health beliefs, such as whether you attribute your health status to a physician (external locus of control) or to yourself (internal locus of control), determine the utilisation of medical specialists and supportive care. Therefore, we could not rule out inequity in the utilisation of medical specialists and supportive care. It is possible that individuals have unmet needs that were not identified in this study; it is sometimes difficult for patients and relatives to determine which support or care they need. Unfamiliarity with available healthcare services plays a role in this problem. In addition, TBI patients may 'disappear' from the healthcare system. New healthcare needs, created by altered circumstances, might thereby remain undetected.

In **Chapter 6** we therefore quantified the prevalence of unmet needs in the domains of autonomy and participation [66-68]. At 3-5 years post-injury, 13 of the 78 patients (17%), reported unmet needs on one or more domains. The most frequently reported unmet needs concerned complex participation at work (31%), education (45%), and supporting others (46%). Patients with a risk profile of possible clinical depression were more likely to experience unmet needs in the long term.

The substantial proportion of unmet needs, especially for the domain of complex participation, suggests that the provision of care 3-5 years post-injury is insufficient or not adequately fine-tuned to the healthcare demands. The actual problem may be worse than reported here because patients can also have unrecognized needs.[69,70] Unfortunately, we could not investigate whether this was the case in this study.

Chapter 7 discusses the main findings of the studies, and relates them to earlier reports on the weaknesses and strengths in the healthcare system for patients with a history of TBI.[4-6] Several strengths and limitations of our studies are also addressed. The clinical implications of our findings are presented; these mainly concern interventions focused on improving or stabilizing long-term participation, and the long-term monitoring of patients. Finally, we discuss possible directions for future research.

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Samenvatting

De prognose na een traumatisch hersenletsel (THL) varieert van een dodelijke afloop tot en met compleet herstel, maar de meeste patiënten hebben langdurige beperkingen.[1] In Nederland, ervaart 45 tot 67% van de patiënten 3 tot 7 jaar na het letsel nog situationele, cognitieve, emotionele of gedragsmatige beperkingen als gevolg van het letsel.[2] Opmerkelijk is dat 41% van de patiënten participatie restricties heeft als gevolg van deze beperkingen,[3] maar dat slechts 10% gebruik maakt van revalidatie voorzieningen.[2] Andere Nederlandse rapporten[4-6] beschrijven de volgende problemen voor patiënten met hersenletsel: 1) onvoldoende kennis bij patiënten, familieleden en professionals over het letsel en de consequenties; 2) het bestaan van een hiaat tussen zorgbehoefte en zorgaanbod; 3) een ontoereikende coördinatie en continuïteit van de zorg. Hierdoor is het grotendeels een kwestie van toeval en geluk of iemand adequate zorg krijgt na een hersenletsel.[4-6]

Deze zorgwekkende situatie is de aanleiding geweest voor het starten van het Rotterdam THL-onderzoek: onderzoek naar de prognose, het beloop en determinanten van het te bereiken niveau van activiteiten en participatie. Daarnaast is onderzoek naar zorggebruik en zorgbehoeften een belangrijk onderdeel van dit proefschrift. We hebben gekeken of het gebruik van zorg gebaseerd is op zorggerelateerde behoeften of dat ook andere factoren zoals mogelijkheden tot zorggebruik of gezondheidsopvattingen een rol spelen. Tenslotte hebben we de lange termijn prevalentie van onvervulde zorgbehoeften bepaald. De Rotterdam THL-studie is uitgevoerd als onderdeel van het project ' functionele prognostiek bij neurologische aandoeningen' (FuPro), gesuperviseerd door de afdeling Revalidatiegeneeskunde van het VU Medisch Centrum in Amsterdam en gesubsidieerd door ZonMw (project: 1435.0020). Het FuPro-onderzoek was gericht op het lange termijn functioneren en de determinanten daarvoor voor vier neurologische aandoeningen: multiple sclerose (MS), cerebrovasculaire aandoeningen (CVA), Amyotrofische Lateraal Sclerose (ALS) en traumatisch hersenletsel. Voor de Rotterdam THL-studie werden patiënten gerekruteerd in drie Nederlandse ziekenhuizen: het Erasmus MC, het Medisch Centrum Haaglanden (lokatie Westeinde) en het Universitair Medisch Centrum Utrecht. Uiteindelijk zijn er 119 patiënten die voldeden aan de inclusiecriteria, ingestroomd.

Hoofdstuk 1 (Introductie) beschrijft de relevantie van de Rotterdam THL-studie. Tot nu toe heeft onderzoek naar uitkomsten en prognose zich hoofdzakelijk gericht op korte termijn uitkomsten en gebruikt gemaakt van meetinstrumenten, die slecht differentieerden in functioneren en participatie. Het 'International Classification of Functioning, Disability

and Health' (ICF) model wordt gepresenteerd als een geschikt model voor het bestuderen van activiteiten en participatie en voor het selecteren van potentiële determinanten hiervan. De volgende onderzoeksvragen worden geformuleerd:

1. Wat is het beloop van functioneren, gedefinieerd als activiteiten en participatie, na een matig tot ernstig THL in de eerste 3 jaar na het letsel?
2. Wat zijn determinanten van activiteiten en participatie 3 jaar na het verkrijgen van een matig tot ernstig THL?
3. In welke mate is het gebruik van gezondheidszorg en gezondheidsgerelateerde sociale voorzieningen bepaald door gezondheidsgerelateerde behoeften 3 tot 5 jaar na een matig tot ernstig THL?
4. Wat is de prevalentie van patiëntgedefinieerde onvervulde zorgbehoeften na een matig tot ernstig THL en wat zijn risicofactoren die gerelateerd zijn aan het ervaren van onvervulde zorgbehoeften?

Tenslotte wordt de opzet van het proefschrift beschreven.

Hoofdstuk 2 beschrijft een systematisch literatuuronderzoek dat uitgevoerd is als voorbereiding op het selectieproces van potentiële determinanten voor beperkingen in activiteiten en restricties in participatie. Van alle gepubliceerde artikelen van 1995 tot en met april 2005, zijn 35 artikelen over 14 prospectieve cohort studies[7-41] geëvalueerd op hun methodologische kwaliteit. Uit de resultaten zijn de data geëxtraheerd en is een synthese op basis van het beste beschikbare bewijs uitgevoerd om de voorspellende waarde van diverse determinanten te bepalen voor het lange termijn functioneren na een THL. De verschillende uitkomstmaten zijn ingedeeld in twee categorieën: 1) lange termijn beperkingen en 2) het niet productief zijn op de lange termijn. Er is sterk bewijs dat de volgende prognostische factoren voorspellend zijn voor lange termijn beperkingen: een hogere leeftijd, premorbide werkeloosheid, bovenmatig alcohol- of drugsgebruik en meer beperkingen bij ontslag van de klinische revalidatie (gemeten met de Disability Rating Scale[42]). Er is onvoldoende bewijs dat vrouwen en een lage Glasgow Coma Scale (GCS) score[43] voorspellers waren voor lange termijn beperkingen.

Er werd sterk bewijs gevonden dat de volgende prognostische factoren voorspellend zijn voor het niet productief zijn op de lange termijn: premorbide werkeloosheid, een langere posttraumatische amnesie, overmatig alcohol of drugsgebruik en meer beperkingen bij de opname in een revalidatiecentrum. Het vrouwelijke geslacht en een lager onderwijsniveau zijn geen voorspellers voor niet productief zijn op de lange termijn. Er is onvoldoende bewijs dat de volgende variabelen voorspellers zijn: een hogere leeftijd, een kortere opleidingsduur, lagere GCS scores, een geweldsgerelateerde oorzaak, een langere coma duur en een langer verblijf in het ziekenhuis en afhankelijkheid bij het ontslag uit het revalidatiecentrum (gemeten met de Functional Independence Measure[44]). Deze profielen zijn voorspellend voor beperkingen en improductiviteit op de lange termijn en kunnen dienen als risicoprofielen voor een ongunstig beloop. De meeste voorspellers

uit deze profielen zijn echter niet veranderbaar door preventie of interventies. Daarnaast is het functioneel herstel na THL multifactorieel bepaald en wordt maar deels voorspeld door deze risicoprofielen.

Ook genetische factoren kunnen van invloed zijn op het herstel na een THL.[45,46] Het dragen van het Apolipoprotein ε4 (APOE-ε4) allel werd geassocieerd met een hogere mortaliteit,[47] langere coma duur,[45] een langer ziekenhuisverblijf,[48] meer cognitieve beperkingen,[45,49,50] een hoger risico van recente posttraumatische epilepsie[51] en ongunstig herstel na een THL.[46,48,52] Het was echter onbekend of APOE-ε4 ook voorspellend was voor beperkingen in activiteiten en participatie of voor de mate van sociale integratie en of de relatie veranderde over de tijd.

In **hoofdstuk 3** is DNA materiaal van 79 patiënten verzameld; 17 patiënten (22%) hadden tenminste één APOE-ε4 allel. Er is geen significante associatie gevonden tussen het dragen van het APOE-ε4 allel en beperkingen in activiteiten en participatie (gemeten met de Sickness Impact Profile-68)[53] of met sociale integratie (gemeten met de Community Integration Questionnaire, CIQ)[54,55] op 3, 6, 12, 18, 24 en 36 maanden na het letsel. Dragerschap van het APOE-ε4 allel is wel geassocieerd met globaal functioneel herstel na een THL (gemeten met de Glasgow Outcome Scale[56]). In tegenstelling tot andere studies, vonden wij een beschermend effect van het APOE-ε4 allel; de patiënten met het APOE-ε4 allel hadden een beter globaal functioneel herstel dan patiënten zonder het APOE-ε4 allel, vooral op 12, 18, 24 en 36 maanden na het letsel. Als verklaring voor het contrast met studies die geen of een negatieve invloed van het APOE-ε4 allel vonden, veronderstellen we dat er meerdere en mogelijk concurrerende mechanismen door het APOE-ε4 allel geïnduceerd worden. Daarnaast geven we aan dat in het algemeen voorzichtigheid geboden is bij het interpreteren van genetische studies. Polymorfismen hebben slechts een klein effect op de uiteindelijke uitkomst en dit effect kan gemakkelijk gemaskeerd worden door omgevingsfactoren.[57] Verder zijn er grote steekproeven nodig om betrouwbare gevolgtrekkingen te maken over de prognostische waarde van genetische factoren, zeker wanneer er meerdere genen bestudeerd worden.[58,59]

In **Hoofdstuk 4** wordt het beloop en determinanten van participatie in de eerste 3 jaar na het letsel beschreven. De CIQ is gebruikt voor het meten van participatie. De CIQ werd speciaal ontwikkeld voor de beoordeling van herstel in THL patiënten omdat andere meetinstrumenten niet sensitief genoeg gevonden werden.[54,55] Het beloop van de CIQ en zijn subschalen toont een verslechtering van de gemiddelde scores kort na het letsel in vergelijking met de gemiddelde niveaus voor het letsel. Daarna zijn langzame verbeteringen gevonden over de tijd. De grootste vooruitgang werd geboekt in het eerste jaar na het letsel, maar zoals we verwachtten, was er ook nog vooruitgang voor de gemiddelde scores op de totale CIQ, de subschaal sociale integratie en de subschaal productiviteit. Drie jaar na het letsel is het gemiddelde niveau op alle subschalen en de totale CIQ echter nog steeds onder het gemiddelde premorbide niveau. Dit met uitzon-

dering voor de subschaal die de thuissituatie meet. Thuis functioneerde men weer op het niveau van vóór het letsel. Potentiële determinanten voor de CIQ werden geïdentificeerd door een literatuurstudie en getest op hun relatie met de CIQ 3 jaar na het letsel. De postacute Barthel Index score,[60,61] de leeftijd ten tijde van het letsel en de premorbide CIQ score bleken de belangrijkste determinanten van participatie in de sociale context 3 jaar na het letsel (R^2=52%). In de analyses selecteerden we de postacute Barthel Index ten gunste van de postacute score op de Functional Independence Measure + Functional Assessment Measure (FIM+FAM),[62,63] omdat de Barthel Index gemakkelijker af te nemen is in de klinische praktijk. Echter, een alternatief model van leeftijd, de premorbide CIQ score en de postacute FIM+FAM score blijkt ook voorspellend voor participatie in de sociale context 3 jaar na het letsel (R^2=53%). Hoewel er onzekerheden blijven omtrent de prognose kunnen deze determinanten gebruikt worden om patiënten en hun naasten te infomeren en om een onderscheid te maken tussen patiënten die extra risico lopen op een slechte participatie in de sociale context.

Door de beperkingen in activiteiten en participatie op lange termijn, hebben veel patiënten gezondheidsvoorzieningen en sociale voorzieningen nodig. In **Hoofdstuk 5** wordt dit geëvalueerd volgens het model ontwikkeld door Andersen.[64,65] Volgens dit model worden gezondheidszorgvoorzieningen terecht gebruikt en dus eerlijk verdeeld wanneer het gebruik bepaald wordt door gezondheidsgerelateerde behoeften en sociaal-demografische factoren. Wanneer individuele omstandigheden en individuele gezondheidsopvattingen bepalend zijn voor het gebruik van gezondheidszorgvoorzieningen wijst dit op onterecht gebruik of op een oneerlijke verdeling. Het gebruik van 16 typen gezondheidszorg is geëvalueerd bij 79 patiënten en deze zijn vervolgens geaggregeerd in 4 typen zorg (huisarts, medisch specialisten, revalidatie en ondersteunende zorg). Na 3 tot 5 jaar gebruikten 26 patiënten (32%) geen gezondheidszorgvoorzieningen. De huisarts werd het meest bezocht (door 48% van de patiënten), 42% had contact met medische specialisten, 38% kreeg revalidatie en 16.5% gebruikte ondersteunende zorg. Zorggerelateerde behoeften, zoals participatie restricties en co-morbiditeit zijn bepalend voor alle geaggregeerde typen gezondheidszorg. Dit suggereert dat de meeste patiënten die zorg nodig hebben, deze ook ontvangen. Echter, gezondheidsovertuigingen zoals de vraag of je de verantwoordelijkheid voor je gezondheid bij een arts legt (externe locus of control) of bij jezelf (interne locus of control) blijken mede bepalend voor het gebruik maken van medisch specialistische en ondersteunende zorg. We kunnen onbillijkheid in het gebruik van medisch specialistische zorg en ondersteunende zorg dan ook niet uitsluiten.

Het is mogelijk dat individuele patiënten onvervulde zorgbehoeften hebben die niet zijn geïdentificeerd in deze studie. Voor patiënten en verwanten kan het moeilijk zijn om te bepalen welke ondersteuning en gezondheidszorg ze nodig hebben. Onbekendheid met de beschikbare zorgvoorzieningen speelt daar een rol in. Bovendien kunnen THL

patiënten uit het gezondheidszorgsysteem verdwijnen, waardoor nieuwe zorgbehoeften door veranderde omstandigheden onopgemerkt kunnen blijven.

In **hoofdstuk 6** is daarom de prevalentie van onvervulde zorgbehoeften bepaald op het gebied van autonomie en participatie[66-68] 3 tot 5 jaar na het THL. Op de lange termijn hadden 13 van de 78 patiënten (17%) onvervulde zorgbehoeften op één of meerdere domeinen. Het vaakst werden onvervulde zorgbehoeften gemeld op het gebied van complexe participatie, zoals werk (31%), onderwijs (45%) en het steunen van anderen (46%). Patiënten met een risicoprofiel van mogelijke klinische depressie rapporteerden vaker onvervulde zorgbehoeften 3 tot 5 jaar na het letsel. Het aanmerkelijke aantal onvervulde zorgbehoeften, vooral op het gebied van complexe participatie, suggereert dat het aanbod van zorg op deze termijn niet voldoende of niet goed afgestemd is op de vraag. Het daadwerkelijke probleem kan groter zijn dan hier gerapporteerd omdat THL patiënten ook zorgbehoeften kunnen hebben, die niet herkend worden.[69,70] Helaas konden we niet onderzoeken of dit ook het geval was in onze studie.

Tot slot bespreekt **hoofdstuk 7** de belangrijkste bevindingen van de studies en relateert deze aan de bevindingen die beschreven zijn in diverse Nederlandse rapporten over de sterke en zwakke punten in het gezondheidszorg systeem waar het betreft de lange termijn afstemming tussen vraag en aanbod van gezondheidszorg voor mensen met een THL in de voorgeschiedenis.[4-6] Daarnaast worden sterke kanten en zwakke kanten van ons onderzoek besproken. We doen suggesties voor klinische toepassingen van de resultaten met betrekking tot lange termijn interventies, die zich richten op het stabiliseren en verbeteren van participatie na het letsel en op het langlopend volgen van patiënten. Tenslotte, bespreken we enkele mogelijkheden voor toekomstig onderzoek.

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Dankwoord

Het voltooien van een proefschrift kan een onoverkomelijke hobbel in het leven lijken. Zeker als je je energie in zaken steekt waarin je niets kunt veranderen. Maar door zelfmanagement, inzet en doorzettingsvermogen is dit proefschrift afgekomen! Voor mij waren het turbulente jaren. Terugziend op mijn promotieperiode, realiseer ik me dat ik bij aanvang van deze periode een aantal pittige doelen had gesteld: promoveren, verbouwen en een gezinsplanning. Sommige dingen zijn gelukt, anderen niet. Hoe dan ook, deze periode is voor mij erg leerzaam geweest en heeft gezorgd voor een groei op wetenschappelijk vlak maar bovenal ook voor een persoonlijke groei. Een quote van een van mijn favoriete schrijvers, Paulo Coelho, lijkt hier heel goed bij te passen: "There are moments when troubles enter our lives and we can do nothing to avoid them, but they are there for a reason; only when we have overcome them will we understand why they were there." *(Paulo Coelho, The Fifth Mountain)*. Met dit proefschrift is een van mijn doelen bereikt en ik wil dan ook graag een aantal mensen bedanken.

Prof. Dr. H.J. Stam: Beste Henk, tijdens dit traject schetste je een duidelijk kader van mijn plichten en rechten. Dit maakte het voor mij mogelijk om mijn werk met vertrouwen te doen. Ik waardeer je pragmatische visie en het feit dat je me niet alleen wees op mijn fouten, maar ook je waardering uitsprak. Bedankt voor een leerzame periode.

Dr. G.M. Ribbers: Beste Gerard, na een turbulente start, hebben wij onze weg vonden. Jij zorgde voor de randvoorwaarden die nodig waren om dit onderzoek te kunnen voltooien. Daarnaast was je klinische kijk een waardevolle aanvulling op mijn onderzoeksblik. Bedankt voor je hulp, respect en vertrouwen.

Prof. Dr. G.A.M. van den Bos: Beste Trudi, uiteindelijk hebben we niet één maar twee artikelen geschreven. Ik heb je kritische feedback enorm gewaardeerd. Mijn artikelen zijn er behoorlijk door verbeterd. Daarnaast waardeerde ik je assertiviteit en vind je een goed voorbeeld van een succesvolle vrouw in de wetenschap. Je werd daarmee voor mij een rolmodel. Hartelijk bedankt voor al je inspiratie!

Dr. A.P. Verhagen: Beste Arianne, jij hebt me begeleid bij het schrijven van mijn eerste artikel. Het was erg fijn om op een 'expert' te kunnen terugvallen. Telkens kwam ik opgelucht bij je vandaan en kon ik weer verder. Je hielp me over mijn eerste hobbel

heen en gaf me daarmee de motivatie om de rest van mijn proefschrift ook te voltooien. Hartelijk bedankt hiervoor!

Dr. Ir. W.C.J. Hop: Beste Wim, jouw kritische blik en nuchtere commentaar over de statistische analyses van mijn artikelen, heeft dit proefschrift aanzienlijk beter gemaakt. Bedankt!

Ik wil **Prof. Dr. C.M. van Duijn**, **Jeannette Vergeer** en **Alejandro Arias** van de afdeling Epidemiologie en Biostatistiek bedanken voor hun hulp bij het derde hoofdstuk van mijn proefschrift en het analyseren van de DNA-samples.

Dit onderzoek is uitgevoerd als onderdeel van het FuPro onderzoek. Ik wil graag alle mensen van het FuPro onderzoek bedanken voor de prettige samenwerking: **Prof. Dr. Guus Lankhorst** en **Prof. Dr. Joost Dekker**, **Dr. Annet Dallmeijer**, **Prof. Dr. Maarten IJzerman**, **Dr. Heleen Beckerman**, **Dr. Vincent de Groot** (VU Medisch Centrum Amsterdam en tevens project coördinatie); **Prof. Dr. Eline Lindeman**, **Dr. Gert Kwakkel**, **Dr. Ingrid van de Port**, **Dr. Vera Schepers** (UMC Utrecht/Revalidatiecentrum de Hoogstraat); en **Prof. Dr. Trudi van den Bos** (Academisch Medisch Centrum/Universiteit van Amsterdam).

Voor hun hulp bij de inclusie en het verkrijgen van de neurologische data, wil ik Prof. Dr. Andrew Maas, **Tineke Landman** en **Frans Slieker** (afdeling Neurochirurgie van het Erasmus MC), **Dr. G.W. van Dijk** en **Joke Nijdeken** (afdeling Neurologie, Universitair Medisch Centrum Utrecht), en **Dr. D.J. Versluis** (Intensive care van het Medisch Centrum Haaglanden, lokatie Westeinde) bedanken.

Bianca van Baalen: Beste Bianca, als voorganger op het TBI-project heb je me wegwijs gemaakt in het project en de metingen. Ik wil je bedanken voor de leuke tijd die we samen gehad hebben.

Ik wil **Martine Eckhart** bedanken voor haar hulp bij het opschonen van de database. Dit was een hele klus en jij hebt me fantastisch geholpen!

Ik wil **Laraine Visser** en **Lous te Boekhorst** bedanken voor het kritisch nakijken van mijn manuscripten op de Engelse en Nederlandse taal.

Natuurlijk wil ik ook **alle deelnemers, partners, familie en hun verzorgers of verpleegkundigen** bedanken voor alle tijd die ze in dit onderzoek gestoken hebben. Een heel groot aantal van de mensen die Bianca en ik gevraagd hebben, wilden mee doen aan

dit onderzoek. Dit was heel bijzonder, zeker gezien het feit dat we jullie vroegen in een zware periode. Maar ook daarna bleven jullie ons ontvangen met koffie, koekjes en heerlijkheden en bleven onze vragen beantwoorden. Aan jullie heb ik de kaft van mijn proefschrift gewijd! Heel erg bedankt voor alles!

Gelukkig zit je niet alleen op een kamer. Op de 16e hebben we altijd een hele leuke sfeer gehad. Ik wil dan ook **Berbke, Janneke, Jorrit, Bart, Diana, Mark, Marian, Channah, Wilma, Wim, Fabienne, Laurien (Buffart), Mireille, Robert en Laurien (Aben)** bedanken voor al hun gezelligheid, steun, en wetenschappelijke input. Samen waren we sterk!

Janneke, bij jouw promotie mocht ik je paranimf zijn. Nu sta jij naast mij en dat betekent heel veel voor me! In al die jaren ben je veel meer dan een collega geworden. Ik zou je niet meer willen missen. Ook op het werk heb je me bij van alles geholpen: met analyses, het ordenen van mijn gedachten en het nakijken van mijn stukken. En daarnaast heb je me gesteund op alle manieren waar ik alleen maar op kon hopen. Fantastisch, ik vind JOU echt super!

Bea, ik vind het heel leuk dat we niet alleen meer partners zijn van onze mannen, maar dat wij ook vriendinnen zijn geworden. Ik vind jou heerlijk nuchter, diplomatiek, en betrokken en ik vind het dan ook fantastisch dat je paranimf wilt zijn!

Johan en Thea, jullie wil ik bedanken voor het fijne uitrusten in Frankrijk, het opnieuw weer opladen, maar ook voor alle lieve telefoontjes in tijden dat ik die wel kon gebruiken. Bedankt!

Papa en mama, jullie hebben stiekem een hele grote bijdrage geleverd aan het tot stand komen van mijn proefschrift. Jullie hebben mij altijd gestimuleerd tot door leren en het uiterste eruit halen. Door jullie ben ik een doorzetter geworden. Het zal voor jullie lang niet altijd duidelijk zijn geweest wat ik allemaal aan het doen was, maar jullie waren erbij. Jullie hebben met mij mijn lief en leed gedeeld, me gesteund en jullie waren trots op me! Dat deed mij heel veel goed!

Marleen, met jou heb ik vele wandelingen over het strand gemaakt, en dan bespraken we (telkens weer) dat ik over een half jaartje vast mijn artikel wel af zou hebben… Uiteindelijk is dat ook gelukt. Helemaal leuk was dat jij ook in de laatste fase van mijn proefschrift betrokken was. Jij hebt mijn ideetje fantastisch uitgewerkt tot een heel mooi resultaat waar ik erg blij mee ben. Bovendien was het heel leuk om weer eens samen te werken als in de goede oude tijd. Thanks goof!

Lieve **Daïm**, natuurlijk hebben **Mac, Maria** en jij het meeste 'leed' moeten aanhoren in de afgelopen zes jaar. Jij hebt alle stormen moeten trotseren èn hebt ze ook getrotseerd! Bovendien heb je me gestimuleerd om als vrouw een gelijkwaardige positie in te nemen en niet met minder genoegen te nemen. Bedankt voor alles!

Curriculum Vitae

Agnes van Son is geboren op 30 juli 1974 te 's-Hertogenbosch. In 1992 behaalde zij haar VWO-diploma aan het Zwijsen College Veghel. Vervolgens behaalde zij in 1993 haar propedeuse HBO-Verpleegkunde aan de Hogeschool Eindhoven. Daarna heeft ze gewerkt in diverse functies en in de avonduren haar NIMA-A certificaat behaald. In 1996 is ze begonnen aan de opleiding Psychologie aan de Katholieke Universiteit Brabant te Tilburg. Tijdens haar studie werkte zij als student-assistent bij de vakgroep Methoden en Technieken van de Sociale Faculteit. Na haar afstuderen in 2002, begon zij direct met haar promotietraject naar de lange termijn gevolgen van een traumatisch hersenletsel. Het promotieonderzoek werd uitgevoerd in opdracht van de afdeling Revalidatiegeneeskunde van het Erasmus MC en Rijndam Revalidatiecentrum te Rotterdam. In 2004 werd haar aanstelling uitgebreid om mee te werken aan een internationale validatiestudie van een kwaliteit van leven vragenlijst (QOLIBRI) voor traumatisch hersenletselpatiënten in opdracht van de afdeling Neurochirurgie.

Agnes is in 2001 getrouwd met Daïm Willemse.

PhD Portfolio Summary

Erasmus MC
Universitair Medisch Centrum Rotterdam

SUMMARY OF PHD TRAINING AND TEACHING ACTIVITIES

Name PhD student: Agnes Willemse-van Son	PhD period:
Erasmus MC Department: Rehabilitation Medicine	01/09/2002 –
Research School: Nihes	28/01/2009
	Promotor(s): Prof.dr. H.J. Stam
	Supervisor: Dr. G.M. Ribbers

1. PhD training

	Year	Workload (Hours/ECTS)
General academic skills		
Biomedical English Writing and Communication	2003	4 ECTS
Research skills		
Statistics		
Classical methods for data-analysis	2003	5.7 ECTS
Regression analysis for clinicians	2008	1.4 ECTS
Survival analysis for clinicians	2008	1.4 ECTS
Longitudinal data-analysis	2006	0.9 ECTS
Methodology		
Principles of research in medicine and epidemiology	2003	0.7 ECTS
In-depth courses (e.g. Research school, Medical Training)		
Clinical decision analysis	2003	0.7 ECTS
Methods of health services research	2003	0.7 ECTS
Medical technology assessment	2003	0.7 ECTS
Topics in evidence based medicine	2003	0.7 ECTS
Methods of clinical research	2003	0.7 ECTS
Presentations		
Workshop 'Het meten van functioneren bij patiënten met een traumatisch hersenletsel: enkele conclusies van de Rotterdam TBI-studie' at the symposium of the 'landelijke werkgroep Niet Aangeboren Hersenletsel', Rotterdam	2004	10 hours
Workshop 'Van onderzoek naar klinische praktijk: traumatisch hersenletsel', at FuPro symposium 'meten en voorspellen in de revalidatie bij neurologische aandoeningen. Wat levert het op?', Amersfoort	2005	8 hours
Presentation 'Lange termijn zorggebruik na een traumatisch hersenletsel'. Presented at the 'Werkgroep Traumatisch Hersenletsel', Utrecht	2007	4 hours
Poster presentation 'Prognostic factors of long-term disability and non-productivity after traumatic brain injury', poster on the 12th EMN annual meeting, Rome, Italy	2007	8 hours

Presentation 'Is there inequity in health care utilization after traumatic brain injury?' Presented at 'the IBIA seventh world congress on brain injury', Lisbon, Portugal	2008	8 hours
Presentation 'Association between Apolipoprotein ε4 and long-term outcome after traumatic brain injury.' Presented at 'the IBIA seventh world congress on brain injury' Lisbon, Portugal	2008	8 hours
Presentation 'Traumatisch hersenletsel: de eerste 3 jaar.' Presented at the '1e Rijndamdag voor patiënten', Rotterdam	2008	8 hours
Presentation 'Apolipoprotein ε4 en lange termijn herstel na een traumatisch hersenletsel.' Presented at the 'neuroreferaat', Rotterdam		4 hours
International conferences		
The 27th annual Williamsburg traumatic brain injury rehabilitation conference, Williamsburg, Virginia, USA	2003	20 hours
The IBIA seventh world congress on brain injury, Lisbon, Portugal	2008	24 hours
Seminars and workshops		
FuPro symposium 'meten en voorspellen in de revalidatie bij neurologische aandoeningen. Wat levert het op?', Amersfoort	2005	8 hours
VRA-lustrum dag, The Hague	2005	8 hours
QOLIBRI meeting, Rome, Italy	2005	16 hours
Symposium 'Hormonale uitval na traumatisch hersenletsel: een onderschat probleem', Utrecht	2006	8 hours
FuPro symposium 'Functionele prognose na CVA: Houvast voor de revalidatie professional?', Utrecht	2007	4 hours
Didactic skills		
Course 'boeiend presenteren met powerpoint', Onderwijs Expertise Centrum Rotterdam, Rotterdam	2006	4 hours
Other		
Training Zelf-management	2005	15 hours

2. Teaching activities

	Year	Workload (Hours/ECTS)
Lecturing		
Partial Lecture for second-year medical students: Research at the Department Rehabilitation.	2003	5 hours
Lecture at the VRA-PAOG course for rehabilitation physicians: 'functionele prognostiek'	2006	8 hours
Supervising practicals and excursions		
Supervising Master's theses		
Supervising of students and assistant physicians with their research	2007-2008	30 hours
Other		