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Fatigue, physical activity and participation in adolescents and young adults with acquired brain injury

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Fatigue, Physical Activity and Participation in Adolescents and Young Adults with Acquired Brain Injury

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Fatigue, Physical Activity and Participation in Adolescents and Young Adults with Acquired Brain Injury

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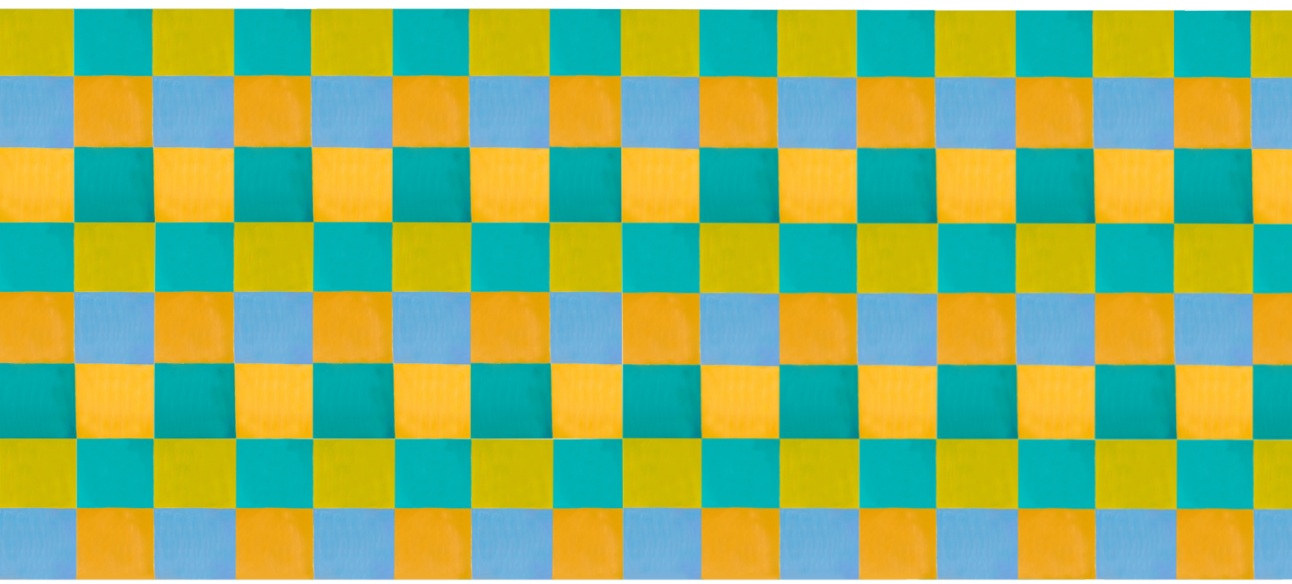
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Chapter 1

General introduction

General introduction

In this general introduction, definitions and epidemiology and etiology of acquired brain injury (ABI), in particular in Adolescents and Young Adults (AYAs), will be outlined. The consequences of ABI in AYAs will be described, with a focus on fatigue, physical activity and participation. Based on gaps in current knowledge, the aims of this thesis are formulated.

Definitions of Acquired Brain Injury (ABI) and Adolescents and Young Adults (AYAs)

ABI is defined as an injury to the brain that affects its structure or function, resulting in impairments of cognition, communication, physical function, or psychosocial behavior. ABI does not include brain injuries that are congenital, degenerative, or induced by birth trauma. ABI can be either due to an external cause (traumatic brain injury; TBI) or an internal cause (non-traumatic brain injury; NTBI).[1]
According to the World Health Organization[2] adolescents are persons from 10 up to and including 18 years, and young adults 15 up to and including 23 years. This thesis is focused on the age group from 15 up to and including 24 years, which is commonly designated as Adolescents and Young Adults (AYAs).

ABI: Epidemiology, etiology, and classification

Until now epidemiological studies on ABI mainly focused on TBI, whereas data on the incidence of NTBI are mostly available for specific causes. ABI is a common injury, with an estimated worldwide incidence of TBI of 54-60 million[3] and stroke of 15 million persons[4] per year.

TBI in AYAs

TBI is defined as any post-neonatal damage to the brain, caused by an external force[1].
The estimated annual incidence of TBI in the Netherlands is 296 per 100 000 in AYAs, based on hospital records, with traffic accidents (40%), followed by (suspicion of) abuse (26%) and sports accidents (10%) as most common causes.[5]
Overall there is a trend towards an increasing incidence and prevalence of ABI in AYAs over the past decades, probably in part related to better registration and improvements in medical care, the latter leading to a larger proportion of patients who survive a trauma.[6]
The classification of TBI is based on severity of symptoms (see Figure 1).[7 8, 9]

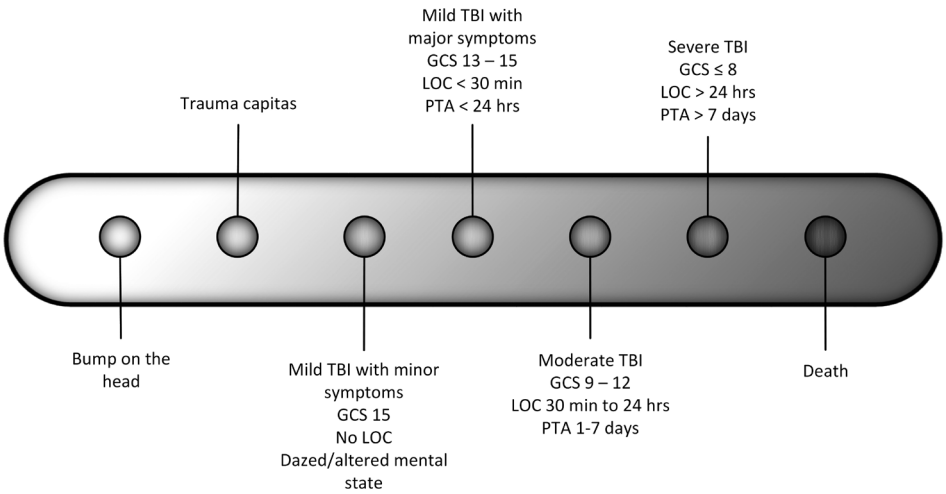


Figure 1. Classification of traumatic brain injury; from left to right increasing severity of injury.

In the abovementioned Dutch study[5] in a defined hospital based cohort of patients with ABI, the large majority (84%) of cases the TBI was classified as mild (mTBI) or concussion, with symptoms often resolving with 4 weeks, whereas in 16% a hospital based diagnosis of "moderate or severe" TBI was reported. That proportion of moderate or severe TBI is relatively high as compared to the age group 0-13 years where 9% was classified as moderate or severe.[5, 10]

NTBI in AYAs

NTBI is defined as any post-neonatal damage to the brain with an internal cause: anoxia, infarction, toxic effect of substances, brain tumors, meningitis, metabolic encephalopathy, encephalitis, or other brain disorders.[1]

For the classification of NBTI the modified Rankin Scale (mRS) is often used. The mRS uses a 0-6 scale ranging from 0=having no symptoms to 6=death.[11]

Population-based research and data on subtypes of pediatric NTBI is limited.[12] Previous research in the Netherlands has shown that the estimated annual incidence of NTBI is 81 per 100 000 per year in the age group 15-24 years, with brain tumors and meningitis being most common among AYAs,[5] in line with literature[12]. Special attention is needed for the patients with NTBI after substance use, since this was the largest subgroup of patients in the Canadian study.[12]

In a Dutch study the percentage of AYAs having moderate/severe consequences after NTBI is higher than after TBI. Within the NTBI group, the rate of mild versus moderate /severe NTBI in AYAs is comparable to that of the younger age group.[5]

Consequences of TBI and NTBI in AYAs

After ABI, depending on its nature and severity, multiple neural systems may be involved, resulting in a large variety of potential consequences for body functions and structures. Regarding the consequences of ABI, many children and AYAs report persistent symptoms.[6,13-16] Fatigue, physical inactivity and participation restrictions are among the most commonly reported sequalae after ABI; both after TBI[17-23] and NTBI[24-29].

The consequences of ABI on a person's health can be classified according to a biopsychosocial model such as the WHO International Classification of Functioning, Disability and Health (ICF) or ICF for Children and Youth (ICF-CY) models.[30] Within these frameworks "functioning" refers to abilities encompassing body functions, structures, activities and participation. Participation is defined as "the nature and extent of a person's involvement in meaningful life situations at home, school, work and community life". Personal and environmental factors may influence body functions and structures as well as activities and participation. In AYAs reduced Quality of Life (QoL), with the ICF code nd-qol, has been found in all injury severities of TBI[31-33] and NTBI[15, 28].

With respect to the course of health problems after ABI, there is a large variation, ranging from a) full recovery, b) persisting and severe impairment, c) absence of impairment initially, with emerging problems over time to d) early slowed development, with catch-up over time.[6,12]

Fatigue

Fatigue is defined as the experience of exhaustion and a decreased capacity for physical or mental activity because of an imbalance in the availability, use or restoration of resources needed to perform activity.[34] For clinical use, fatigue is best defined as difficulty in initiating or sustaining voluntary activities.[35] Fatigue is among the most commonly reported sequelae after ABI.[17, 36] Fatigue can be divided in physical or mental fatigue, with a continuous mutual influence on several functions and activities.

With respect to fatigue after ABI in children and AYAs, the literature is limited. Depending on the study population and research design, 58-75% of children and adolescents with ABI report fatigue,[25,36-38] including a study 13 years post-injury with fatigue being one of the most reported symptoms[39]. Fatigue is a common symptom in adolescence as well; research in healthy adolescents reported fatigue in 20.5% of girls and 6.5% of boys.[40]

Specifically for the young adult population a limited number of studies on fatigue are available, reporting more fatigue in the stroke group (age 15–49 years)[27]and an mixed ABI group (age 15-30 years)[41]as compared to healthy controls. Fatigue has been found

irrespective of severity of ABI.[17, 18] Fatigue is associated with worse outcomes after NTBI in everyday activities in the school, home, and social environments[42-44] with limited knowledge on these associations in AYAs with TBI.
Fatigue in chronic conditions has a dominant negative impact in multiple cognitive, social and functional domains, as well as in transitions from childhood to adulthood, i.e. social network and activities, education and work, and quality of life of AYAs and their families.[45]

Physical activity

Physical activity refers to "any bodily movement produced by skeletal muscles that results in energy expenditure".[46] Persons with disabilities more often lead a sedentary lifestyle than healthy individuals.[47] Like fatigue, physical inactivity has been reported as an important consequence of ABI in the adult population.[21, 48] No literature has been found specifically addressing the AYA age group with ABI except for studies on sports concussions with a focus on a sports group, e.g. college sports, which include AYAs.[49] Studies on physical activity levels after ABI have been merely focusing on "return to play"[50] and "sports participation"[51, 52] or participation in activities[53, 54]. Overall, studies reporting physical activity in terms of time spent on moderate or high intensity level physical activity per day or per week, either measured by means of self-report, activity monitors or pedometers are scarce. A general finding in adult TBI studies is that persisting fatigue is related to decreased PA.[55-57]

Participation

Participation concerns "involvement in life situations"[58] and reflects the extent of engagement in the full range of activities that accomplish a larger goal[59]. In research, participation is defined and operationalized using two key elements/themes: attendance ("being there") and involvement 'in-the-moment'.[60] Participation of AYAs include artistic, creative, cultural, active physical, education, civic, sports, play, social, skill-based, and work activities. Participation is vital for the development of physical, psychological and social emotional skills, competences and well-being, shaping of identity and subsequently a major determinant of healthy living and future outcome. Studies have shown that AYAs with ABI, as well as other age groups, have restrictions in participation throughout the lifespan, particularly when compared to peers without a disability.[22] Factors associated with participation include pre-injury characteristics, such as age, sex, social economic status[53] as well as post-injury characteristics such as injury severity, motor impairments, cognitive impairments, behavior, mood and environmental barriers[22] and specifically fatigue[42, 61].
The most common environmental facilitators for participation were found to be social

support of family and friends and geographic location. The most commonly reported barriers included attitudes of peers and the lack of support from staff and service providers.[53, 62] Better participation is often related to a better quality of life.[32]
In summary, although there is a relatively large body of knowledge on ABI, this is mainly focused on children and physical and cognitive outcomes. ABI literature for the age group 15-24 is relatively scarce, specifically on the impact of ABI on fatigue, physical activity and participation, aspects generally known to be affected after ABI,[19, 36, 63] and inter-related. This thesis therefore focuses on ABI and these particular consequences in AYAs.

Aims of this thesis

Given the relative lack of knowledge on the consequences of ABI in AYAs, in particular regarding the aspects of fatigue, physical activity and participation, this thesis aims to:

1. Describe the occurrence of fatigue, physical inactivity and participation restrictions and their mutual relationships in a hospital-based cohort and in AYAs with ABI in a rehabilitation setting.
2. Describe the work status of unemployed AYAs with ABI who take part in an age-specific vocational rehabilitation program.

These aims are addressed in the following chapters:

- **Chapter 2** describes a multi-center retrospective cohort study on ABI in children and youth and parent-reported fatigue and relationships with patient and family characteristics.
- **Chapter 3** presents fatigue and physical activity levels, at least 6 months post-injury, in a rehabilitation-based cohort of AYAs with TBI.
- **Chapter 4** concerns a multi-center retrospective cohort study of fatigue and physical activity in AYAs with mild TBI and orthopedic controls 6 to 18 months after their visit to the emergency department of a general hospital.
- **Chapter 5**, using the data of the mild TBI patients in the study described in Chapter 4, focuses on the relationship between physical activity, fatigue and sleep.
- **Chapter 6** presents the results of a multi-center prospective cohort study of AYAs with ABI admitted to an outpatient clinic of a rehabilitation center, with emphasis on their symptoms and activities and participations restrictions at admission.
- **Chapter 7** describes the processes and outcomes of a vocational rehabilitation program for unemployed adolescents and young adults with ABI.
- In **Chapter 8** the findings of the studies in this thesis are summarized and discussed.

References

1. Greenwald B, Burnett D, Miller M. Congenital and acquired brain injury. 1. Brain injury: epidemiology and pathophysiology. Arch Phys Med Rehabil. 2003;84:S3-S7.
2. *World Health Organization: Adolescence: a period needing special attention*, internet site: http://apps.who.int/adolescent/second-decade/section2/page1/recognizing-adolescence.html [cited Oct 16 2019].
3. Feigin V, Theadom A, Barker-Collo S, et al. Incidence of traumatic brain injury in New Zealand: a population-based study. *Lancet Neurol*. 2013;Jan;12(1):53-64.
4. *The Internet Stroke Center: Stroke statistics,* internet site: http://www.strokecenter.org/patients/about-stroke/stroke-statistics. [cited Oct 16 2019].
5. de Kloet A, Hilberink S, Roebroeck M, et al. Youth with acquired brain injury in The Netherlands: a multi-centre study. *Brain Inj*. 2013;27(7-8):843-9.
6. Anderson V, Godfrey C, Rosenfeld J, Catroppa C. 10 years outcome from childhood traumatic brain injury. *Int J Dev Neurosci*. 2012;May;30(3):217-24.
7. Choe M, Valino H, Fischer J, et al. Targeting the epidemic: Interventions and follow-up are necessary in the pediatric traumatic brain injury clinic. *J Child Neurol*. 2016;Jan;31(1):109-15.
8. Kristman V, Borg J, Godbolt A, et al. Methodological issues and research recommendations for prognosis after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil*. 2014;Mar;95(3 Suppl):S265-77.
9. *Department of Defense and Department of Veterans Affairs: Traumatic Brain Injury Task Force*. 2008; Washington, DC US Armed Forces.
10. Stam C, Blatter B. [*Injuries 2017: Key data Injury Information System (LIS)*]. 2018; Amsterdam, The Netherlands:VeiligheidNL.
11. Delsing B, Catsman-Berrevoets C, Appel I. Early prognostic indicators of outcome in ischemic childhood stroke. *Pediatr Neurol*. 2001;24: 283–289.
12. Chan V, Pole J, Keightley M, Mann R, Colantonio A. Children and youth with non-traumatic brain injury: a population based perspective. *BMC Neurol*. 2016;20;16:110.
13. Catroppa A, Anderson V, Morse S, Haritou D, Rosenfeld J. Outcome and predictors of functional recovery 5 years following pediatric traumatic brain injury. *J Pediatr Psychol*. 2008;33:707–718.
14. Kristiansen I, Strinnholm M, Strömberg B, Frisk P. Clinical characteristics, long-term complications and health-related quality of life (HRQoL) in children and young adults treated for low-grade astrocytoma in the posterior fossa in childhood. *J Neurooncol*. 2019;Mar;142(1):203-210.
15. Neuner B, von Mackensen S, Krümpel A, et al. Health-related quality of life in children and adolescents with stroke, self-reports, and parent/proxies reports: cross-sectional investigation. *Ann Neurol*. 2011;70:70–78.
16. Barlow K. Postconcussion Syndrome: A Review. *J Child Neurol*. 2014;Jan;31(1):57-67.
17. Gagner C, Landry-Roy C, Lainé F, Beauchamp M. Sleep-Wake Disturbances and fatigue after pediatric traumatic brain injury: A systematic review of the literature. *J Neurotrauma*. 2015;Oct 15;32(20):1539-52.
18. Crichton A, Anderson V, Oakley E, et al. Fatigue following traumatic brain injury in children and adolescents: A longitudinal follow-up 6 to 12 months after injury. *J Head Trauma Rehabil*. 2018;May/Jun;33(3):200-209.
19. Lequerica A, Botticello A, Lengenfelder J, et al. Factors associated with remission of post-traumatic brain injury fatigue in the years following traumatic brain injury (TBI): a TBI model systems module study. *Neuropsychol Rehabil*. 2017;27(7):1019-1030.
20. Englander J, Bushnik T, Oggins J, Katznelson L. Fatigue after traumatic brain injury: Association with neuroendocrine, sleep, depression and other factors. *Brain Inj*. 2010;24(12):1379-88.
21. Hamilton M, Khan m, Clark R, Williams G, Bryant A. Predictors of physical activity levels of individuals following traumatic brain injury remain unclear: A systematic review. *Brain Inj*. 2016;30(7):819-28.
22. de Kloet A, Gijzen R, Braga L, Meesters J,

Schoones J, Vliet Vlieland T. Determinants of participation of youth with acquired brain injury: A systematic review. *Brain Inj*. 2015;Sep;29(10):1135-1145.
23. Larsson J, Björkdahl A, Esbjörnsson E, Sunnerhagen K. Factors affecting participation after traumatic brain injury. *J Rehabil Med*. 2013;Sep;45(8):765-70.
24. Johansson B, Starmark A, Berglund P, Rödholm M, Rönnbäck L. A self-assessment questionnaire for mental fatigue and related symptoms after neurological disorders and injuries. *Brain Inj*. 2010;Jan;24(1):2-12.
25. Macartney G, Harrison H, VanDenKerkhof E, Stacey D, McCarthy P. Quality of life and symptoms in pediatric brain tumor survivors: a systematic review. *J Pediatr Oncol Nurs*. 2014;Mar-Apr;31(2):65-77.
26. Cormie P, Nowak A, Chambers S, Galvão D, Newton R. The potential role of exercise in neuro-oncology. *Front Oncol*. 2015;Apr 8;5:85.
27. Ness K, Morris, Nolan V, et al. Physical performance limitations among adult survivors of childhood brain tumors. *Cancer*. 2010;Jun 15;116(12):3034-44.
28. Gupta P, Jalali R. Long-term Survivors of Childhood Brain Tumors: Impact on General Health and Quality of Life. *Curr Neurol Neurosci Rep* 2017;Nov 8;17(12):99.
29. Goeggel Simonetti B, Cavelti A, Arnold M, et al. Long-term outcome after arterial ischemic stroke in children and young adults. *Neurology*. 2015;May 12;84(19):1941-7.
30. *International classification of functioning, disability and health: children and youth version: ICF-CY*. 2010; Switserland: World Health Organization.
31. Anderson V, Brown S, Newitt H, Hoile H. Long-term outcome from childhood traumatic brain injury: intellectual ability, personality, and quality of life. *Neuropsychology*. 2011;Mar;25(2):176-84.
32. Di Battista A, Soo C, Catroppa C, Anderson V. Quality of life in children and adolescents post-TBI: a systematic review and meta-analysis. *J Neurotrauma*. 2012;29:1717–1727.
33. Limond J, Dorris L, McMillan T. Quality of life in children with acquired brain injury: parent perspectives 1-5 years after injury. *Brain Inj*. 2009;Jul;23(7):617-22.
34. Aaronson L, Teel C, Cassmeyer V, et al. Defining and measuring fatigue. *Image J Nurs Sch*. 1999;31(1):45-50.
35. Chaudhuri A, Behan P. Fatigue in neurological disorders. *Lancet*. 2004;363(413): 978-988.
36. Wilkinson J, Marmol N, Godfrey C, et al. Fatigue following paediatric acquired brain injury and its impact on functional outcomes: A systematic review. *Neuropsychol Rev*. 2018;28(1):73-87.
37. Eisenberg M, Meehan Wr, Mannix R. Duration and course of post-concussive symptoms. *Pediatrics*. 2014;Jun;133(6): 999-1006.
38. Sumpter R, Brunklaus A, McWilliam R, Dorris L. Health-related quality-of-life and behavioural outcome in survivors of childhood meningitis. *Brain Inj*. 2011;25(13-14):1288-95.
39. Aaro Jonsson C, Emanuelson I, Smedler A. Variability in quality of life 13 years after traumatic brain injury in childhood. *Int J Rehabil Res*. 2014;Dec;37(4):317-22.
40. ter Wolbeek M, van Doornen L, Kavelaars A, Heijnen C. Severe fatigue in adolescents: a common phenomenon? *Pediatrics*. 2006;117(6):e1078-86.
41. Norup A, Svendsen S, Doser K, et al. Prevalence and severity of fatigue in adolescents and young adults with acquired brain injury: A nationwide study. *Neuropsychol Rehabil*. 2017;Sep 12:1-16.
42. Greenham M, Gordon A, Cooper A, et al. Social functioning following pediatric stroke: contribution of neurobehavioral impairment. *Dev Neuropsychol*. 2018;43(4):312-328.
43. Meeske K, Katz E, Palmer S, Burwinkle T, Varni J. Parent proxy-reported health-related quality of life and fatigue in pediatric patients diagnosed with brain tumors and acute lymphoblastic leukemia. *Cancer*. 2004;Nov 1;101(9):2116-25.
44. Maaijwee N, Arntz R, Rutten-Jacobs L, et al. Post-stroke fatigue and its association with poor functional outcome after stroke in young adults. *J Neurol Neurosurg Psychiatry*. 2015;Oct;86(10):1120-6.
45. Crichton A, Knight S, Oakley E, Babl F, Anderson V. Fatigue in child chronic health conditions: a systematic review

of assessment instruments. *Pediatrics*. 2015;Apr;135(4):e1015-31.
46. *World Health Organization: Physical Activity*. Internet site: https://www.who.int/dietphysicalactivity/pa/en/ [cited Oct 16 2019].
47. Rimmer J, Rowland J. Physical activity for youth with disabilities: a critical need in an underserved population. *Dev Neurorehabil*. 2008;Apr-Jun;11(2):141-8.
48. *Rehabilitation of persons with traumatic brain injury. NIH Consensus Statement*. 1998;16:1-41.
49. Schmidt J, Rubino C, Boyd L, Virji-Babul N. The role of physical activity in recovery From concussion in youth: A neuroscience perspective. *J Neurol Phys Ther*. 2018;Jul;42(3):155-162.
50. Cancelliere C, Hincapié C, Keightley M, et al. Systematic review of prognosis and return to play after sport concussion: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil*. 2014;Mar;95(3 Suppl):S210-29.
51. Howell D, Osternig L, Chou L. Adolescents demonstrate greater gait balance control deficits after concussion than young adults. *Am J Sports Med*. 2015;43(3):625-32.
52. Gagnon I, Swaine B, Friedman D, Forget R. Exploring children's self-efficacy related to physical activity performance after a mild traumatic brain injury. *J Head Trauma Rehabil*. 2005;20(5):436-49.
53. Anaby D, Law M, Hanna S, Dematteo C. Predictors of change in particpation rates following acquired brain injury: results of a longitudinal study. *Dev Med Child Neurol*. 2012;54(4):339-46.
54. Grool A, Aglipay M, Momoli F, et al. Association between early participation in physical activity following acute concussion and persistent postconcussive symptoms in children and adolescents. *JAMA*. 2016;316(23):2504-2514.
55. Ponsford JL, Ziino C, Parcell DL, et al. Fatigue and Sleep Disturbance Following Traumatic Brain Injury-Their Nature, Causes, and Potential Treatments. *J Head Trauma Rehabil*. 2012;27(3):224-233.
56. Ponsford J, Schönberger M, Rajaratnam S. A model of fatigue following traumatic brain injury. *J Head Trauma Rehabil*. 2015;30(4):277-282.
57. Jankowski L, Sullivan S. Aerobic and neuromuscular training: effecton the capacity, efficiency, and fatigability of patients with traumatic brain injuries. *Arch Phys Med Rehabil*. 1990;71(7):500-4.
58. *International classification of functioning, disability and health*. 2001; Switserland: World Health Organization.
59. Imms C, Adair B, Keen D, Ullenhag A, Rosenbaum P, Granlund M. 'Participation': a systematic review of language, definitions, and constructs used in intervention research with children with disabilities. *Dev Med Child Neurol*. 2016;Jan;58(1):29-38.
60. Bedell G, Coster W, Law M, et al. Community participation, supports, and barriers of school-age children with and without disabilities. *Arch Phys Med Rehabil*. 2013;Feb;94(2):315-23.
61. Ezekiel L, Collett J, Mayo N, Pang L, Field L, Dawes H. Factors Associated With Participation in Life Situations for Adults With Stroke: A Systematic Review. *Arch Phys Med Rehabil*. 2019;May;100(5):945-955.
62. Driver S, Ede A, Dodd Z, Stevens L, Warren A. What barriers to physical activity do individuals with a recent brain injury face? *Disabil Health J*. 2012;5(2):117-25.
63. Cantor J, Ashman T, Gordon W, et al. Fatigue after traumatic brain injury and its impact on participation and quality of life. *J Head Trauma Rehabil*. 2008;23(1):41-51.



Chapter 2

Factors related to fatigue after pediatric acquired brain injury (ABI)

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Poster presentation IBIA World Congress March 2016, The Hague, The Netherlands

Abstract

Objective

To assess the degree of fatigue in children and youth after traumatic and non-traumatic brain injury (TBI and NTBI) and related factors.

Methods

Follow-up study including patients with a hospital-based diagnosis of acquired brain injury (ABI), aged 4–20 years at onset and their parents. Parents and children (dependent on age) completed the Pediatric Quality of Life Inventory™ Multidimensional Fatigue Scale (PedsQL™ MFS), which measures general fatigue (GF), sleep/rest fatigue (SRF) and cognitive fatigue (CF). Additional assessments included the Child & Family Follow-up Survey (CFFS) and PedsQL™ 4.0 General Core Scales and sociodemographic and disease characteristics.

Results

Eighty-eight parents completed the PedsQL™ MFS 24–30 months after diagnosis, with 49/88 patients (56%) completing the child version. The median age of the patients was 11 years (interquartile range [IQR] = 7). There were 69 patients with TBI (16% moderate/severe TBI) and 19 patients with NTBI (16% moderate/severe NTBI). The median parent-reported and child-reported PedsQL™ MFS Total Scale Scores were 77.8 (IQR 25.0) and 79.2 (18.1), respectively (Spearman r = 0.450, p = 0.001). Apart from NTBI, increasing age and a single-parent household were significantly associated with more fatigue according to the parent-reported PedsQL™ MFS Total Score (and/or one or more subscale scores).

Conclusions

Two years after onset, in particular, the parent-reported fatigue after NTBI was considerable. Moreover, older children and children from a single-parent household were found to have higher fatigue levels.

Introduction

Acquired brain injury (ABI) refers to any damage to the brain that occurs after birth, due to a traumatic (TBI) or non-traumatic (NTBI) cause.[1] In children and youth the yearly incidence of ABI is substantial, with estimated incidence rates for the age group 0–24 years in the Netherlands being 585 per 100.000 for TBI and 190 per 100.000 for NTBI,[2] similar to incidence rates reported in the international literature.[3,4] In the pediatric population, ABI was found to have a considerable impact on the participation and quality of life of patients with TBI[5–9] and NTBI.[10–12]

One of the most common symptoms after ABI is fatigue.[13–15] Fatigue is defined as the experience of exhaustion and a decreased capacity for physical or mental activity because of an imbalance in the availability, use or restoration of resources needed to perform activity.[16] For clinical use, fatigue is best defined as difficulty in initiating or sustaining voluntary activities.[17] For fatigue occurring after TBI, the term 'post-traumatic brain injury fatigue' (PTBIF) has been established. PTBIF is generally viewed as a form of 'central fatigue', a category of fatigue that is secondary to neurological conditions and is distinct from 'peripheral fatigue', which is experienced as muscle fatigue following a period of exertion.[17,18]

Research on fatigue after ABI has so far focused mainly on the adult population. For TBI, a systematic review including 22 clinical studies[19] showed that fatigue is relatively frequently present before and immediately following injury and can persist in the long-term. The reported rates in the literature range from 21–73%, with at 10 years post-injury, on average 50% of the patients suffering from fatigue.[19] A systematic review including nine studies on fatigue in an adult population with NTBI (stroke) found that fatigue varied from 35–92% at admission to hospital to 38–86% at 12–36 months post-stroke.[20]

With respect to the prevalence of fatigue in children after ABI, data on fatigue are scarce. Recent studies reported varying fatigue rates in children after TBI, with reported frequencies ranging from 30–74% 2–3 weeks post-injury [21,22] and 11% after 3 months[23]. In a recent systematic review on long-term consequences of TBI in children under 18 years of age [24] including 24 studies, fatigue was found to be one of the most persistent symptoms at 13 years post-injury.

For the pediatric population with NTBI, data on fatigue are even more scarce, with a recent study in children under 16 years of age showing that 13% reported fatigue on average 6.9 years after stroke.[25]

Regarding the factors related to the occurrence and/or severity of fatigue in children and youth with ABI, there are currently no studies available. Yet in adults, socio-demographic and injury characteristics as well as pre-injury fatigue and depression were found to be associated with fatigue after ABI.[19]

As the literature on the occurrence and determinants of fatigue in children and youth with ABI is scarce, the aim of this study was to determine the severity of fatigue after TBI and NTBI in a hospital-based cohort, as well as factors related to fatigue.

Methods

Design and setting

This study on parent-reported and child-reported fatigue was part of a larger, multi-center, hospital-based study on the incidence of ABI in The Netherlands.[2] In that study, performed in 2010, 1892 patients, aged 1 month to 24 years, with a first hospital-based diagnosis of ABI made in 2008 or 2009, were identified using the emergency ward databases and the patient admission registries of three large hospitals in The Netherlands (Erasmus University Medical Center in Rotterdam, Haga Hospital and Medical Center Haaglanden, both in The Hague). In a follow-up study, the health status of a sub-group of patients aged 4–20 years at onset of injury, ~ 2 years after onset of ABI, was determined. Data on family functioning in this follow-up study have already been published.[26] The study (including the follow-up) was approved by the Medical Ethical Committee (METC) of the Erasmus University Medical Center Rotterdam (METC-2009-440). All parents and patients (if > 18 years) participating in the follow-up assessment gave written informed consent.

Participants

For the larger study patients were selected from the databases and registries of the participating hospitals using the following clinical diagnoses: skull/brain trauma, concussion, contusion cerebrum and neurological trauma comprised traumatic brain injury (TBI) and brain tumor, meningitis or encephalitis, stroke, acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS) or acute central nervous system (CNS) demyelinating disease and hypoxia-ischaemia were labelled as non-traumatic brain injury (NTBI). Patients were excluded if they were diagnosed with trauma capitis (minor head injury without brain symptoms). Inclusion criteria for the follow-up study were: age at onset of ABI 4–20 years and the ability to understand and complete questionnaires in Dutch.

Of all patients participating in the larger study, the age at onset, gender, year of onset, the type of injury (TBI or NTBI) and the severity had been extracted from the medical records. The severity of TBI was determined by means of the Glasgow Coma Scale (GCS) at hospital admission. According to the GCS, the severity of TBI was considered mild if the GCS was 13–15, moderate if the GCS was 9–12 or severe if the GCS was < 9.[27]

The severity of NTBI was determined at the time of discharge after the first admission to the hospital for this particular problem and was scored by means of an adapted version of the modified pediatric Rankin Scale (mRS) [11,28] (school performance not taken into consideration): mild injury: no limitations (mRS score 0, 1); moderate injury: mild motor impairments and/or mild problems with learning (mRS 2, 3); severe injury: severe motor impairments and/or severe problems with learning (mRS 4, 5). In addition, mRS 6 was used in cases of death during admission.

To select patients for the follow-up study, the total group of participants was categorized by age (4–12 or 13–20 years at onset), year of onset (2008 or 2009), type (TBI or NTBI) and severity of injury (mild–moderate–severe), yielding 24 sub-groups in total. Aiming at a total number of 400 patients to be invited for follow-up, with an expected response of 50%, 18–20 patients per sub-group were selected from the database using the statistical software program Statistical Package For Social Sciences (SPSS).[29] This procedure yielded a selection of 433 patients. These patients and/or their parents were subsequently approached by mail to participate in the study.

Follow-up assessments

Follow-up assessments consisted of the completion of a set of questionnaires as well as a visit to the hospital outpatient clinic for an interview and neurological examination.[26] In the week before the scheduled examination, parents received questionnaires to be completed at home: for this study, the Child & Family Follow-up Survey (CFFS),[30] the PedsQL™ 4.0 General Core Scale[31] and the PedsQL™ Multidimensional Fatigue Scale (MFS)[32]. According to their age, children received two questionnaires to be completed at home: the PedsQL™General Core Scale and the PedsQL™ MFS.

Parent- and child-reported multidimensional fatigue scale

The 18-item questionnaire yields a PedsQL™ MFS Total Scale Score and three subscale scores: general fatigue (GF) (six items), sleep/rest fatigue (SRF) (six items) and cognitive fatigue (CF) (six items). In this study, parent and child report versions for children of 5–7, 8–12 and 13–18 years old were used. In the parent version, items are reversely scored using a 5-point Likert scale with the scores being linearly transformed to a 0–100 scale (0 = 100, 1 =75, 2 =50, 3 =25, 4 =0), so that higher scores indicate less fatigue. Only for the young child (5–7 years) version was a 3-point scale used. Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). If more than 50% of the items in a subscale were missing, the subscale score was not computed. The Dutch language version of the PedsQL™ MFS has been validated for children and young adults (18–25 years).[33,34]

Overall functioning

Another module of the PedsQL™ 4.0, pertaining to the child's health status, and available in a Dutch language version, the General Core Scales, was used.[35,36] It measures physical (eight items), emotional (five items), social (five items) and school functioning (five items). In this study, parent and child report versions for children of 5–7, 8–12 and 13–18 years old were applied. The scoring system is similar to that of the PedsQL™ MFS. To create the Total Scale Score, the mean is computed as the sum of all the items over the number of items answered on all the subscales.

Participation and environmental factors

The Child & Family Follow-up Survey (CFFS), parent version,[37,38] comprising the Child and Adolescent Scale of Participation (CASP), the Child and Adolescent Factors Inventory (CAFI) and the Child and Adolescent Scale of Environment (CASE), was used. For both the CAFI and the CASE, higher scores indicate a greater number of problems, a greater impact of problems or a combination of the two.

Physical and mental problems of the child before ABI

The presence of physical and/or mental problems of the child before the ABI and/or at present was determined by means of two structured interview questions for the parents (yes/no).

Statistical analysis

Characteristics of patients and parents were analyzed using descriptive statistics. All continuous variables were expressed as means with standard deviations or medians with IQRs, depending on their distribution.

Comparisons of socio-demographic and injury characteristics of the patients included in the present analysis with those of all patients in the follow-up study were done by means of the unpaired Student's t-test, Mann-Whitney U-test or Chi-Square-test, where appropriate. Likewise, comparisons of socio-demographic and injury characteristics, the PedsQL™ MFS Total and subscale scores and all other outcome measures in patients with TBI and NTBI were done.

The parent-reported and child-reported PedsQL™ MFS Total and subscale scores were compared by means of the Wilcoxon signed ranked test. Moreover, the Spearman rank correlation coefficient and the Intra Class Correlation Coefficients[39] between the parent and child scores were computed.

To determine which factors were univariably associated with fatigue, the parent-reported PedsQL™MFS Total and subscale scores were compared between sub-groups of patients. Subgroups were made for the following variables: characteristics before

or at onset of ABI (socio-demographic: patient age at onset and gender; educational level of parents and single or double parent household; presence of mental and/or physical health problems in patient before ABI; injury characteristics: type, severity); functioning 2 years after onset of ABI (presence of mental and/or physical health problems, activities and participation, fatigue, quality of life). For the independent variables, patients were divided into sub-groups according to fixed categories for nominal variables or by the median score for numeric variables. Comparisons of parent-reported PedsQL™ MFS Total and subscale scores between the sub-groups were done by means of unpaired t-tests.

Then, a multivariable analysis was performed, based on the results of the univariable analysis (qualifying p-value < 0.20) with the parent-reported PedsQL™MFS Total and subscale scores as dependent variables and socio-demographic, pre-injury and injury characteristics as independent variables. The variables concerning actual functioning (CFFS, and PedsQL™ General Core) were not entered into the multivariable prediction model, as they concerned the outcome of ABI rather than its starting point. The variables which were not significantly associated with the outcome were dropped from the model, after a stepwise analysis. Results were presented as regression coefficients and explained variance. The use of different classification systems for severity in TBI and NTBI warranted the need to conduct the analyses separately in those sub-groups. As this categorization yielded a relatively small number of patients in the various categories of severity, this study combined severity levels to examine the impact of TBI and NTBI on parent-reported fatigue. The sample size of n = 88 supports the number of analyses conducted.

In addition, for all analyses except for the variables entered into the multivariable regression analysis, a p-value less than 0.05 was adopted as the criterion for statistical significance. All data were analyzed using SPSS version 22.0 software.[29] Missing values were processed according to instructions for each questionnaire.

Results

Participants

The flow of patients is presented in Figure 1. In total, 141 of the 433 invited parents agreed to participate in the follow-up study. There were no significant differences in age or type of injury between responders and non-responders.[26]

Of the 141 parents and/or patients willing to participate, 108 returned a set of questionnaires and took part in the examination. Due to the accidental sending of an incomplete set of questionnaires, only 88 of these 108 parents completed the PedsQL™ MFS.

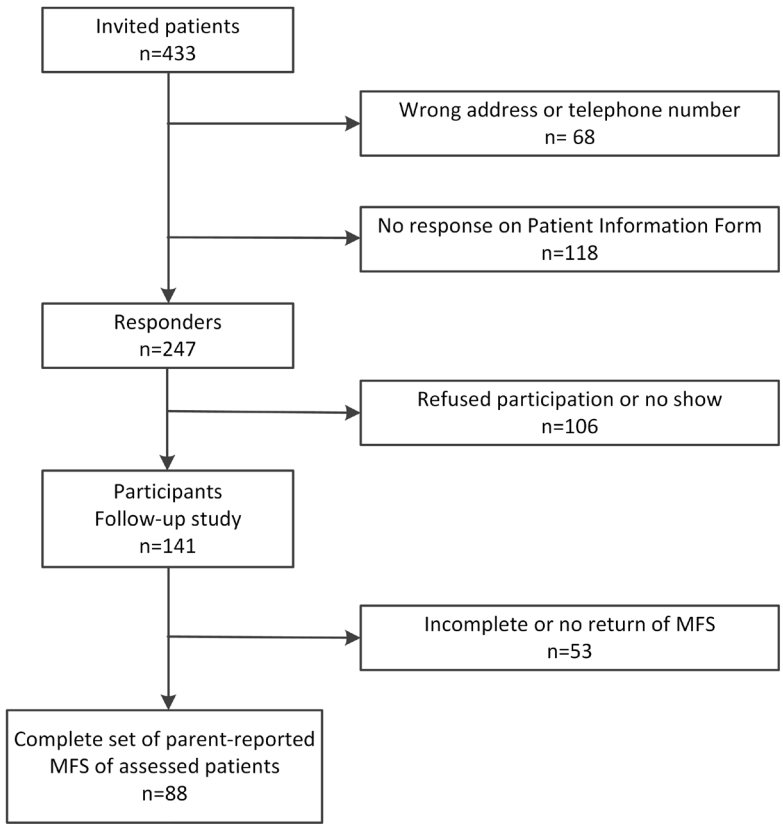


Figure 1. Flow chart recruitment of participants

The 88 patients included in the present analysis were significantly younger than the other 53 taking part in the follow-up study (median age = 11 years, IQR = 7 vs. median age 18 years, IQR = 5, respectively, $p < 0.001$), whereas all other characteristics were similar. The numbers (%) of parents completing the other assessments were: CASP (79, 90%), CAFI (82, 93%), CASE (73, 83%) and PedsQL™ General Core Scale (82, 93%). Forty-nine children of the 88 parents (56%) completed the child-reported PedsQL™ MFS and General Core Scales.

Table 1 shows the characteristics of the children with ABI of the 88 participating parents and/or children. The participants with NTBI were significantly older than those with TBI ($p = 0.040$). Other pre-injury characteristics were not significantly different between the two groups.

Table 1. Characteristics of 88 patients with traumatic or non-traumatic brain injury (TBI or NTBI) approximately 2 years after onset.

	Total Group n=88	**TBI n=69**	**NTBI n=19**	**p value* TBI vs. NTBI**
Age at onset in years; median, (IQR)	11 (7)	11 (6)	14.0 (7)	**0.040**
Sex, male; number (%)	43 (49)	32 (46)	11 (58)	0.380
Severity of injury[1,2]; number (%)				
Mild		58 (84)	15 (79)	
Moderate-severe		11 (16)	3 (16)	
Unknown			1 (5)	
Educational level parents[3]; number (%)				
Low	9 (10)	9 (13)	0	
Intermediate	29 (33)	21 (30)	8 (42)	0.187
High	40 (46)	30 (44)	10 (53)	
Unknown	10 (11)	9 (13)	1 (5)	
Single parent household; number (%)	20 (23)	14 (20)	6 (32)	0.455
Pre-injury physical or mental health problems child; number (%)	21 (26)	16 (23)	5 (26)	0.841
Actual physical or mental health problems child; number (%)	31 (35)	26 (38)	5 (26)	0.208
PedsQL FIM Total Scale Score[4], median (IQR)	82.1 (26.6) n=83	91.4 (24.7) n=64	72.3 (28.2) n=19	**0.003**
CFFS-DLV CASP Total Score[5], median (IQR)	96.3 (10.0) n=79	98.8 (7.5) n=60	92.5 (13.4) n=19	**0.043**
CFFS-DLV CAFI Total Score[6], median (IQR)	40.0 (12.8) n=82	37.8 (11.7) n=63	44.4 (15.6) n=19	**0.010**
CFFS-DLV CASE Total Score[7], median (IQR)	35.2 (5.6) n=73	34.3 (1.9) n=55	39.8 (9.7) n=18	**0.001**
PSOM-SNE DSS[8], median (IQR)	1.0 (2.0) n=81	0.5 (2.0) n=62	2.0 (2.0) n=19	**0.001**
PedsQL General Core Scales[9], median (IQR)	77.8 (28.0) n=82	81.5 (23.2) n=63	73.4 (24.2) n=19	0.202

[1] TBI: severity determined by means of the Glasgow Coma Scale (GCS) at hospital admission.
[2] NTBI: severity determined by means of a disability scale based on the Modified Rankin Scale (mRS) at hospital discharge.
[3] low (pre-vocational practical education or less), intermediate (pre-vocational theoretical education and upper secondary vocational education), or high (secondary education, higher education, and/or university level education).
[4] FIM: PedsQL™ Family Impact Module, score range 0-100, higher scores indicate better functioning.
[5] CFFS-DLV CASP Total: Child & Family Follow-up Survey, Dutch Language Version; Child and Adolescent Scale of Participation, score range 0-100, higher scores indicate better functioning and less participation problems.
[6] CFFS-DLV CAFI Total Score: Child & Family Follow-up Survey, Dutch Language Version; Child and Adolescent Factors Inventory, score range 33.3-100, higher scores indicate more limitations in functions.
[7] CFFS-DLV CASE Total Score: Child & Family Follow-up Survey, Dutch Language Version, Child and Adolescent Scale of Environment, score range 0-100, higher scores indicate more environmental limitations.
[8] PSOM-SNE Disability Severity Score: Pediatric Stroke Outcome Measure Short Neuro Exam, score range 0-10, lower scores indicate better functioning.
[9] PedsQL™ General Core Scales: score range 0-100, higher scores indicate better HRQOL (Health-Related Quality of Life).
*= p-value of Student t test, Mann-Whitney U or Chi Square test, where appropriate.
IQR: interquartile range

Overall, scores of measures of actual functioning were worse in patients with NTBI than in patients with TBI, with the differences for the DFFS-DLV CAFI, –CASP and –CASE reaching statistical significance.

Fatigue after pediatric ABI

Table 2 shows the results of the PedsQL™MFS Total Scale score and the subscale scores as reported by parents and children. The median scores on the parent reported PedsQL™MFS Total Scale Score and Cognitive Fatigue in the TBI group were significantly better than in the NTBI group, whereas General Fatigue and Sleep/rest Fatigue scores were not significantly different. For the child-reported scores there was no significant difference between the TBI and NTBI groups, neither for the Total Score nor the subscale scores.

For the 49 pairs of parents and children both filling in the questionnaire, only Sleep/rest Fatigue differed significantly from one another: median = 87.5 (IQR = 25.0) vs 83.3 (IQR = 22.9), p = 0.020. The Total Score, General Fatigue and Cognitive Fatigue showed no significant difference between parent- and child reported fatigue. The Spearman rank correlations between the Total and Subscale scores of the PedsQL™ MFS of parents and children were low-to moderate (Total Scale Score, r = 0.450, p < 0.001; General Fatigue, r = 0.235, p = 0.103; Sleep/rest Fatigue, r = 0.354, p = 0.013 and Cognitive Fatigue, r = 0.561, p = 0.001). The intra-class correlation coefficient between

Table 2. Parent- and child-reported fatigue as measured with the Pediatric Quality of Life Inventory™ Multidimensional Fatigue Scale (PedsQL™ MFS) in patients with traumatic or non-traumatic brain injury (TBI or NTBI). All values are medians (interquartile range).

	Parent-reported PedsQL™ MFS				**Child-reported PedsQL™ MFS**			
	Total group n=88	**TBI n=69**	**NTBI n=19**	**p value[2]**	**Total group n=49**	**TBI n=39**	**NTBI n=10**	**p value[2]**
Total Fatigue Score [1]	77.8 (25.0)	79.2 (27.8)	68.1 (31.9)	**0.038**	79.2 (18.1)	79.2 (19.4)	78.5 (13.9)	0.568
General Fatigue [1]	83.3 (33.3)	87.5 (29.2)	75.0 (33.3)	0.081	83.3 (20.8)	83.3 (20.8)	85.4 (24.0)	0.635
Sleep/rest Fatigue[1]	87.5 (25.0)	87.5 (25.0)	79.2 (29.2)	0.402	83.3 (22.9)	83.3 (20.8)	87.5 (21.9)	0.330
Cognitive Fatigue[1]	70.8 (45.8)	79.2 (47.9)	58.3 (29.2)	**0.011**	83.3 (31.3)	83.3 (33.3)	64.6 (29.2)	0.122

[1] total and subscores range from 0-100; higher scores indicate better functioning and less fatigue.
[2] p-value of comparison between TBI and NTBI calculated with the Mann-Whitney U test.

parent reported and child reported scores for the Total and subscale scores were fair-to-moderate (Total score ICC = 0.458, $p < 0.001$, moderate correlation; General Fatigue ICC = 0.220, $p = 0.061$, fair correlation; Sleep/rest Fatigue ICC = 0.276, $p = 0.025$, fair correlation; Cognitive Fatigue ICC = 0.516, $p < 0.001$, moderate correlation).[40]

With respect to floor and ceiling effects, in the total group the highest possible score was reported by 11 parents (13%) for the PedsQL™ MFS Total Fatigue Score (no fatigue problems) and eight parents (9%) for the Health-Related Quality of Life Score. Children had the highest possible score in two cases (3%) for the PedsQL™ MFS Total Scale Score (no fatigue problems) and for the child reported Health-Related Quality of Life Score in one (2%) case.

Table 3 shows the results of the univariable analyses with the PedsQL™ MFS Total Scale Score, General Fatigue, Sleep/rest Fatigue and Cognitive Fatigue as dependent variables and socio-demographic, pre-injury and injury characteristics and actual functioning as independent variables. For the independent variables, patients were divided in sub-groups according to fixed categories for nominal variables or by the median score for numeric variables.

The parent-reported PedsQL™ MFS Total Scale Score and one or more subscale scores were significantly different between younger and older patients, with lower scores (more fatigue) in older patients.

Moreover, there were significant associations between the PedsQL™ MFS Total Scale Score and one or more subscale scores and the household composition, the presence of preinjury health problems of the child, the type of injury and the CASP, CAFI, CASE and PedsQL™ General Core Scales.

Table 4 shows the results of the multivariable univariate analysis. There was no indication of possible collinearity among the independent variables (Variance Inflation Factor (VIF) < 10) to be entered in the multivariable model (socio-demographics: patient age at onset and gender; educational level parents and single or double parent household; presence of health problems before ABI; injury characteristics: type, severity).

In the multivariable linear regression models, increasing age, NTBI and a single-parent household were significantly associated with more fatigue (lower scores) according to the parent-reported PedsQL™ MFS Total Score and/or one or more subscale scores.

Table 3. Results of the univariable analysis of on the parent reported PedsQL™ Fatigue Total Score and General, Sleep/rest and Cognitive subscores as dependent variables, related to baseline characteristics at onset (sociodemographic, pre-injury health, injury characteristics) and results at follow-up (actual functioning) approximately 2 years after onset of ABI, as independent or predictor variables*. All values are means (standard deviation).

	Predictor Variables	**n=88**	**Fatigue Total Score**	**General Fatigue**	**Sleep/rest Fatigue**	**Cognitive Fatigue**
Socio-demographic Characteristics of the child	*Age (At Onset) Median 11 yrs*	*≤11 y (n=50)* ‡	80.5 (17.3)**	82.9 (19.6)**	83.8 (17.8)***	74.6 (25.4)***
		>11y (n=38)	71.3 (20.4)**	72.8 (22.8)**	75.6 (22.8)***	65.6 (22.3)***
	Sex	*Male (n=43)*†	77.5 (17.5)	80.5 (18.2)	81.7 (17.8)	70.3 (25.0)
		Female (n=45)	75.6 (20.8)	76.7 (24.4)	78.9 (22.8)	71.1 (24.0)
	Educational Level Parents [a]	*Low (n=9)* †	67.1 (23.9)	69.0 (29.1)	71.6 (31.9)	60.4 (28.3)
		Intermediate (n=29)	75.8 (17.3)	82.4 (16.4)	79.0 (19.5)	68.5 (23.6)
		High (n=40)	76.9 (20.1)	76.9 (22,8)	82.0 (17.6)	71.9 (24.7)
	Single Parent Household	*Yes (n=20)* †	66.4 (19.9)**	67.3 (25.9)**	73.1 (23.4)***	58.8 (23.9)**
		No (n=60)	78.9 (18.0)**	82.2 (18.2)**	81.8 (19.1)***	73.7 (23.7)**
Pre-injury Functioning	*Health Problems*	*Yes (n=21)* †	70.8 (18.5)***	76.5 (19.7)	72.6 (23.3)***	66.1 (24.6)
		No (n=60)	77.4 (19.6)***	79.1 (22.0)	81.7 (19.6)***	71.3 (24.6)
Injury Characteristics	*Type of Injury*	*TBI (n=69)* †	78.7 (18.4)**	80.8 (20.1)***	81.2 (20.3)	74.1 (24.3)**
		NTBI (n=19)	68.6 (20.2)**	70.4 (24.9)***	77.0 (20.9)	58.4 (20.7)**
	Severity TBI [b]	Mild (n=58)	78.1 (17.5)	80.2 (19.2)	81.3 (18.8)	72.9 (24.5)
		Moderate/severe (n=11)	81.6 (23.6)	83.7 (25.5)	80.7 (28.2)	80.3 (23.8)
	Severity NTBI [c]	Mild (n=15)	73.1 (17.5)	77.2 (19.8)	80.8 (18.9)	61.2 (20.9)

Table 3. Continued

	Predictor Variables	n=88	Fatigue Total Score	General Fatigue	Sleep/rest Fatigue	Cognitive Fatigue
		Moderate/severe (n=3)	58.8 (22.6)	54.2 (25.3)	68.1 (26.8)	54.2 (16.7)
Activities and Participation *parent reported*	*CASP* [d]	Low (≤95) (n=40)	70.5 (17.1)**	73.5 (21.6)***	77.9 (19.2)	60.2 (24.2)**
		High (>95) (n=39)	79.7 (20.3)**	81.1 (21.7)***	80.3 (22.2)	77.8 (21.9)**
	CAFI [e]	Low (≤40) (n=46)	85.2 (12.8)**	87.2 (13.5)**	86.6 (13.7)**	81.7 (19.1)**
		High (>40) (n=36)	62.4 (18.3)**	64.8 (23.7)**	69.3 (23.8)**	53.0 (20.8)**
	CASE [f]	Low (≤35) (n=32)	83.2 (17.4)**	85.8 (17.5)**	86.1 (15.9)**	77.6 (24.7)**
		High (>35) (n=41)	67.8 (18.5)**	69.2 (23.0)**	73.8 (22.6)**	60.4 (22.2)**
Quality of Life *parent reported*	*PedsQL General Core Scales*	Low (≤78) (n=40)	60.9 (15.5)**	63.4 (21.3)**	67.9 (22.1)**	51.1 (17.5)**
		High (>78) (n=42)	88.8 (10.1)**	90.5 (11.8)**	89.7 (11.4)**	86.3 (16.2)**

[a] low (pre-vocational practical education or less), intermediate (pre-vocational theoretical education and upper secondary vocational education), or high (secondary education, higher education, and/or university level education)
[b] TBI: determined by means of the Glasgow Coma Scale (GCS) at hospital admission
[c] NTBI: determined by means of a disability scale based on the Modified Rankin Scale (mRS) at hospital discharge
[d] CFFS-DLV CASP Total: Child & Family Follow-up Survey, Dutch Language Version; Child and Adolescent Scale of Participation, score range 0-100, higher scores indicate better functioning and less participation problems
[e] CFFS-DLV CAFI Total Score: Child & Family Follow-up Survey, Dutch Language Version; Child and Adolescent Factors Inventory, score range 33.3-100, higher scores indicate more limitations in functions
[f] CFFS-DLV CASE Total Score: Child & Family Follow-up Survey, Dutch Language Version, Child and Adolescent Scale of Environment, score range 0-100, higher scores indicate more environmental limitations
[g] PedsQL General Core Scale: score range 0-100, higher scores indicate better HRQOL (Health-Related Quality of Life).
*= p-value determined by Student t test, Mann-Whitney U or Chi Square test, where appropriate.
** p value < 0.05; *** p value < 0.20
† group split in categories
‡ group split in categories by median score.

Table 4. Multivariable regression analysis with the PedsQL™ Multidimensional Fatigue Scale (MFS) Total Score and Subscores as dependent variables, ~2 years after onset of acquired brain injury (ABI) related to significant patient and injury characteristics at onset of ABI.

MFS		β	95% CI	p
Total Score	Age at onset			
	11 and under	9.3	1.1—17.4	0.026
	Older than 11	0[a]		
	One parent household			
	No	12.0	2.7—21.3	0.012
	Yes	0[a]		
General Fatigue	Age at onset			
	11 and under	10.6	1.3—19.8	0.025
	Older than 11	0[a]		
	One parent household			
	No	13.6	3.1—24.1	0.012
	Yes	0[a]		
Sleep/rest Fatigue	Age at onset			
	11 and under	9.2	0.3—18.2	0.044
	Older than 11	0[a]		
	One parent household			
	No	8.2	-1.9—18.4	0.111
	Yes	0[a]		
Cognitive Fatigue	Type of injury			
	TBI	13.7	1.5—25.8	0.028
	NTBI	0[a]		
	One parent household			
	No	13.5	1.5—25.4	0.028
	Yes	0[a]		

[a] This parameter is set to zero because it is redundant.
NTBI=non traumatic brain injury; TBI=traumatic brain injury.

Discussion

This study was performed to assess the degree of fatigue in children and youth after traumatic and non-traumatic brain injury (TBI and NTBI) and factors related to fatigue. Two scores, with more parent reported fatigue being related to NTBI, higher age (11 years and older) at onset of injury and the presence of a single-parent household.
In this study the average fatigue scores after TBI were similar to those reported in healthy cohorts.[33,34] Fatigue after NTBI, most commonly being a brain tumor, stroke or status after infection, was higher than in patients with TBI, corresponding to data found in other chronic conditions.[33] In studies with pediatric cancer patients, similar fatigue scores have been reported for leukemia and brain tumor patients.[41,42] Meeske et al.[42] found more fatigue in the brain tumor group compared to the leukemia group.
Concerning the comparison of parent and child reported fatigue, in this study parents

reported more fatigue than the children themselves; overall, children with ABI, either TBI or NTBI, reported scores similar to healthy peers. The intraclass correlation found between parent-proxy and child-reported fatigue according to the PedsQL™ MFS is similar to earlier studies and other diagnosis groups.[34,43] It is known that children report a better quality of life than that reported by their parents. In this small study group, fatigue scores mimic the better scoring of quality of life as reported by children. It is of interest that children and adolescents themselves score no difference between the subscales, but parents do, with a lower score for cognitive fatigue. Extra effort used to maintain schoolwork is often taken for granted by children themselves, while their parents see the extra effort as cognitive fatigue.

In the literature, fatigue has been found to be one of the most reported symptoms after childhood TBI,[44] but there are few studies that specifically focus on post-ABI fatigue in children and adolescents.

Regarding the nature of fatigue it is important to distinguish between different types of fatigue. This study used the PedsQL™ MFS to obtain this difference. The PedsQL™ MFS has three subscales, allowing patients to score their fatigue in different manners according to their symptoms. Cognitive fatigue is an important symptom after brain injury. Many studies on pediatric ABI focus on the cognitive changes after injury. Cognitive fatigue is an important factor related to school functioning and participation. In this study indeed there was an association between cognitive fatigue and the CASP score for participation and quality of life (PedsQL General Core Scales).

With respect to the factors related to fatigue, this study took the socio-demographic and injury characteristics of the child and family into account, showing that the presence of NTBI, age at injury and single parent household were associated with more parent-reported fatigue. Due to the limited studies done on fatigue after pediatric ABI, these findings cannot be compared to previous research.[24] Severity of injury, in patients with TBI as well as NTBI, was not found to be a predictor of parent-reported fatigue in this study.

Other studies have looked at factors associated with functional outcome. Severity of injury,[5,45–48] age at onset[49–53] and SES[54,55] have been found as predictors of long-term impairment.

In adult populations of patients with TBI, the evidence over factors related to fatigue is conflicting. Age, gender, educational level, time since injury, severity of injury, sleep problems, anxiety and length of disability leave[56–60] have been suggested as factors related to fatigue. In a review containing 22 studies in adult populations with TBI, no factors being consistently related to the presence of long-term fatigue were identified, except pre-injury fatigue and fatigue measured at baseline (baseline measured commonly within 1 month after onset of injury).[19] For stroke patients, similar results

have been reported. In a review using five longitudinal studies (n=762), pre-stroke fatigue predicted fatigue shortly after stroke and late onset fatigue. Pre-stroke depression as a determinant for post-stroke fatigue has been inconsistent. Age and gender have also been suggested determinants for fatigue, but not consistently.[61]
Regarding the determinants of fatigue in adults with ABI, fatigue has been found to predict anxiety, depression and daytime sleepiness.[62] Assessment and treatment of anxiety, depression and pain in this patient population is important.[63] A relationship between fatigue and cognitive functioning (attention, processing speed and effort) has also been found.[63] This study used the PedsQL™ MFS to measure the severity of fatigue. This is only one of many instruments developed to report fatigue. This measurement has good psychometric qualities and can distinguish between different types of fatigue. The parent proxy and child report enables comparison between parent and patient perceived fatigue.
Several limitations of this study should be noted. The small study population with a hospital based diagnosis of ABI and low numbers of patients with moderate/severe TBI and NTBI make a generalization to the larger population of children and youth with ABI difficult. The data show a trend in children with NTBI having more fatigue than children with TBI and youth. There is no previous literature to compare this data to. Severity has often been found to be a factor related to outcome, with more severely injured individuals having a poorer outcome. In this study severity was not found to be a factor related to fatigue; and the trend in the data show that individuals with mild injuries are more fatigued; a trend that is supported by research in an adult population with ABI in The Netherlands.[64] In addition, the relatively high proportion of non-responders may indicate the presence of a selection bias; however, a comparison of patients who did and did not participate in the follow-up study showed no significant differences in patient characteristics. However, the patients in the present analysis were somewhat younger than those patients in the follow-up study who did not.
Further comparison to previous studies is difficult because one cannot compare this hospital based population to the often used rehabilitation center-based populations. Patients were recruited ~ 2 years after onset of ABI and were asked to score the symptoms that they had at that moment; it is not possible to make a direct relationship between current symptoms and the presence of ABI. Parents were retrospectively asked if there were pre-injury problems during the onsite interview; this is not an objective measure.
The PedsQL™ MFS questionnaire allows for distinguishing between different types of fatigue. However, it cannot differentiate between 'healthy' adolescent fatigue and fatigue caused by ABI. Fatigue is an often reported symptom in healthy children and

youth, increasing during adolescence.[65] The increase with age is seen in this study as well.

Fatigue that limits activities and participation after ABI should be considered seriously and more research into the symptoms should be performed. When studying fatigue, the causes of the symptoms needs to be explored; primary fatigue due to the brain injury itself, or secondary fatigue due to pain, depression, anxiety or inactive lifestyle.[66] The PedsQL™ MFS is a good instrument to examine fatigue symptoms, but more in-depth knowledge of possible causes of fatigue, such as anxiety, depression, sleep, physical activity, or hormone status, needs to be acquired.

Despite a number of limitations, the results of this study show that fatigue after pediatric ABI is related to activities and participation and distinguishes between general fatigue, cognitive fatigue and sleep/rest problems. The questionnaire is short and easy to fill in. A larger cohort with more focus specifically on fatigue is warranted.

Conclusions

Two years after onset, the parent-reported fatigue after pediatric acquired brain injury (ABI) is considerable, in particular in children with NTBI. In particular, children with an increasing age (11 years and older) at onset of ABI and children from a one parent household appeared to have a higher risk of fatigue. Further research on fatigue after pediatric ABI, its causes and related factors, specifically in NTBI, is warranted.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Greenwald BD, Burnett DM, Miller MA. Congenital and acquired brain injury. Brain injury: epidemiology and pathophysiology. *Archives of Physical Medicine & Rehabilitation* 2003;84:S3–S7.
2. de Kloet AJ Hilberink SR, Roebroeck ME, Catsman-Berrevoets CE, Peeters E, Lambregts SAM, van Markus-Doornbosch, Vliet Vlieland TPM. Youth with acquired brain injury in the Netherlands: a multicenter study. *Brain Injury* 2013;27:843–849.
3. Hawley CA Ward AB, Long J, Owen DW, Magnayd AR. Prevalence of traumatic brain injury amongst children admitted to hospital in one health district: a population-based study. *Injury* 2003; 34:256–260.
4. Langeois JA Rutland-Brown W, Thomas KE. The incidence of traumatic brain injury among children in the United States. *Journal of Head Trauma Rehabilitation* 2005;20:229–239.
5. Catroppa A, Anderson VA, Morse SA, Haritou F, Rosenfeld JV. Outcome and predictors of functional recovery 5 years following pediatric traumatic brain injury. *Journal of Pediatric Psychology* 2008;33:707–718.
6. Rivara FP, Koepsell TD, Wang J, Temkin N, Dorsch A, Vavilala MS, Durbin D, Jaffe KM. Incidence of disability among children 12 months after traumatic brain injury. *American Journal of Public Health* 2012;102:2074–2079.
7. Horneman G, Folkesson P, Sintone H, von Wendt L, Emanuelson I. Health-related quality of life of adolescents and young adults 10 years after serious traumatic brain injury. *International Journal of Rehabilitation Research* 2005;28:245–249.
8. Di Battista A, Soo C, Catroppa C, Anderson V. Quality of life in children and adolescents post-TBI: a systematic review and meta-analysis. *Journal of Neurotrauma* 2012;29:1717–1727.
9. Green L, Godfrey C, Soo S, Anderson V, Catroppa C. A preliminary investigation into psychosocial outcome and quality-of-life in adolescents following childhood traumatic brain injury. *Brain Injury* 2013;7–8:872–877.
10. Delsing BJP, Catsman-Berrevoets CE, Appel IM. Early prognostic indicators of outcome in ischemic childhood stroke. *Pediatric Neurology* 2001;24:283–289.
11. Neuner B, von Mackensen S, Krümpel A, Manner D, Friefeld S, Nixdorf S, Frühwald M, deVeber G, Nowak-Göttl U. Health-related quality of life in children and adolescents with stroke, self-reports, and parent/proxies reports: cross-sectional investigation. *Annals of Neurology* 2011;70:70–78.
12. Aarsen FK, Paquier PF, Reddingius RE, Streng IC, Arts WFC, Evera-Preesman M, Catsman-Berrevoets CE. Functional outcome after low-grade astrocytoma treatment in childhood. *Cancer* 2006;106:396–402.
13. Overweg-Plandsoen WCG, Kodde A, van Straaten M. van der Linden EAM, Neyens LGJ, Aldenkamp AP, Vermeulen M. Mild closed head injury in children compared to traumatic fractured bone; neurobehavioural sequelae in daily life 2 years after the accident. *European Journal of Pediatrics* 1999;158:249–252.
14. Ponsford JL, Ziino C, Parcell DL, Shekleton JA, Roper M, Redman JR, Phipps-Nelson J, Rajaratnam SMW. Fatigue and sleep disturbance following traumatic brain injury-their nature, causes, and potential treatments. *Journal of Head Trauma Rehabilitation* 2012;27:224–233.
15. Ponsford JL, Downing MG, Olver J, Ponsford M, Acher R, Carty M, Spitz G. Longitudinal follow-up of patients with traumatic brain injury: outcome at two, five, and ten years post-injury. *Journal of Neurotrauma* 2014;31:64–77.
16. Aaronson LS, Teel CS, Cassmeyer V, Neuberger GB, Pallikkathayil L, Pierce J, Press AN, Williams PD, Wingate A. Defining and measuring fatigue. *Journal of Nursing Scholarship* 1999;31:45–50. Review.
17. Chaudhuri A, Behan PO. Fatigue in neurological disorders. *Lancet* 2004;363:978–988. Review.
18. Elovic EP, Dobrovic NM, Fellus JL, Fatigue after traumatic brain injury. In: DeLuca J, editor. *Fatigue as a window to the brain*. London: The MIT Press; 2005. p 91–105.

19. Mollayeva T, Kendzerska T, Mollayeva S, Shapiro CM, Colantonio A, Cassidy JD. A systematic review of fatigue in patients with traumatic brain injury: the course, predictors and consequences. *Neuroscience & Biobehavioral Reviews* 2014;47:684–716. Review.
20. Duncan F, Wu S, Mead GE. Frequency and natural history of fatigue after stroke: a systematic review of longitudinal studies. *Journal of Psychosomatic Research* 2012;73:18–27.
21. Blinman TA, Houseknecht E, Snyder C, Wiebe DJ, Nance ML. Postconcussive symptoms in hospitalized pediatric patients after mild traumatic brain injury. *Journal of Pediatric Surgery* 2009;44:1223– 1228.
22. Falk AC. A nurse-led pediatric head injury follow-up service. *Scandinavian Journal of Caring Sciences* 2013;27:51–56.
23. Barlow KM Crawford S, Stevenson A, Sandhu SS, Belanger F, Dewey D. Epidemiology of postconcussion syndrome in pediatric mild traumatic brain injury. *Pediatrics* 2010;257:1692–1702.
24. Gagner C, Landry-Roy C, Lainé F, Beauchamp MH. Sleep-wake disturbances and fatigue after pediatric traumatic brain injury: a systematic review of the literature. *Journal of Neurotrauma* 2015; 32:1539–1552.
25. Goeggel Simonetti B, Cavelti A, Arnold M, Bigi S, Regényi M, Mattle HP, Gralla J, Fluss J, Weber P, Hackenberg A, Steinlin M, Fischer. Long-term outcome after arterial ischemic stroke in children and young adults. *Neurology* 2015;84:1941–1947.
26. de Kloet AJ, Lambregts SA, Berger MA, van Markus F,Wolterbeek R, Vliet Vlieland TPM. Family impact of acquired brain injury in children and youth. *Journal of Developmental & Behavioral Pediatrics* 2015;36:342–351.
27. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet* 1974;13:81–84.
28. Bonita R, Beaglehole R. Modification of rankin scale: recovery of motor function after stroke. *Stroke* 1988;19:1497–1500.
29. IBM SPSS Statistics for Windows, Version 22.0. Armonk (NY): IBM Corp; 2015.
30. Bedell GM. Developing a follow-up survey focused on participation of children and youth with acquired brain injury after inpatient rehabilitation. *NeuroRehabilitation* 2004;19:191–205.
31. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. *Medical Care* 1999;37:126–139.
32. Varni JW, Limbers CA. The PedsQL Multidimensional Fatigue Scale in young adults: feasibility, reliability and validity in a university student population. *Quality of Life Research* 2008;17:105–114.
33. Haverman L, Limperg PF, van Oers HA, van Rossum MAJ, Maurice-Stam H, Grootenhuis MA. Psychometric properties and Dutch norm data of the PedsQL Multidimensional Fatigue Scale for Young Adults. *Quality of Life Research* 2014;23:2841–2847.
34. Gordijn MS, Cremers EMP, Kaspers GJL, Gemke RJBJ. Fatigue in children: reliability and validity of the Dutch PedsQLTM Multidimensional Fatigue Scale. *Quality of Life Research* 2011;20:1103–1108.
35. McCarthy ML MacKenzie EJ, Durbin DR, Aitken ME, Jaffe KM, Paidas CN, Slomine BS, Dorsch AM, Berk RA, Christensen JR, Ding R; CHAT Study Group. The Pediatric Quality of Life Inventory (PedsQL™4.0): an evaluation of its psychometric characteristics for children with traumatic brain injury. *Archives of Physical Medicine and Rehabilitation* 2005;86:1901–1909.
36. Varni JW, Limbers CA, Burwinkle TM. Parent proxy-report of their children's health-related quality of life: an analysis of 13,878 parents' reliability and validity across age subgroups using the PedsQL 4.0 Generic Core Scales. *Health Quality and of Life Outcomes* 2007;5:1–10.
37. de Kloet AJ, Berger MAM, Bedell GA, Catsman-Berrevoet CE, van Markus-Doornbosch F, Vliet Vlieland TP. Psychometric evaluation of the Dutch language version of the Child and Family Follow-up Survey. *Developmental Neurorehabilitation* 2015;24:1–8.

38. Bedell GM. Developing a follow-up survey focused on participation of children and youth with acquired brain injury after inpatient rehabilitation. *NeuroRehabilitation* 2004;19:191–205.
39. Streiner DL, Norman GR. *Health measurement scales: A practical guide to their development and use.* Oxford: Oxford University Press; 2003.
40. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159–174.
41. Gordijn MS, Litsenburg RR van, Gemke RJ, Huisman J, Hoogerbrugge, Hoogerbrugge PM, Kaspers GJL. Sleep, fatigue, depression, and quality of life in survivors of childhood acute lymphoblastic leukemia. *Pediatric Blood & Cancer* 2013;60:479–485.
42. Meeske K, Katz ER, Palmer SN, Burwinkle T, Varni JW. Parent proxy-reported health-related quality of life and fatigue in pediatric patients diagnosed with brain tumors and acute lymphoblastic leukemia. *Cancer* 2004;101:2116–2125.
43. Panepinto JA, Torres S, Bendo CB, McCavit TL, Dinu B, Sherman-Bien S, Bemrich-Stolz C, Varni JW. PedsQL™ Multidimensional Fatigue Scale in sickle cell disease: feasibility, reliability and validity. *Pediatric Blood & Cancer* 2014;61:171– 177:
44. Aaro Jonsson CC, Emanuelson IM, Smedler AC. Variability in quality of life 13 years after traumatic brain injury in childhood. *International Journal of Rehabilitation Research* 2014;37:317–322.
45. Anderson VA, Catroppa C, Dudgeon P, Morse SA, Haritou F, Rosenfeld JV. Understanding predictors of functional recovery and outcome 30 months following early childhood head injury. *Neuropsychology* 2006;20:42–57.
46. Rivara FP, Koepsell TD, Wang J, Temkin N, Dorsch A, Vavilala MS, Durbin D, Jaffe KM. Incidence of disability among children 12 months after traumatic brain injury. *American Journal of Public Health* 2012;102:2074–2079.
47. Di Battista A, Soo C, Catroppa C, Anderson V. Quality of life in children and adolescents post-TBI: a systematic review and meta-analysis. *Journal of Neurotrauma* 2012;29:1717–1727.
48. Anderson VA, Godfrey C, Rosenfeld JV, Catroppa C. 10 years outcome from childhood traumatic brain injury. *International Journal of Developmental Neuroscience* 2012;30:217–224.
49. Anderson V, Brown S, Newitt H, Hoile H. Educational, vocational, psychosocial, and quality-of-life outcomes for adult survivors of childhood traumatic brain injury. *Journal of Head Trauma Rehabilitation* 2009;24:303–312.
50. Anderson V, Catroppa C, Morse S, Haritou F, Rosenveld JV. Intellectual outcome from preschool traumatic brain injury: a 5-year prospective, longitudinal study. *Pediatrics* 2009;124:e1064–1071.
51. Anderson VA, Catroppa C, Haritou F, Morse S, Rosenfeld JV. Identifying factors contributing to child and family outcome 30 months after traumatic brain injury in children. *Journal of Neurology, Neurosurgery & Psychiatry* 2005;76:401–408.
52. Ewing-Cobbs L, Fletcher JM, Levin HS, Francis DJ, Davidson K, Miner ME. Longitudinal neuropsychological outcome in infants and preschoolers with traumatic brain injury. *Journal of the International Neuropsychological Society* 1997;3:581–591.
53. Giza CC, Prins ML. Is being plastic fantastic? Mechanisms of altered plasticity after developmental traumatic brain injury. *Developmental Neuroscience* 2008;28:364–379.
54. Yeates KO, Swift E, Taylor HG, Wade SL, Drotar D, Stancin T, Minich N. Short- and long-term social outcomes following pediatric traumatic brain injury. *Journal of the International Neuropsychological Society* 2004;10:412–426.
55. Yeates KO, Taylor HG, Walz NC, Stancin T, Wade SL. The family environment as a moderator of psychosocial outcomes following traumatic brain injury in young children. *Neuropsychology* 2010;24:345–356.
56. Ouellet MC, Morin CM. Subjective and objective measures of insomnia in the context of traumatic brain injury: a preliminary study. *Sleep Medicine* 2006;7:486–497.
57. Cantor JB, Bushnik T, Cicerone K, Dijkers MP, Gordon W, Hammond FM, Kolakowsky-Hayner SA, Lequerica A, Nguyen M, Spielman LA. Insomnia, fatigue, and sleepiness in the first 2 years after trau-

matic brain injury: an NIDRR TBI model system module study. *Journal of Head Trauma Rehabilitation* 2012;27:E1– 14.
58. Cantor JB, Ashman T, Gordon W, Ginsberg A, Engmann C, Egan M, Spielman L, Dijkers M, Flanagan S. Fatigue after traumatic brain injury and its impact on participation and quality of life. *Journal of Head Trauma Rehabilitation* 2008;23:41–51.
59. Ziino C, Ponsford J. Vigilance and fatigue following traumatic brain injury. *Journal of the International Neuropsychological Society* 2006;12:100–110.
60. Winward C, Sackley C, Metha Z, Rothwell PM. A population based study of the prevalence of fatigue after transient ischemic attack and minor stroke. *Stroke* 2009;40:757–761.
61. Wu S, Mead G, Macleod M, Chalder T. Model of understanding fatigue after stroke. *Stroke* 2015;46:893–898.
62. Ponsford JL Sinclair KL. Sleep and fatigue following traumatic brain injury. *Psychiatric Clinics of North America* 2014;37:77–89.
63. Ponsford JL, Ziino C, Parcell DL, Shekleton JA, Roper M, Redman JR, Phipps-Nelson J, Rajaratnam SM. Fatigue and sleep disturbance following traumatic brain injury-their nature, causes, and potential treatments. *Journal of Head Trauma Rehabilitation* 2012;27:224–233.
64. Visser-Keizer AC, Hogenkamp A, Westerhof-Evers HJ, Egberink IJL, Spikman JM. Dutch Multifactor Fatigue Scale: a new scale to measure the different aspects of fatigue after acquired brain injury. *Archives of Physical Medicine & Rehabilitation* 2015;96:1056– 1063.
65. ter Wolbeek M, Doornen JP van, Kavelaars A, Heijnen CJ. Predictors of persistent and new-onset fatigue in adolescent girls. *Pediatrics* 2008;121:e449–457.
66. Bushnik T, Englander J, Wright J. Patterns of fatigue and its correlates over the first 2 years after traumatic brain injury. *Head Trauma Rehabilitation* 2008;23:25–32.



Chapter 3

Fatigue and its relationship with physical activity in adolescents and young adults with traumatic brain injury: a cross-sectional study

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Abstract

Background
Physical activity (PA) in patients with traumatic brain injury (TBI) may be impaired leading to secondary health issues and limitations in participation.

Aim
This study aims to determine the level of PA and its determinants in adolescents and young adults with TBI.

Design
Cross-sectional survey study.

Setting
Outpatient clinic of a rehabilitation center.

Population
Discharged patients aged 12-39 years with a diagnosis of TBI >6 months treated in the rehabilitation center between 2009-2012.

Methods
The Activity Questionnaire for Adults and Adolescents (AQuAA) measuring PA, with results dichotomized for meeting or not meeting Dutch recommendations for health-enhancing physical activity (D-HEPA) and the Checklist Individual Strength questionnaire (CIS; range 20-140, higher scores represent higher levels of fatigue), measuring fatigue, were administered.

Results
Fifty (47%) of the 107 invited patients completed the questionnaire. Mean age was 25.0±7.2 years and 22 (44%) were male. Eighteen (36%) had a mild injury, 13 (26%) a moderate injury and 19 (38%) a severe injury. Median time spent on moderate–vigorous physical activity was 518 minutes/week (IQR 236-1725) (males performing significantly more minutes on moderate-vigorous activity than women) and on sedentary activity 2728 minutes/week (IQR 1637-3994). Thirty-two (64%) participants met the D-HEPA. According to the CIS, 19 participants (38%) were severely fatigued. Both the CIS total score and the subscales motivation and physical activity were associated with meeting the D-HEPA.

Conclusions
The proportion of individuals with TBI meeting D-HEPA was similar to the general population, with the PA level being associated with self-reported fatigue.

Clinical rehabilitation impact
Physical activity programs are continuously being developed to increase the percentage of individuals meeting public health recommendations for PA; when developing programs for individuals with TBI extra consideration should be taken for the presence of fatigue. As in the general population, females with TBI are less active, PA programs should probably consider gender differences in their development.

Key words
Traumatic brain injuries, adolescent, fatigue, physical activity, young adult

Introduction

Traumatic brain injury (TBI) is one of the leading causes of death and disability in youth and young adults, with the estimated yearly incidence ranging between 70-798 per 100 000 people per year in the age group 0-14 years[1] in Europe and the North Americas and 296 per 100 000 among young adults (15-24 years old) in The Netherlands.[1] Disability following TBI is common and includes limitations in physical, emotional and social functioning.

One of the long-term consequences of TBI addressed in the literature is physical inactivity and deconditioning.[2] Literature has shown that in general, persons with disabilities more often lead a sedentary lifestyle than healthy individuals,[3, 4] and thus increase their risk for, among other things, cardiovascular problems,[5] mood disturbances,[6] and decreased quality of life.[7, 8] Physical inactivity has been identified as the fourth leading risk factor for global mortality causing an estimated 3.2 million deaths globally. According to the World Health Organization (WHO), physical activity (PA) is defined as any bodily movement produced by skeletal muscles that requires energy expenditure. Significant health benefits can be acquired through regular moderate intensity PA.[9] Many countries, including the Netherlands, have set national guidelines for health-enhancing PA (HEPA) for children and adults.

Overall, the literature on physical activity in patients after TBI is scarce. In a study with 28 outpatients with TBI, on average 46 minutes per week of moderate-intensive exercise was performed,[10] this being 31% of the recommended amount of exercise for individuals with a disability.[11] Fleming[12] found in a group of outpatients that time spent on leisure activities decreased after TBI, with the proportions of those engaging in

sports decreasing from 81% pre-injury to 61% post-injury. Gordon et al.[13] found in a population of 240 patients with TBI that 73% were non-exercisers (defined as exercising less than once a week) compared to 52% in the healthy cohort. In the same study exercisers in the TBI group (defined as exercising for more than 30 minutes three time a week for the preceding 6 months) were more often those with a more severe injury. With respect to factors associated with physical activity after TBI, physical[14] and cognitive impairments,[15, 16] environmental and societal barriers,[10] injury severity, age at time of injury and time since injury,[17, 18] number of symptoms[13] as well as depression[19,20] have been reported in the literature. In addition, fatigue was found to be related to level of PA in adult patients with TBI.[21, 22] Improving physical activity after TBI can be approached in different ways. Increasing levels of PA can be considered as an intervention to manage fatigue. On the other hand, addressing fatigue and/or sleep disorders may lead to increased energy and thus decreasing one of the barriers in participating in physical activities.

So far, research on PA in individuals with TBI has focused on either pediatric populations, up to and including 18 years of age, or adult populations with a mean age in the forties and fifties.[23] The group of (young) adults in their late teens, twenties and thirties with TBI has not been the focus of previous research. This is an age group, where from a developmental perspective physical fitness and social participation predominate. According to Levinson, this is also the period in life where "motivation and enthusiasm for the future" are created.[24] This period can therefore be used to pursue primary prevention of cardiovascular problems by creating a healthy lifestyle.

Pediatric studies on TBI have focused on participation[25] or return to play[26] but not specifically on physical activity after injury. Other pediatric studies have focused on deficits in motor skills after concussion[27] and alterations in self-esteem[28] and the relationship with (sports) participation.

Given the lack of knowledge on PA after TBI in adolescents and young adults, the aim of the current study was to describe the level of physical activity after TBI in adolescents and young adults well as its association with injury characteristics and fatigue symptoms.

Materials and Methods

This cross-sectional study, involving a patient survey, was executed at the largest of four outpatient locations of Sophia Rehabilitation in The Hague, The Netherlands. The included participants had all completed inpatient and/or outpatient rehabilitation. The study was judged to be non-medical research by the Medical Ethics Review Committee of the LUMC. Patients provided written informed consent.

Participants

In June 2012, all patients between 12 and 39 years of age with a diagnosis of TBI treated over the last 3 years in the outpatient clinic of the rehabilitation center were identified using the electronic patient registry. Subsequently, their medical records were checked by the treating physician and principle investigator (FvMD) to verify the diagnosis. Inclusion criteria were: onset TBI 6 months or more before start of the study; sufficient knowledge of the Dutch language and intellectual level to complete questionnaires independently. Intellectual level was either known from neurocognitive testing (Wechsler Adult Intelligence Scale IV-NL: WAIS-IV)[29] or achieved educational level; an IQ above 70 was considered adequate. Patients with other medical conditions having an impact on functioning (such as congenital disorders, rheumatic disease, chronic fatigue syndrome, epilepsy, stroke or encephalitis) were excluded. For all eligible patients, the injury characteristics and medical history were extracted from the medical records by the principle investigator, using a standardized registration form. The date of birth, year of onset, gender and the severity of TBI were recorded. The severity of TBI was determined by means of the Glasgow Coma Scale (GCS) at hospital admission. According to the GCS, the severity of TBI was considered mild if the GCS was 13-15, moderate if the GCS was 9-12 or severe if the GCS was <9.[30]
Participants were approached by postal mail. Non-responders were approached once by telephone, 2 weeks after the mailing, to ask for their response.

Assessments

Assessments included a one-time survey comprising two validated Patient Reported Outcome Measures (PROM's), to be completed by participants (if necessary with help from their parents) at home, either electronically or on paper. Those completing the paper version returned the questionnaire with an pre-stamped envelope. The questionnaires were coded to match the medical records and made anonymous. By providing 2 methods for completing the questionnaire the problems of not having a computer or having computer problems was avoided.

General and sociodemographic characteristics

Participants were asked to report length and weight, from which Body Mass Index (BMI; weight/height^2 [kg/ m^2]) was calculated. For participants aged 12 to 17 years the presence of underweight, overweight and obesity was determined using international cut-off points according to gender and age.[31,32] For participants 18 years and older cut-off points according to international criteria, <18.5, 25, and >30 kg/m2, respectively, were used.[33]

In addition, their living situation was recorded (living with parent(s) or independently). Socio-economic status (SES) was assessed by recording the highest completed educational level of one of the parents (for participants living with their parents) or of the participant (if living independently); it was classified into three groups: low (pre-vocational practical education and lower education), intermediate (pre-vocational theoretical education and upper secondary vocational education) and high (secondary non-vocational, higher education and university).[34]

Physical activity

The Activity Questionnaire for Adults and Adolescents (AQuAA) is a 5-category self-assessment of physical activity based on the SQUASH (Short Questionnaire to ASsess Health enhancing physical activity), a questionnaire for PA, validated in the Netherlands.[35] The AQuAA is identical to the SQUASH, containing questions in the domains of commuting activities, household activities, leisure time and sport activities, and activities at school and/or work but comprises several additional questions to assess sedentary activities. Adolescents and adults were asked about frequency (number of days per week), duration (time spent) and intensity (low, moderate, or vigorous) spent on commuting activities, physical activities at work or school, household activities, leisure time activities and active sports in the past 7 days with examples of activities to facilitate completion. According to the AQuAA protocol data were excluded if the total minutes of an activity (all intensities combined) exceeded 960 minutes per day. Each activity has a metabolic equivalent of task (MET) score related to the intensity of the activity, and is reported as milliliter oxygen use per kilogram bodyweight per minute. The METS compendium developed by Ainsworth[36] was used in this study. Activities were further categorized, using the MET's for each activity, into low, moderate or vigorous activities. Time spent on moderate to vigorous activities and sedentary activities was calculated for this study.

The Dutch public health recommendation on healthy PA (D-HEPA) is calculated by the summation of the minutes spent on moderate and vigorous activities per day and per week as reported in the AQuAA. In The Netherlands a health enhancing PA level has been established for children and adults (D-HEPA).[37, 38] Children aged 4-17 years must be physically active 60 minutes/ day, 7 days a week with moderate to vigorous activities (minimum 5 METS). Adults meet the criterium if they are physically active (minimum 4 METS) for 30 minutes/day, 5 days a week. For this study the data were dichotomized for meeting or not meeting the D-HEPA.

This questionnaire proved to be fairly reliable and reasonably valid for the healthy Dutch population, test-retest reliability ICC (intraclass correlation) ranging from 0.30-0.59 for adolescents, and for adults an ICC ranging from 0.49-0.60 for sedentary, light and moderate intensity activities and an ICC=-0.005 (poor) for vigorous activities.[39] The

D-HEPA corresponds with the international standard as formulated by the American College of Sports Medicine[40] and the American Heart Association.[41]

Fatigue

The Checklist Individual Strength (CIS) is a 20-item self-report multidimensional scale for assessing fatigue and associated behavior during the past two weeks. It is composed of four domains, namely severity of fatigue (8 items, score range 8 to 56), concentration problems (5 items, score range 5 to 35), reduced motivation (4 items, score range 4 to 28), and reduced physical activity (3 items, score range 3 to 21). Each item was scored on a seven point Likert scale. The total score is calculated by the sum of the 20 items (range 20 to140). High scores indicate high levels of fatigue, high levels of concentration problems, lower motivation, and lower level of physical activity.[42] According to an adolescent chronic fatigue syndrome study by Stulemeijer et al.,[20] the cut-off point for severe fatigue was set at a score of 40 on the severity of fatigue subscale. The CIS has been validated for use in the adult and youth Dutch population.[43]

Statistical analysis

Normality of the data was tested using the Kolmogorow-Wallis test. When data was normally distributed means and standard deviations and for skewed data the medians and interquartile ranges (IQR) were reported. For the CIS with four subscales, each subscale was tested for normality; 2 of the subscales were not normally distributed. To keep the data uniform, all CIS data is reported in medians and IQR.

Descriptive statistics were used for the sociodemographic and TBI characteristics of all eligible patients and compared between participants and non-participants by means of χ^2-tests or independent-sample t-tests, or Mann-Whitney U-tests, where appropriate. The AQuAA scores in minutes per week were calculated as medians and interquartile ranges (IQR, i.e. the 25th-75th percentile) for the TBI cohort as a whole, males and females separately, and mild, moderate and severe injuries separately. Within participants, BMI, socio-economic status, physical (in)activity levels and fatigue scores were compared among subgroups by means of χ^2 tests, one-way ANOVA, unpaired t-tests, Mann-Whitney U or Kruskal-Wallis tests, where appropriate.

Multivariate logistic regression analysis was performed to determine if age at injury, time since injury, severity of injury or fatigue are associated with not meeting the D-HEPA norm (inactivity) while adjusting for current age, sex, and BMI as potential confounders. The results are reported as odds ratio's and 95% confidence intervals. Factors were analyzed separately with potential confounders included in each analysis. For the comparison of characteristics, the level of statistical significance was defined as $p<0.05$.

All analyses were performed using SPSS v. 22 for Windows.[44]

Results

Of the 128 patients identified from the registry, 21 were excluded based on the information in the medical records (Figure 1). Of the 107 eligible subjects, 50 participants (47%) agreed to participate, and returned a completed questionnaire.
Table 1 shows the characteristics of the participants and non-participants, showing no differences between the two groups, except for the proportion of female patients which was higher among participants.
Among participants 18 (36%) had mild TBI, 13 (26%) a moderate injury and 19 (38%) a severe injury, based on the GCS at hospital admission. There were no significant differences between the participant characteristics: sex, age at injury, time since injury, BMI or SES. Current age was significantly different in the 3 groups with the moderately injured group being the youngest. Fatigue symptoms were not significantly different between the 3 groups (Table 2). In Table 3, the self-reported physical activity of the participants, as measured with the AQuAA, is shown, with 32 (64%) participants meeting

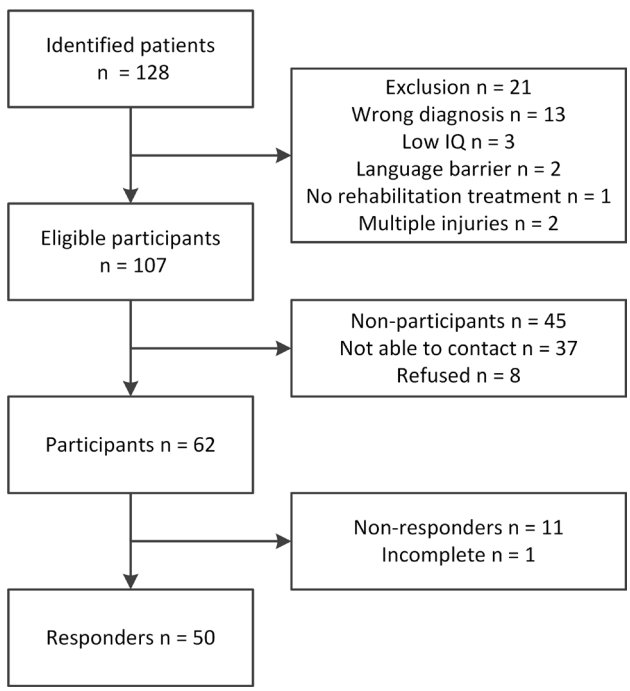


Figure 1. Flowchart of participants in a study on physical activity and fatigue in patients with traumatic brain injury (TBI)

Table 1. Characteristics of participants and non-participants in a cohort of adolescents and young adults with traumatic brain injury (TBI).

	Non-participants n=57	**Participants n=50**	**p-value**
Sex, male	38 (67%)	22 (44%)	0.02* [c]
Age at onset, in years	18.1±7.6	19.6±8.3	0.34 [t]
Current age, in years	24.0±7.1	25.0±7.2	0.48 [t]
Time since injury, in years	5.9±4.8	5.4±4.8	00.60 [t]
Injury severity, n (% of total TBI)			
Mild	23 (40%)	18 (36%)	
Moderate	14 (25%)	13 (26%)	0.90 [c]
Severe	20 (35%)	19 (38%)	
Current age of patients			
12-17 years	12 (21%)	7 (14%)	0.34 [c]
≥18 years	45 (79%)	43 (86%)	

Injury severity is based on the Glasgow Coma Scale (GCS) at hospital admission. Mild injury: GCS 13-15; moderate injury 9-12; severe injury <9.
*Statistically significant difference between the groups (P<0.05). P values were calculated by means of χ^2-Square-tests ([c]), independent-sample t-tests ([t]), as appropriate.

the Dutch recommendation for healthy PA, with males performing significantly more moderate to vigorous activities than females (p=0.002). When comparing individuals with a mild injury to those with a moderate or severe injury, there were no statistically significant differences in activity levels between the three groups.

In Table 4, the characteristics of participants meeting or not meeting the PA recommendation (D-HEPA) were compared. There was no statistically significant difference regarding proportions of participants with mild, moderate or severe injury, time since injury, age at injury, current age, BMI or SES between the active (those fulfilling the PA recommendation) and inactive participants (those not fulfilling the PA recommendation). The CIS Total Fatigue score as well as the subscales Motivation and Physical Activity subscale scores were however statistically significantly different between inactive and active participants (p=0.01, p=0.03, and p=0.001, respectively).

In the multivariate logistic regression analysis, correcting for current age, sex, and BMI, not meeting the D-HEPA guidelines (being inactive) was associated with more fatigue: subscale Motivation (OR 1.14; 95%CI 1.01, 1.29, p=0.04) and subscale Physical Activity (OR 1.25, 95%CI 1.08, 1.43, p=0.002), whereas all other variables were not associated with not meeting the D-HEPA (Table 5).

Table 2. Characteristics of participants in a cohort of adolescents and young adults with traumatic brain injury (TBI). Participants' self-reported fatigue is based on the Checklist Individual Strength (CIS). Data is reported as a total cohort and split into 3 groups based on Glasgow Coma Scale (GCS).

Characteristics	Total cohort n=50	Mild injury [a] n=18	Moderate injury n=13	Severe injury n=19	p-value
Sex, male	22 (44%)	5 (28%)	8 (62%)	9 (47%)	0.16 [c]
Age at onset, years	19.6±8.3%	21.3±9.5	16.4±4.1	20.1±8.7	0.26 [A]
Current age, years	25.0±7.2	25.3±8.8	20.2±4.5	26.4±5.9	0.04 [A]
Time since injury, years	5.4±4.8	4.6±4.3	4.4±2.6	6.9±6.2	0.25 [A]
BMI, kg /m² (n=48)	23.1±3.9	23.0±4.2	23.7±4.9	22.9±2.8	0.82 [A]
SES/Educational level (n=36)					
Low	3 (4%)	1 (6%)	2 (15%)	0	
Medium	12 (26%)	4 (22%)	3 (23%)	5 (26%)	0.46 [c]
High	21 (42%)	10 (55%)	6 (47%)	5 (26%)	
Missing	14 (25%)	3 (17%)	2 (15%)	9 (48%)	
CIS-scores; median (IQR)					
Total score	85.5 (61.0-99.3)	97.0 (67.3-113.8)	78.0 (57.5-96.5)	84.0 (54.0-98.0)	0.27 [KW]
Fatigue	35.0 (25.8-46.0)	40.5 (25.8-51.8)	34.0 (26.5-42.5)	34.0 (20.0-46.0)	0.47 [KW]
Concentration	23.0 (15.8-30.0)	28.0 (15.0-31.3)	23.0 (13.5-31.5)	22.0 (17.0-23.0)	0.30 [KW]
Motivation	13.0 (7.0-16.3)	12.5 (8.0-21.3)	12.0 (6.5-16.5)	13.0 (6.0-16.0)	0.54 [KW]
Physical activity	11.0 (6.0-16.5)	12.0 (6.8-20.3)	9.0 (6.0-15.0)	7.0 (3.0-16.0)	0.28 [KW]
Severely fatigued (based on Fatigue subscale)[d]	19 (38%)	9 (50%)	4 (31%)	6 (32%)	0.42 [c]

BMI: Body Mass Index; SES: socioeconomic status; CIS: Checklist Individual Strength.
Underweight is BMI < 18 kg/m² and < 18.5 kg/m² for children and adults, respectively; healthy BMI is 18.1-24.9 kg/m² 18.6-24.9 kg/m² for children and adults, respectively; overweight BMI is 25-29.9 kg/m²; obesity is BMI >30 kg/m².
SES is based on highest educational level of one of the parents for a participant living at home or participant himself when living independently; low: pre-vocational practical education and lower; intermediate: pre-vocational theoretical education and upper secondary vocational education; high: secondary non-vocational, higher education and university.
Total CIS score range 20-140; subscale fatigue range 8-56; subscale concentration range 5-35; subscale motivation range 4-28; subscale physical activity 3-21. Higher scores represent higher levels of fatigue.
Severe fatigue is defined as score > 40 on CIS subscale Fatigue.
*Statisticalliy significant difference between the groups ($p<0.05$). P values were calculated by means χ^2 tests ([c]), 1 way ANOVA ([A]) or Kruskal-Wallis ([KW]) test, as appropriate.

Table 3. Self-reported physical activity in adolescents and young adults with traumatic brain injury (TBI) assessed with the Activity Questionnaire for Adults and Adolescents (AQuAA), analyzed separately for gender and severity of injury.

	All TBI n=50	Male n=22	Female n=28	p-value	Mild TBI [b] n=18	Moderate TBI n=13	Severe TBI n=19	p-value
Time spent on low intensity physical activity per week (> 2 METS), min/week	1693 (766-2779)	2063 (963-3608)	1448 (488-2505)	0.06 [MW]	1350 (823-1933)	2020 (570-3983)	2100 (805-3310)	0.27 [KW]
Time spent on moderate-vigorous physical activity per week (> 5 METS), min/week	518 (236-1725)	1168 (493-2883)	305 (30-660)	0.002* [MW]	343 (199-1255)	500 (200-2118)	615 (255-2760)	0.45 [KW]
Time spent on sedentary activities per week (<1.5 METS), min/week	2728 (1637-3994)	2310 (1592-3760)	2940 (1635-4455)	0.39 [MW]	2848 (1632-3855)	2445 (1710-4755)	2760 (1440-3750)	0.95 [KW]
Subjects who fulfil the Dutch public health recommendation for PA (D-HEPA)[c]	32 (64%)	17 (77%)	15 (54%)	0.08 [c]	9 (50%)	9 (69%)	14 (74%)	0.29 [c]

Results are presented as median minutes per week and interquartile range (IQR) unless specified otherwise.
AQuAA: 5 category self-assessment of physical activity containing questions in the domains of commuting activities, household activities, leisure time and sport activities, activities at school and/or work, and sedentary activities, scoring minutes per day and number of days per week performing the activity.
Injury severity is based on the Glasgow Coma Scale (GCS) at hospital admission. Mild injury: GCS 13-15; moderate injury 9-12; severe injury <9.
D-HEPA: children (≤ 17 years) meet the recommendation if they perform moderate to vigorous (minimum 5 METS) activities for a minimum of 60 minutes, 7 days a week. Adults (≥ 18years) meet the recommendation if they perform moderate to vigorous (minimum 4 METS) activities for a minimum of 30 minutes, 5 days a week.
*Statistically significant difference between groups ($p<0.05$). P values were calculated by χ^2 tests ([c]), Mann-Whitney U-test ([MW]) or Kruskal-Wallis ([KW]) test, as appropriate.

Table 4. Characteristics of adolescents and young adults with traumatic brain injury (TBI) categorized by meeting or not meeting the Dutch health recommendation for physical activity (D-HEPA).

Parameters	Patients meeting the D-HEPA, n=32	Patients not meeting the D-HEPA, n=18	p value
Sex, male)	17 (53%)	5 (28%)	0.08 [c]
Age at onset, years	18.6±7.6	20.0±9.7	0.45 [t]
Current age, years	24.2±6.7	24.7±8.2	0.63 [t]
Time since injury, years	5.9±5.4	4.9±3.8	0.56 [t]
Injury severity			
Mild	9 (50% of mild group)	9 (50% of mild group)	0.29 [c]
Moderate	9 (69% of moderate group)	4 (31% of moderate group)	
Severe	14 (74% of severe group)	5 (26% of severe group)	
BMI, kg /m² (n=48)	23.4 (3.6)	23.2 (3.0)	0.86 [t]
SES/Educational level (n=36)			
Low	1 (3%)	2 (11%)	0.39 [c]
Medium	9 (28%)	3 (17%)	
High	13 (41%)	8 (44%)	
CIS scores; median (IQR)			
Total score	75.5 (58.3-95.0)	99.5 (64.8-125.3)	0.01* [MW]
Fatigue	33.5 (25.0-44.8)	40.5 (28.8-50.3)	0.16 [MW]
Concentration	22.0 (16.3-28.0)	28.5 (13.0-32.5)	0.22 [MW]
Motivation	11.0 (7.0-15.8)	16.0 (9.0-22.0)	0.03* [MW]
Physical Activity	7.0 (4.3-12.0)	17.0 (11.3-20.3)	0.001** [MW]
Severely fatigued patients (based on subscale Fatigue)	10 (31%)	9 (50%)	0.19 [MW]

Injury severity is based on the Glasgow Coma Scale (GCS) at hospital admission; mild injury: GCS 13-15, moderate injury: GCS 9-1; severe injury GCS <9.
D-HEPA: children (≤ 17 years) meet the recommendation if they perform moderate to vigorous (minimum 5 METS) activities for a minimum of 60 minutes, 7 days a week. Adults (≥ 18years) meet the recommendation if they perform moderate to vigorous (minimum 4 METS) activities for a minimum of 30 minutes, 5 days a week.
Underweight is BMI < 18 kg/m² and < 18.5 kg/m² for children and adults, respectively; healthy BMI is 18.1-24.9 kg/m² 18.6-24.9 kg/m² for children and adults, respectively; overweight BMI is 25-29.9 kg/m²; obesity is BMI >30 kg/m².
SES (socio-economic status) is based on highest educational level of one of the parents for a participant living at home or participant himself when living independently; low: pre-vocational practical education and lower; intermediate: pre-vocational theoretical education and upper secondary vocational education; high: secondary non-vocational, higher education and university.
CIS (Checklist Individual Strength): total score range 20-140; subscale fatigue range 8-56; subscale concentration range 5-35; subscale motivation range 4-28; subscale physical activity 3-21, higher scores represent higher levels of fatigue.
Severe fatigue is defined as score > 40 on CIS subscale Fatigue
Significant differences between the groups (* p< 0.05, **p<0.001) were calculated by χ^2 tests ([c]) or Mann-Whitney U-test ([MW]), as appropriate.

Table 5. Logistic regression analysis of not meeting the D-HEPA (inactive) as the dependent variable and all independent variables (injury characteristics and CIS scores) entered separately in the model, adjusted for age, sex, and BMI. Odds ratios represent the multiplication factor for the odds of not meeting the D-HEPA criteria with higher levels of fatigue.

	Odds ratio	**95% CI**		**p-value**
		lower	upper	
Age at injury	1.11	0.95	1.31	0.19
Time since injury	0.90	0.77	1.06	0.21
Severity of injury				
Mild injury	2.83	0.62	12.94	0.18
Moderate injury	1.85	0.30	11.63	0.51
Severe injury	1			
Fatigued				
based on CIS Total Score	1.02	1.00	1.05	0.06
based on CIS Subscale Fatigue	1.02	0.97	1.08	0.38
based on CIS Subscale Concentration	1.06	0.98	1.16	0.15
based on CIS Subscale Motivation	1.14*	1.01	1.29	0.04*
based on CIS Subscale Physical Activity	1.25*	1.08	1.43	0.002*

D-HEPA: children (≤ 17 years) meet the recommendation if they perform moderate to vigorous (minimum 5 METS) activities for a minimum of 60 minutes, 7 days a week. Adults (≥ 18years) meet the recommendation if they perform moderate to vigorous (minimum 4 METS) activities for a minimum of 30 minutes, 5 days a week. Injury severity is based on the Glasgow Coma Scale (GCS) at hospital admission; mild injury: GCS 13-15, moderate injury: GCS 9-12, severe injury: GCS <9.
CIS: Checklist Individual Strength: total score range 20-140; subscale fatigue range 8-56; subscale concentration range 5-35; subscale motivation range 4-28; subscale physical activity 3-21, higher scores represent higher levels of fatigue.
* Statistically significant difference ($p < 0.05$).

Discussion

This study among 50 adolescents and young adults with TBI describes their self-reported levels of physical activity and fatigue symptoms. Our results show that the number of subjects meeting public health recommendations for healthy PA was similar to the general population, whereas physical inactivity was associated with more fatigue.

The study population included 3 subgroups (mild, moderate, and severe injury) with, as compared to a hospital-based population of TBI patients[1] a relatively high proportion of subjects with moderate and severe injuries. Their characteristics reflect the specific selection of patients in the rehabilitation setting, where in general patients with more severe TBI injuries are treated. There were few participants under the age of 18 years so the cohort was analyzed as a whole. The mean BMI for the participants corresponds

to a healthy weight. The percentage with overweight (21% and 4% obese) is comparable to the national Dutch statistics for the age group 20-30 years (21% with overweight, 7% with obesity).[45]

In our study, we found that persons with TBI report physical activity at levels similar to the healthy Dutch population. Healthy Dutch adults are on average 202 minutes per day physically active;[46] our study population of adults with TBI reported 229 minutes of physical activity per day. Healthy adolescents are on average 138 minutes per day active[46] compared to 289 minutes per day on physical activities in our study population, with a similar male-to-female ratio, with males being more active than females.[46] The number of adolescents in this study (n=7) is limited thus a generalization to the whole adolescent TBI population cannot be made. Studies on PA in children with TBI are lacking but Gordon et al. found that 14.9% of adults with TBI were exercisers (more than 3 times a week 30 minutes of exercise) compared to 23% of the comparison (healthy) group.[13] Meessen et al. found in a study of orthopedic patients that individuals with a physical disability may be more physically active than the healthy population due to active rehabilitation or being more conscious of the importance of physical activity after their injury.[47] Overall, there were no statistically significant differences in activity levels between individuals with a mild, moderate or severe injury, however it should be noted that the subgroups were very small, with the power of the study being too small to draw firm conclusions on the association between physical activity levels and severity of TBI.

Sedentary activities, such as watching television, using the computer, tablet or smartphone, were reported by adolescents with TBI on average to be 578 minutes per day and adults 349 minutes per day, exceeding the international norm for 'screen time' for children and adolescents of two hours per day.[48] There are no percentages known for healthy Dutch children and adolescents but it is known that the norm is often exceeded, possibly leading to increased health issues on the long term.[49]

Thirty seven percent of the participants in this study reported severe fatigue; these findings support earlier research in the adult TBI population: in a review by Mollayeva 21% to 73% of adults with TBI reported fatigue, with at 10 years post-injury 50% of patients reporting fatigue.[50] Pediatric TBI data on fatigue is limited; 11% report fatigue after 3 months;[51] in a systematic review including 24 studies, fatigue was found to be one of the most persistent symptoms among TBI patients 13 years post injury.[52]

The CIS is a multidimensional fatigue questionnaire focusing on reported fatigue symptoms and related behavior, such as motivation to perform activities, the ability to concentrate on an activity or having the energy to perform physical activities.

Indeed, fatigue appeared to be related to physical (in)activity in our study in line with previous research. In a large cohort (n=299) of adults with mild TBI 32% were severely fatigued, compared to 12% of the control group and the higher rates of fatigue were associated with limitations in physical and social functioning.[21]

Interestingly, lack of motivation was significantly related to the level of physical inactivity, substantiating the need to address not only physical but also mental aspects of PA. Knittle et al. found that rheumatoid arthritis patients that were more motivated were more likely to improve long term PA levels.[53] Within a TBI population in an active rehabilitation program, 28 individuals were asked about their barriers to physical activity; it was found that those perceiving more barriers, including lack of motivation, were more often less physically active.[10]

Limitations of the study

This study has a number of limitations. An important limitation of the study concerns its relatively small sample size. It remains to be established to what extent in PA or fatigue according to, e.g., injury severity or specific associations between aspects of fatigue and PA are in fact type II errors.

Moreover, patients were recruited in a rehabilitation center thereby constitute a specific subgroup of all Dutch individuals with TBI.

In particular, our study includes a lower proportion of males with TBI (44%) than the reported 71% in the age group 15-24 in a hospital-based population.[1] The total percentage of males in the total cohort (n=107, 56%) is comparable to studies involving populations in the outpatient rehabilitation setting.[10,54,55] The relatively low proportion of men in our sample is in part caused by fewer male than female patients responding to our survey. This is not unusual, as in general, women are more likely to participate in surveys than men.[56, 57] Although the response rate is relatively low, it is quite similar to response rates reported in TBI literature.[58]

Another limitation concerns the lack of categorization into specific age groups. People in the age range of 12-39 are in very different stages of development, some of them still growing, and therefore it would have been most accurate to analyze the data separately, e.g. 12-17 and 18-39 age groups. This analysis was however not possible, due to the relatively low number of subjects, underpinning the need for larger, multicenter studies in the future. For the measurement of physical activity and fatigue in such studies it is recommended to use the same instruments as used by national surveys among the general population, allowing to adjust for the base risk in the various age and sex groups. Beyond the limitations of this study there are broader issues in the field of physical activity research. There are several definitions and norms for physical activity. This creates a barrier when comparing data from different studies, although the PA norms in the United States are similar to those in The Netherlands. Activities can also be classified according to health status. For example, The American College of Sports Medicine exercise guidelines for people with a brain injury recommend an exercise frequency of three to five times per week, at an intensity of 40% to 70% of

peak oxygen uptake or a 13/20 rating of perceived exertion (RPE), and a duration of 20 to 60 minutes using the appropriate mode (e.g. walking, swimming, cycling) depending on the individual's physical ability.

Studies have shown that measuring physical activity retrospectively with questionnaires has its limitations. In studies with TBI individuals it has been suggested that cognitive deficits influence the answers reported on the questionnaires.[10] Use of accelerometers to quantify PA after TBI has been suggested and implemented in TBI studies.[59] In studies with children objective PA measures have shown to be superior to subjective questionnaires.[60, 61] Several questionnaires rating fatigue are used in this patient group, adults and children. Recently a fatigue questionnaire specifically for adults with TBI has been developed;[62] the feasibility of a child/adolescent specific fatigue questionnaire should be explored.

Conclusions

Adolescents and young adults with TBI are just as active as the Dutch healthy population, meeting the Dutch recommendation for physical activity in 64% of the cases (healthy Dutch population: 53-69%). Injury severity is not related to PA levels. Although fatigue is common after TBI, higher levels of fatigue were not associated with inactivity (not meeting the D-HEPA), but motivation to undertake activities was significantly related to activity levels. It is important to improve or maintain physical activity in this population of adolescents and young adults to decrease secondary effects in the future. It is important to take (lack of) motivation and other possible barriers of the individual into account when examining PA and in development of new PA programs. As in the general population, females with TBI tend to be less active; PA programs should probably consider gender differences in their development.

References

1. de Kloet AJ, Hilberink SR, Roebroeck ME, Catsman-Berrevoets CE, Peeters E, Lambregts SA, et al. Youth with acquired brain injury in The Netherlands: a multi-center study. *Brain Inj* 2013;27:843-9.
2. KA, Ayala D, Baker T, Heard J, Masel B. Aerobic capacity after traumatic brain injury: comparison with a nondisabled cohort. *Arch Phys Med Rehabil* 2007;88:315-20.
3. Consensus conference. Rehabilitation of persons with traumatic brain injury. NIH Consensus Development Panel on Rehabilitation of Persons With Traumatic Brain Injury. *JAMA* 1999;282:974-83.
4. Driver S, Rees K, O'Connor J, Lox C. Aquatics, health-promoting self-care behaviours and adults with brain injuries. *Brain Inj* 2006;20:133-41.
5. Booth FW, Gordon SE, Carlson CJ, Hamilton MT. Waging war on modern chronic diseases: primary prevention through exercise biology. *J Appl Physiol* (1985) 2000;88:774-87.
6. Penedo FJ, Dahn JR. Exercise and well-being: a review of mental and physical health benefits associated with physical activity. *Curr Opin Psychiatry* 2005;18:189-93.
7. Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, et al. Physical activity and public health. A recommendation from the Centres for Disease Control and Prevention and the American College of Sports Medicine. *JAMA* 1995;273:402-7.
8. Rimmer JH, Wang E, Smith D. Barriers associated with exercise and community access for individuals with stroke. *J Rehabil Res Dev* 2008;45:315-22.
9. World Health Organization. Physical activity; 2017 [Internet]. Available from: http://www.who.int/topics/physical_activity/en/ [cited Jun 16 2017].
10. Driver S, Ede A, Dodd Z, Stevens L, Warren AM. What barriers to physical activity do individuals with a recent brain injury face? *Disabil Health J* 2012;5:117-25.
11. Committee PAGA. Physical Activity Guidelines Advisory Committee Report; 2008: Washington, DC, USA. Available from: https://health. gov/paguidelines/report/pdf/CommitteeReport.pdf [cited Jun 16 2017].
12. Fleming J, Braithwaite H, Gustafsson L, Griffin J, Collier AM, Fletcher S. Participation in leisure activities during brain injury rehabilitation. *Brain Inj* 2011;25:806-18.
13. Gordon WA, Sliwinski M, Echo J, McLoughlin M, Sheerer MS, Meili TE. The benefits of exercise in individuals with traumatic brain injury: a retrospective study. *J Head Trauma Rehabil* 1998;13:58-67.
14. Kleffelgaard I, Roe C, Soberg HL, Bergland A. Associations among self-reported balance problems, post-concussion symptoms and performance-based tests: a longitudinal follow-up study. *Disabil Rehabil* 2012;34:788-94.
15. Chin LM, Keyser RE, Dsurney J, Chan L. Improved cognitive performance following aerobic exercise training in people with traumatic brain injury. *Arch Phys Med Rehabil* 2015;96:754-9.
16. Novack TA, Alderson AL, Bush BA, Meythaler JM, Canupp K. Cognitive and functional recovery at 6 and 12 months post-TBI. *Brain Inj* 2000;14:987-96.
17. Sendroy-Terrill M, Whiteneck GG, Brooks CA. Aging with traumatic brain injury: cross-sectional follow-up of people receiving inpatient rehabilitation over more than 3 decades. *Arch Phys Med Rehabil* 2010;91:489-97.
18. Brown AW, Moessner AM, Mandrekar J, Diehl NN, Leibson CL, Malec JF. A survey of very-long-term outcomes after traumatic brain injury among members of a population-based incident cohort. *J Neurotrauma* 2011;28:167-76.
19. Wise EK, Hoffman JM, Powell JM, Bombardier CH, Bell KR. Benefits of exercise maintenance after traumatic brain injury. *Arch Phys Med Rehabil* 2012;93:1319-23.
20. Driver S, Ede A. Impact of physical activity on mood after TBI. *Brain Inj* 2009;23:203-12.
21. Stulemeijer M, van der Werf S, Bleijenberg G, Biert J, Brauer J, Vos PE. Recovery from mild traumatic brain injury: a focus on fatigue. *J Neurol* 2006;253:1041-7.
22. Jankowski LW, Sullivan SJ. Aerobic and neuromuscular training: effect on the capacity, efficiency, and fatigability of patients with traumatic brain injuries. *Arch*

Phys Med Rehabil 1990;71:500-4.
23. Jones TM, Dean CM, Hush JM, Dear BF, Titov N. A systematic review of the efficacy of self-management programs for increasing physical activity in community-dwelling adults with acquired brain injury (ABI). *Syst Rev* 2015;4:51.
24. Birch A. *Developmental Psychology*. Second edition. London: Palgrave; 1997. p. 220.
25. Anaby D, Law M, Hanna S, Dematteo C. Predictors of change in participation rates following acquired brain injury: results of a longitudinal study. *Dev Med Child Neurol* 2012;54:339-46.
26. Echemendia RJ, Giza CC, Kutcher JS. Developing guidelines for return to play: consensus and evidence-based approaches. *Brain Inj* 2015;29:185-94.
27. Howell DR, Osternig LR, Chou LS. Adolescents demonstrate greater gait balance control deficits after concussion than young adults. *Am J Sports Med* 2015;43:625-32.
28. Gagnon I, Swaine B, Friedman D, Forget R. Exploring children's self-efficacy related to physical activity performance after a mild traumatic brain injury. *J Head Trauma Rehabil* 2005;20:436-49.
29. Benelux P. Wechsler Adult Intelligence Scale IV-NL; 2017 [Internet]. Available from: www.pearsonclinical.nl/wais-iv-nl-wechsler-adultintelligence-scale [cited Jun 16 2017].
30. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974;2:81-4.
31. Cole TJ, Flegal KM, Nicholls D, Jackson AA. Body mass index cut offs to define thinness in children and adolescents: international survey. *BMJ* 2007;335:194.
32. van Buuren S. [Body-mass index cut-off values for underweight in Dutch children]. *Ned Tijdschr Geneeskd* 2004;148:1967-72.
33. World Health Organization. BMI classification; 2016 [Internet]. Available from: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html [cited Jun 16 2017].
34. Donkervoort M, Roebroeck M, Wiegerink D, van der Heijden-Maessen H, Stam H, Transition Research Group South West N. Determinants of functioning of adolescents and young adults with cerebral palsy. *Disabil Rehabil* 2007;29:453-63.
35. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess healthenhancing physical activity. *J Clin Epidemiol* 2003;56:1163-9.
36. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR Jr. Montoye HJ, Sallis JF, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc* 1993;25:71-80.
37. Kemper HGC, Ooijendijk WM, Stiggelbout M. Consensus over de Nederlandse Norm voor Gezond Bewegen. *Tijdschr Soc Gezondheidsz* 2000;78:180-3.
38. Hildebrandt VH, Ooijendijk WTM, Hopman-Rock M. [TNO Trends Report - Physical activity and health 2004/2005] [Internet]. Available from: file://psf/Home/Downloads/hildebrandt-2007-trendrapport.pdf [cited Jun 16 2017].
39. Chinapaw MJ, Slootmaker SM, Schuit AJ, van Zuidam M, van Mechelen W. Reliability and validity of the Activity Questionnaire for Adults and Adolescents (AQuAA). *BMC Med Res Methodol* 2009;9:58.
40. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* 2011;43:1334-59.
41. American Heart Association. American Heart Association Recommendations for Physical Activity in Adults; 2015 [Internet]. Available from: www.heart.org/HEARTOR G/HealthyLiving/PhysicalActivity/FitnessBasics/American-Heart-Association-Recommendations-for-Physical-Activity-in-Adults_UCM_307976_Article.jsp#.WUOMGuvyiUl [cited Jun 16 2017].
42. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994;38:383-92.
43. ter Wolbeek M, van Doornen LJ, Kavelaars A, Heijnen CJ. Severe fatigue in adolescents: a common phenomenon? *Pediatrics* 2006;117:e1078-86.

44. IBM SPSS Statistics for Windows, Version 22.0. Armonk (NY): IBM Corp; 2015.
45. Statistics Netherland (CBS). [People's length and weight, underweight and overweight; since 1981]; 2017 [Internet]. Available from: http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=81565n ed&D1=a&D2=0&D3=a&D4=0&D5=0,10,20,30-33&VW=T [cited Jun 16 2017].
46. Hildebrandt VH, Bernaards CM, Hofstetter H. [TNO Trends Report - Physical activity and health 2000-2014]; 2013 [Internet]. Available from: file://psf/Home/Downloads/hilberhof-2015-trendrapport.pdf [cited Jun 16 2017].
47. Meessen JM, Peter WF, Wolterbeek R, Cannegieter SC, Tilbury C, Benard MR, et al. Patients who underwent total hip or knee arthroplasty are more physically active than the general Dutch population. *Rheumatol Int* 2017;37:219-27.
48. American Academy of Pediatrics. Children, adolescents, and television. *Pediatrics* 2001;107:423-6.
49. Hildebrandt VH, Bernaards CM, Stubbe JH. [TNO Trends Report -Physical activity and health 2010-2011]; 2013 [Internet]. Available from: www.volksgezondheidenzorg.info/sites/default/files/hildebrandt_trendrapport_bewegen_gezondheid_2010_2011.pdf [cited Jun 16 2017].
50. T, Kendzerska T, Mollayeva S, Shapiro CM, Colantonio A, Cassidy JD. A systematic review of fatigue in patients with traumatic brain injury: the course, predictors and consequences. *Neurosci Biobehav Rev* 2014;47:684-716.
51. Barlow KM, Crawford S, Stevenson A, Sandhu SS, Belanger F, Dewey D. Epidemiology of postconcussion syndrome in pediatric mild traumatic brain injury. *Pediatrics* 2010;126:e374-81.
52. Gagner C, Landry-Roy C, Laine F, Beauchamp MH. Sleep-wake disturbances and fatigue after pediatric traumatic brain injury: A systematic review of the literature. *J Neurotrauma* 2015;32:1539-52.
53. Knittle K, de Gucht V, Hurkmans E, Vliet Vlieland T, Maes S. Explaining physical activity maintenance after a theory-based intervention among patients with rheumatoid arthritis: process evaluation of a randomized controlled trial. *Arthritis Care Res* 2016;68:203-10.
54. Dillard C, Ditchman N, Nersessova K, Foster N, Wehman P, West M, et al. Post-concussion symptoms in mild traumatic brain injury: findings from a paediatric outpatient clinic. *Disabil Rehabil* 2017;39:544-50.
55. Bay E, de-Leon MB. Chronic stress and fatigue-related quality of life after mild to moderate traumatic brain injury. *J Head Trauma Rehabil* 2011;26:355-63.
56. Curtin R, Presser S, Singer E. The effects of response rate changes on the index of consumer sentiment. *Public Opin Q* 2000;64:413-28.
57. Moore DL, Tamai J. Evaluating nonresponse error in mail surveys. In: Groves RM, Dillman DA, Eltinge JL, Little RJA. *Survey Nonresponse*. New York: John Wiley & Sons; 2000. p. 197-211.
58. Anderson V, Godfrey C, Rosenfeld JV, Catroppa C. 10 years outcome from childhood traumatic brain injury. *Int J Dev Neurosci* 2012;30:217-24.
59. Hassett L, Moseley A, Harmer A, van der Ploeg HP. The reliability, validity, and feasibility of physical activity measurement in adults with traumatic brain injury: an observational study. *J Head Trauma Rehabil* 2015;30:E55-61.
60. Rockette-Wagner B, Storti KL, Edelstein S, Delahanty LM, Galvin B, Jackson A, et al. Measuring Physical Activity and Sedentary Behavior in Youth with Type 2 Diabetes. *Child Obes* 2017;13:72-7.
61. Maatta S, Nuutinen T, Ray C, Eriksson JG, Weiderpass E, Roos E. Validity of self-reported out-of-school physical activity among Finnish 11-year-old children. *Arch Public Health* 2016;74:11.
62. Visser-Keizer AC, Hogenkamp A, Westerhof-Evers HJ, Egberink IJ, Spikman JM. Dutch multifactor fatigue scale: a new scale to measure the different aspects of fatigue after acquired brain injury. *Arch Phys Med Rehabil* 2015;96:1056-63.



Chapter 4

Physical activity, fatigue and sleep quality at least 6 months after mild traumatic brain injury in adolescents and young adults: a comparison with orthopedic injury controls

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Abstract

Objectives
To compare physical activity (PA), fatigue and sleep quality in adolescents and young adults (AYAs) after mild TBI (mTBI) to persons of similar age after orthopedic injury (OI) on the longer term.

Setting
Follow-up at least 6 months after visiting the emergency department of one of 2 general hospitals.

Participants
Forty-nine patients aged 12-25 years (mean 18.4 years), diagnosed with mTBI and 54 patients aged 12-25 years (mean 15.8 years) with OI.

Design
Cross-sectional electronic survey study.

Main outcome measures
The Activity Questionnaire for Adults and Adolescents with results dichotomized for meeting/not meeting Dutch Health Enhancing PA recommendations (D-HEPA), the Checklist Individual Strength (range 20-140, low-high) measuring fatigue, and the Pittsburgh Sleep Quality Index (range 0-21, high-low) measuring sleep quality were administered.

Results
Patients with mTBI less frequently met D-HEPA recommendations than patients with OI (49% vs. 70%; OR 2.87, 95%CI 1.07, 7.72) and reported more concentration-related fatigue problems (mean 19.1 (SD 8.0), mean 13.9 (SD 7.8), respectively; β 3.98, 95%CI 0.39, 7.56), after adjusting for potential confounders, sex, BMI, age and time since injury. No differences were found in sleep quality.

Conclusions
Identifying symptoms and limitations in activities is important after mTBI so that rehabiliation treatment can be initiated. Whether physical activity or fatigue is the best target for treatment remains to be established.

Key words
brain injuries, orthopedic injuries, fatigue, sleep, physical activity, pediatric, adolescent

Introduction

Traumatic brain injury (TBI) is one of the leading causes of death and disability in adolescents and young adults (AYAs), with an estimated yearly incidence of 2.25-2.96 per 100 for the age group 15-25 years.[1, 2] The majority is classified as mild TBI (mTBI), with symptoms often resolving within 4 weeks. However, a significant minority reports persistent symptoms.[3, 4] These longer-term consequences of mTBI in AYAs are often multiple and complex, affecting physical, emotional, cognitive and/or social functioning.[4]

Among the persistent symptoms after mTBI in AYAs impaired physical activity (PA),[5] fatigue[6-9] and sleep disorders[6, 10-13] are relatively often reported. With the interpretation of their reported rate or severity, it is important to consider that it may be difficult to unravel to what extent the complaints are a result of damage to the brain or the trauma as such. In this respect, comparisons with a control group of AYAs who have had a trauma involving other body regions, such as orthopedic injury, may be more informative than using controls from the general population. In addition, apart from the control group, potential confounders that need to be taken into account are factors associated with the trauma (e.g. time since injury)[7] and factors associated with PA, fatigue and/or sleep quality in general (i.e. sex, age, Body Mass Index).[14, 15]

Regarding physical activity after mTBI, various studies in adults using self-report questionnaires reported lower levels of physical activity as compared to the general population[16] and decreased PA in individuals after TBI without a control group.[17, 18] Research on PA after mTBI in the pediatric population, particularly in AYAs, focus predominantly on "return to play" or influence of exercise on symptoms and not on the the physical activity levels themselves,[19-21] while literature has identified numerous health benefits of physical activity during adolescence[22] as well as a general decline in physical activity during adolescence.[23]

With respect to fatigue after mTBI in AYAs, the literature is conflicting. Previous studies in (mild) TBI and orthopedic controls in children have found both more fatigability in the children with mTBI at 1 week post injury[24] and 2 years post injury[25] or no difference between the mTBI and control group 2 years post injury.[26]

Concerning sleep difficulties after mTBI in AYA populations, sleep disorders were more often reported as compared to orthopedic and/or healthy controls.[11]

The abovementioned studies make it clear that, although it is conceivable that fatigue and sleep problems are interrelated[27, 28] , most studies in mTBI were so far focussing on only one or two of these dimensions.[6, 9, 11, 29] In addition, only few studies used an appropriate control group.[6, 11, 12] Therefore, the aim of the present study was to compare PA levels, fatigue and sleep quality at least 6 months post injury in AYAs who were

diagnosed in a hospital with mTBI or OI. We hypothesised that, due to the nature of the trauma, PA levels would be lower and fatigue and sleep quality would be worse in patients with mTBI as compared to patients with OI.

Methods

Study design

This cross-sectional study was executed at the Haaglanden Medical Center Haga Hospital (location Leyweg and Juliana Children's Hospital), both large teaching hospitals in The Hague. The study included AYAs registered with a trauma in one of the above mentioned hospitals.

The study was approved by the Medical Ethics Review Committee of the Leiden University Medical Center (P12.156) and all patients and their parents (when patient was under 18 years of age) provided written informed consent.

Participants

Patients were eligible for the study if they met all of the following criteria: a.) aged 12-25 years at injury; b.) registered with the diagnosis mild brain injury (Glasgow Coma Scale 13-15) or a fracture of the arm, clavicula, or leg; c.) visited the Emergency Department (ED) of one of the two hospitals between March 1, 2012 and March 1, 2013. Patients were not eligible if they: a.) visited the ED for other head injuries or orthopedic injuries more than once in the same year; b.) underwent surgery related to the trauma; c.) had a diagnosis of both mTBI and OI; d.) had pre-injury medical conditions potentially interfering with their current functioning (such as congenital disorders, rheumatic disease, chronic fatigue syndrome, pain syndrome, sleep disorder, epilepsy, psychiatric disorder i.e. autism spectrum disorder, depression, schizophrenia, conversion disorder or attempted suicide); e.) had an intellectual level with an IQ< 70 based on self-report in ED report or based on school level; f.) were non-fluent in the Dutch language (based on ED report or self-report) or lived outside of The Netherlands. Date of birth, sex, and date of ED visit were extracted from the medical files (all data extracted by the principle investigator, FvM-D). Medical history (reported in categories: congenital disorder, rheumatic disorder, neurologic disorder, chronic fatigue syndrome, psychiatric disorder or other), multiple ED visits in the past year (yes/no) and surgery (yes/no) were extracted from of the medical files. Location of trauma was categorized in street/traffic related, sport/field, or other: home, school or work).

The severity of TBI was determined by means of the Glasgow Coma Scale (GCS) at hospital admission. According to the GCS, the severity of TBI was considered mild if

the GCS was 13–15, moderate if the GCS was 9–12 or severe if the GCS was <9.[30] When GCS was not reported but the patient was fully conscious (ie, walked into the ED, cycled to the hospital) they were included in the mild TBI group.
For the orthopedic injury group, patients with a fracture of the arm, leg or clavicula without brain injury were identified, as done in an earlier study.[25]

Assessments

Assessments included a one-time survey comprising three validated Patient Reported Outcome Measures (PROMs), to be completed by patients at home, either electronically (NetQ, www.netq.nl) or on paper. Those completing the paper version returned the questionnaire in a pre-stamped envelope. The questionnaires were coded to match the medical records and made anonymous. By providing 2 methods for completing the questionnaire the problems of not having a computer or having computer problems was avoided.
All eligible patients and/or their parents were invited by postal mail in September 2013 and, if they agreed to participate, asked to return the signed informed consent and to state whether they preferred a paper or electronic questionnaire. Patients and/or their parents who did not respond were contacted once by postal mail 2 weeks after the first mailing, and once again by telephone after 3 months. Patients received an incentive (€10 voucher) for completing the questionnaire. Patients were able to respond through the end of December 2014.

General and sociodemographic characteristics

Patients were asked to report their current height and weight; from which body mass index: BMI=weight (kg)/height squared (m^2) was calculated. For patients aged 12 to 17 underweight was defined as BMI < 17.0 and overweight (BMI 25.1-30.0) and obesity (BMI above 30.0).[31,32] For patients 18 years and older cut-off points for underweight, overweight and obesity according to international criteria: <18.5, 25 and >30 kg/m^2, respectively, were used.[33] Current age was determined using the moment of questionnaire completion; for non-responders the mean date of completion was used (June 1, 2014).

Physical activity

Physical activity was measured using the Activity Questionnaire for Adults and Adolescents (AQuAA), a 5 category self-assessment of physical activity based on the SQUASH (Short QUestionnaire to ASsess Health enhancing physical activity). The AQuAA has been validated in the Netherlands for children and adults.[34] However, its psychometric properties were found to be moderate to poor.[35] Patients were asked

about the frequency (number of days per week), duration (time spent) and intensity (low, moderate, or vigorous) spent on activities in the past 7 days with examples of activities to facilitate questionnaire completion. Each activity has a MET (Metabolic Equivalent of Task) score related to the intensity of the activity, and is reported as mililiter oxygen use per kilogram bodyweight per minute. The METS compendium developed by Ainsworth[36] was used in this study. Activities were furthur categorized, using the METS for each activity, into low, moderate or vigorous activities,[37] with the total amount of PA being expressed as minutes spent on low, moderate and vigorous activities per week. In addition, the achievement of the Dutch Health Enhancing PA recommendations (D-HEPA) (yes/no) was calculated from the data. In The Netherlands a healthy PA level has been established for children and adults: children (4-17 years of age) should be physically active 60 minutes with moderate to vigorous activities (minimum 5 METS), 7 days a week.[37] Adults meet the criterion if they are physically active (minimum 4 METS) for 30 minutes, 5 days a week.[38] Similar guidelines have been developed by the American College of Sports Medicine,[39] and the World Health Organization.[40] To obtain a more clinically comparable position the data was dichotimized into meeting or not-meeting the D-HEPA.

Fatigue

The Checklist Individual Strength (CIS), was used to measure fatigue. It is a 20-item self-report rating scale for assessing fatigue and associated behavior during the last two weeks. Four domains, (1) severity of fatigue (8 items, score range 8 to 56), (2) concentration problems (5 items, score range 5 to 35), (3) reduced motivation (4 items, score range 4 to 28), and (4) reduced physical activity (3 items, score range 3 to 21) are measured. Each item is scored on a seven point Likert scale. The Total Score is calculated by the sum of the 20 items (range 20 to140). Higher scores indicate higher levels of fatigue, higher levels of concentration problems, decreased motivation, and lower levels of physical activity.[41] A score of 40 or higher on the subscale Fatigue indicates severe fatigue.[42]. The CIS has been validated for use in the adult and pediatric Dutch population.[43]

Sleep Quality

To evaluate sleep quality the Pittsburgh Sleep Quality Index (PSQI)[44] was administered. It is a self-rated questionnaire which evaluates sleep quality and disturbances over a 1 month interval. Seven items (subjective sleep quality, sleep latency (the time from lying down for sleep to the start of actual sleep), sleep duration, habitual sleep efficiency (the proportion of actual sleep time spent in bed), sleep disturbances, use of sleep medication and day time dysfunction) are scored on 4 point Likert scales (0-3, low to

high), with a total score ranging from 0 to 21. A global score greater than 5 indicates poor sleep quality.[44] The PSQI has been used in pediatric[45] and adult studies.[46]

Statistical analysis

Among participants, injury (mTBI vs OI) and sociodemographic characteristics (sex, age at injury, time since injury, current age, mechanism of injury and BMI) were analyzed descriptively with Fisher's exact test, independent samples *t*- test or Mann-Whitney-U test, where appropriate. Due to the non-normal distribution of the data, the AQuAA scores in minutes per week were calculated as medians and interquartile ranges (IQR, i.e. the 25th – 75th percentile).

Physical activity levels (AQuAA minutes/week and meeting D-HEPA recommendations yes/no), fatigue (CIS), and sleep quality (PSQI) between the patients with mTBI and OI were analyzed by means of unadjusted linear and logistic regression analysis. Multivariable linear regression was performed to determine the relationship between type of injury (independent variable) and physical activity, fatigue symptoms, and sleep quality (dependent variables) while adjusting for sex, BMI, age, and time since injury. Results were reported as beta and 95% confidence intervals. The natural logarithm of the AQuAA data was used to meet the assumption of normality.

Multivariate logistic regression was performed to assess the impact of type of injury (independent variable) on the likelihood of not meeting the D-HEPA, having severe fatigue symptoms or poor sleep quality (dependent variable), while correcting for sex, BMI, age, and time since injury. Results are reported as odds ratios and 95% confidence intervals. For the comparison of characteristics the level of statistical significance was defined as $p < 0.05$. All analyses were performed using SPSS 22 for Windows.[47]

Results

Four hundred and six patients were identified with mTBI and 464 patients with OI. One hundred patients with TBI were excluded: 7 had a GCS under 13, 12 had multiple ED visits in the same year, 18 underwent surgery, 35 had a medical condition, 7 had a low intellectual level, 11 had a language barrier and 10 had no current address. One hundred and forty-three patients were excluded from the OI group: 27 had multiple ED visits in the same year, 87 underwent surgery, 14 had a medical condition, 8 had a language barrier and 7 had no current address. Three hundred and six patients with mTBI and 321 patients with OI were selected from the registries, considered to be eligible for the present study and were approached for participation in the study (Figure 1).

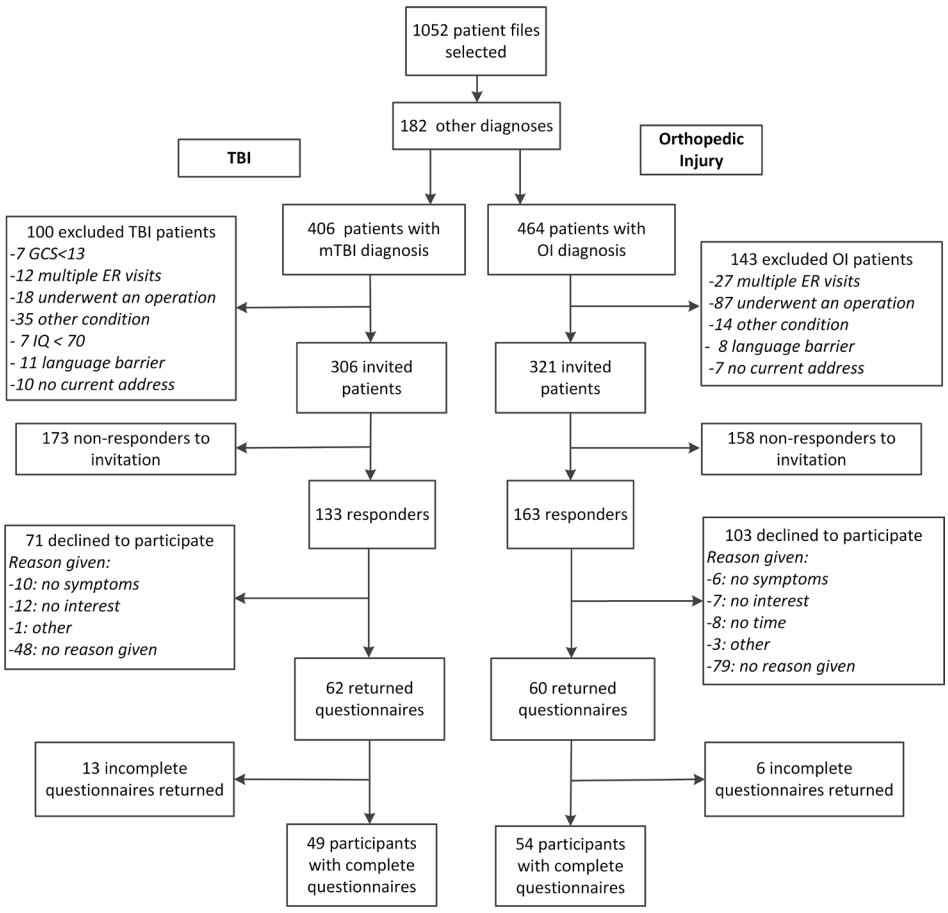


Figure 1. Flowchart of participants adolescents and young adults with mild traumatic brain injury (mTBI) and participants with an orthopedic injury (OI) seen at the Emergency Department.

Regarding the participants, there was no significant difference in sex (p=0.43) or time since injury (p=0.13) between patients with mTBI or OI. There was, however, a significant difference between patients with mTBI and OI regarding age at injury and current age, with the patients in the OI group being younger (current age mean 18.4 years (SD 3.6), 15.8 years (SD 3.2), respectively; p<0.01)). Patients with OI had a significantly lower BMI (19.7 (SD 2.8) than the patients with mTBI (22.2 (SD 2.7), p<0.01) with both groups having a similar distribution of weight categories, predominantly in the normal weight range. There was a significant difference in the mechanism of the injury, in the mTBI group 49% of the injuries were sport-related, compared to 48% of the OI group having street/traffic related injuries (p=0.01) (Table 1).

Table 1. Characteristics of participants and non-participants with mild traumatic brain injury (mTBI) and orthopedic injury (OI).

	mTBI		OI	
	participants n=49	**non-participants n=257**	**participants n=54**	**non-participants n=267**
Sex, male; no. (%)	22 (45)	159 (62)	29 (54)	197 (74)
Age at injury, years; mean (SD)	16.8 (3.6) *	17.7 (3.6)	14.3 (3.2)	15.3 (3.5)
Time since injury, years; mean (SD)	1.6 (0.5)	1.8 (0.3)	1.5 (0.4)	1.8 (0.3)
Current age, years; mean (SD)	18.4 (3.6) *	19.5 (3.6)	15.8 (3.2)	17.1 (3.5)
Under 18 years, no. (%)	24 (49)	93 (36)	43 (80)	187 (70)
18 years and older, no. (%)	25 (51)	164 (64)	11 (20)	80 (30)
Location of injury; no. (%)				
home/school/work/other	14 (28)	73 (28)	15 (28)	76 (28)
street/traffic-related	11 (23)	39 (15)	26 (48)	136 (51)
sport/field	24 (49)	145 (57)	13 (24)	54 (20)
missing				1 (1)
BMI (kg /m^2) [a]; mean (SD)	22.2 (2.7) *		19.7 (2.8)	
Underweight, no. (%)	4 (8)		10 (19)	
Normal weight, no. (%)	35 (72)		36 (67)	
Overweight, no. (%)	9 (18)		4 (7)	
Missing	1 (2)		4 (7)	

***** p<0.05 between participants with mTBI and OI.
[a] Body Mass Index (BMI; weight (kg) / height squared (m^2)). Underweight is BMI under 18.5 above 18 years of age and under 17.0 for young adults under 18 years of age, normal weight 17.0/18.5-25.0, overweight 25.1-30.0, obesity above 30.0.
No BMI data was available for the non-participants.

Based on the unadjusted analyses for the AQuAA, patients with mTBI were significantly less active compared to patients with OI for moderate to vigorous activities (median 710 minutes/week (IQR 218-1105), median 945 minutes/week (IQR 645-1433), respectively; β -0.84, 95%CI -1.38, -0.30), with no significant difference in time spent on general activities or sedentary activities. Linear regression analyses adjusting for potential confounders sex, BMI, age, and time since injury show that having a mTBI was not significantly associated with general activities (β -0.31, 95%CI -0.66, 0.04), time spent on moderate to vigorous activities (β -0.58, 95%CI -1.19, 0.04) or sedentary activities (β -0.12, 95%CI -0.40, 0.17) (Table 2).

Significantly more patients with mTBI did not meet the D-HEPA recommendations (25 vs 16, OR 2.47, 95%CI 1.10, 5.56). The difference between the patients with mTBI and OI regarding the D-HEPA recommendations remained significant after adjusting for potential confounders (sex, BMI, age, and time since injury) in the logistic regression analysis (OR 2.87, 95%CI 1.07, 7.72).

Table 2. Physical activity (AQuAA) in a cohort of adolescents and young adults with mild traumatic brain injury (mTBI) compared to orthopedic controls (OI). Physical activity reported as minutes per week for general activities, moderate to vigorous activities and sedentary activities. Patients further categorized for meeting or not meeting the Dutch Health Enhancing Physical Activity (D-HEPA) recommendations.

	Unadjusted analyses			Adjusted analyses				
	mTBI n=49 Median (IQR)	**OI n=54 Median (IQR)**	**β (95%-CI)**	**mTBI injury β (95%-CI)**	**Female sex β (95%-CI)**	**BMI β (95%-CI)**	**Age β (95%-CI)**	**Time since injury β (95%-CI)**
AQuAA[a], min/week								
General activities, > 2 METS	1350 (755-2250)	1873 (1335-2561)	-0.28 (-0.57, 0.02)	-0.31 (-0.66, 0.04)	0.05 (-0.26, 0.37)	0.00 (-0.06, 0.07)	0.00 (-0.05, 0.06)	0.13 (-0.18, 0.45)
Moderate-vigorous activities, >5 METS	710 (218-1105)	945 (645-1433)	-0.84 (-1.38, -0.30)*	-0.58 (-1.19, 0.04)	-0.48 (-1.03, 0.08)	0.01 (-0.10, 0.13)	-0.10 (-0.19, -0.01)*	0.05(-0.50, 0.61)
Sedentary activities, < 2 METS	2670 (1750-4405)	3480 (2453-4454)	-0.22 (-0.46, 0.03)	-0.12 (-0.40, 0.17)	0.05 (-0.21, 0.31)	-0.05 (-0.10, 0.00)	0.01 (-0.03, 0.05)	-0.05 (-0.30, 0.21)
			OR (95%-CI)	**OR (95%-CI)**	**OR (95%-CI)**	**OR (95%-CI)**	**OR (95%-CI)**	**OR (95%-CI)**
Not meeting D-HEPA[b] recommendations, nr (%)	25 (51%)	16 (30%)	2.47 (1.10, 5.56)*	2.87 (1.07, 7.72)*	1.60 (0.66, 3.86)	1.11 (0.93, 1.32)	0.90 (0.78, 1.04)	0.53 (0.12, 2.30)

Linear regression analysis performed for the continuous variables on the natural logarithm of the data and reported as β and 95% CI and logistic regression analysis for the dichotomous variable (D-HEPA yes/no), reported as odds ratio (OR) and 95% confidence interval (CI). Analyses assess the relationship between type of injury (mTBI/OI; independent variable) and physical activity (dependent variable). Adjusted analyses correct for potential confounders: age, gender, BMI, and time since injury.
[a] Activity Questionnaire for Adults and Adolescents (AQuAA): 5 category self-assessment containing questions in the domains of commuting activities, household activities, leisure time and sport activities, activities at school and/or work, and sedentary activities. Data reported as medians and interquartile ranges (IQR).
[b] Dutch Health Enhancing Physical Activity recommendations (D-HEPA): children (≤ 17 years) meet the recommendation when performing moderate to vigorous (minimum 5 Metabolic Equivalent of Task (METS)) activities for a minimum of 60 minutes, 7 days a week. Adults (≥ 18years) meet the recommendation when performing moderate to vigorous (minimum 4 METS) activities for a minimum of 30 minutes, 5 days a week.
* $p < 0.05$

In the unadjusted analyses, patients with mTBI reported significantly higher levels of fatigue based on the CIS Total Score (β 16.87, 95%CI 7.71, 26.03), subscale Fatigue (β 7.77, 95%CI 3.31, 12.22), subscale Concentration (β 5.21, 95%CI 2.14, 8.29), and subscale Physical Activity (β 2.25, 95%CI 0.59, 3.92). After adjusting for potential confounders in the linear regression analyses only subscale Concentration remained significantly higher in the mTBI group (β 3.98, 95%CI 0.39, 7.56), indicating more concentration problems related to fatigue in this group. Based on the subscale Fatigue 16% of the mTBI group and 6% of the OI group were severely fatigued. In the unadjusted as well as the adjusted analyses the diffference between the two groups was not significant (Table 3).

In the unadjusted analysis, patients with mTBI reported significantly lower sleep quality based on the PSQI Total Score (β 1.34, 95%CI 0.22, 2.45) but this significance did not hold after adjusting for potential confounders in the adjusted analysis (β 0.82, 95%CI -0.49, 2.14). Thirty-seven percent of the mTBI group and 22% of the OI group reported poor sleep quality (PSQI Total Score greater than 5). The difference between the groups was not significant for the unadjusted or adjusted analyses (Table 3).

Table 3. Fatigue (CIS) and sleep quality (PSQI) in a cohort of adolescents and young adults with mild traumatic brain injury (mTBI) compared to orthopedic controls (OI).

		Unadjusted analyses			Adjusted analyses				
		mTBI n=49	OI n=54		mTBI injury	*Female sex*	*BMI*	*Age*	*Time since injury*
		Mean (SD)	Mean (SD)	β (95%-CI)	β (95%-CI)	β (95%-CI)	β (95%-CI)	β (95%-CI)	β (95%-CI)
CIS[a]	Total Score (range 20-140)	66.2 (24.8)	49.3 (22.1)	16.87 (7.71, 26.03)*	8.15 (-2.13, 18.42)	7.01 (-2.21, 16.23)	1.99 (0.13, 3.84)*	1.01 (-0.46, 2.49)	3.41 (-7.03, 13.86)
	Fatigue (range 8-56)	27.3 (12.3)	19.5 (10.5)	7.77 (3.31, 12.22)*	2.66 (-2.10, 7.42)	6.34 (2.06, 10.62)*	1.26 (0.40, 2.12)*	0.53 (-0.16, 1.21)	-0.10 (-4.94, 4.75)
	Concentration (range 5-35)	19.1 (8.0)	13.9 (7.8)	5.21 (2.14, 8.29)*	3.98 (0.39, 7.56)*	-1.29 (-4.51, 1.93)	0.38 (-0.27, 1.03)	0.05 (-0.46, 0.57)	1.83 (-1.82, 5.47)
	Motivation (range 4-28)	11.7 (5.4)	10.0 (5.1)	1.64 (-0.41, 3.68)	0.28 (-2.07, 2.63)	0.46 (-1.65, 2.56)	0.12 (-0.31, 0.54)	0.32 (-0.02, 0.66)	1.50 (-0.89, 3.89)
	Physical Activity (range 3-21)	8.1 (4.60)	5.9 (3.9)	2.25 (0.59, 3.92)*	1.18 (-0.74, 3.11)	1.53 (-0.20, 3.26)	0.26 (-0.09, 0.60)	0.10 (-0.17, 0.38)	0.16 (-1.80, 2.12)
PSQI[b]	Total Score (range 0-21)	5.4 (3.1)	4.0 (2.6)	1.34 (0.22, 2.45)*	0.82 (-0.49, 2.14)	0.59 (-059, 1.77)	0.14 (-0.10, 0.37)	0.03 (-0.16, 0.22)	0.26 (-1.08, 1.59)
				OR (95%-CI)	**OR (95%-CI)**	**OR (95%-CI)**	**OR (95%-CI)**	**OR (95%-CI)**	**OR (95%-CI)**
Severely fatigued based on CIS subscale Fatigue, nr (%)		8 (16%)	3 (6%)	3.32 (0.83, 13.31)	-0.30 (0.12, 4.63)	3.82 (3.62, 576.04)*	0.58 (1.19, 2.71)*	0.10 (0.86, 1.43)	-0.27 (0.05, 10.96)
Poor sleep quality, based on PSQI Total Score, nr (%)		18 (37%)	12 (22%)	2.03 (0.86, 4.83)	0.23 (0.45, 3.49)	0.38 (0.57, 3.72)	0.17 (0.98, 1.43)	-0.01 (0.86, 1.14)	0.21 (0.27, 5.66)

Analyses performed with linear regression analysis assessing the relationship between type of injury (mTBI/OI; independent variable) and fatigue/sleep quality (dependent variable) while correcting for potential confounders sex, BMI, age, and time since injury; results reported as β and 95% confidence interval (CI). Logistic regression analysis for the dichotomous variables (severe fatigue or sleep disorder, yes/no), reported as odds ratio (OR) and 95% CI; adjusted for the same confounders.

[a] Checklist Individual Strength (CIS): higher scores represent higher levels of fatigue. A score ≥ 40 on the subscale Fatigue indicates severe fatigue.

[b] Pittsburgh Sleep Quality Index (PSQI): higher scores represent lower sleep quality. A score > 5 on the Total Score indicates poor sleep quality.

* p< 0.05, **p<0.001

Discussion

This study comparing PA, fatigue and sleep in AYAs at least 6 months after mTBI and OI, recruited from the ED of 2 hospitals, found significantly less AYAs with mTBI meeting Dutch recommendations for physical activity than AYAs with an orthopedic injury. The two cohorts differed significantly in fatigue symptoms related to concentration but not on total amount of time spent on physical activity, other dimensions of fatigue or sleep quality.

Regarding the amount of PA and the proportion of patients meeting HEPA guidelines observed in the mTBI group, comparisons with the literature are difficult to make because it is the first study to look at quantitatively measured PA. Most of the literature on PA after mTBI reports outcomes in terms of return to play,[48] resumption of sport activities,[49] activity patterns[50] or capacity in general[15] instead of the amount of PA or meeting PA recommendations. A previous study, from our own research group, included AYAs with TBI who had taken part in a rehabilitation program, found that 50% of the AYAs with mTBI met D-HEPA recommendations[5] which is comparable to the current study with 49% of AYAs with mTBI meeting the D-HEPA recommendations. In the multivariate analyses increasing age was related to less time spent on moderate to vigorous activities, supporting earlier studies in this population.[23, 51]

Concerning fatigue, in this study we found significant differences between the mTBI and OI group regarding fatigue related to concentration. Only two other studies on the long-term, 2 years post injury, compared fatigue in children with mTBI to an orthopedic control group[25, 52] with other studies only reporting fatigue on the short-term.[9] These studies report contradictory results; in one study parents of the mTBI group (children aged 4-14 years) reported more fatigue than the OI group of the same age group[25] compared to no difference between the groups of 4-15 year old children in terms of frequency and severity of fatigue.[52] Concentration problems are more often reported by children with a post-concussion syndrome,[4] supporting our results. Fatigue is an often reported symptom in the AYA population[43] which may be reflected in our data with few differences between the mTBI and OI groups. In the multivariate analyses female sex was related to general fatigue, supporting earlier studies where female adolescents report more fatigue.[43] Increasing BMI was also related to total fatigue and general fatigue in our study population, supporting an earlier study done with adults aged 20-59 years.[53]

With respect to sleep quality, the observed absence of a difference between the mTBI and OI groups in the current study is similar to those found by Necajauskaite et al.,[52] in their cohort of 102 children aged 4-15 years compared to children with OI, with no significant difference between groups for frequency and severity of sleep disorders

27 months post injury. The mTBI group in another study by Tham et al.[54] initially reported more sleep disturbances compared to the OI control group with sleep disturbances returning to pre-injury baseline level over time (12 and 24 months post injury) supporting the non-significant difference found in our cohort. The results differ with a previous study where sleep quality in children with mTBI 1-year post-injury was significantly lower than healthy controls.[12] Discrepancies between studies in sleep quality may be explained by the time since injury or patient age in the study cohorts.

In this study, PA, fatigue and sleep quality were considered separately. The interrelationship among PA, fatigue and sleep disorders is complex.[55-57] It would require a profound theoretical background and the use of a large number of hypotheses considering all potential relationships, including all possibilities of one or more of these three factors mediating the effect of the other(s). For this reason this study did not focus on this complex interaction, but merely described and compared the three variables separately. Further research however would definitely need to explore the relationships between physical activity, fatigue and sleep quality in AYAs with a mTBI and possible causality leading to opportunities to develop more specific treatment programs.

Limitations and directions for future research

There are several limitations in this study. We only collected post-injury data and have no data concerning PA levels, fatigue or sleep quality before the trauma. In TBI research collection of such pre-injury data is not possible unless registry data or similar data from other sources are available, or retrospective reporting is used, which is prone to bias. Moreover, we did not use a control group from the general population, hampering the interpretation of the observations regarding PA, fatigue and sleep quality done in the two study populations. The response rate is low but is similar to other studies concerning TBI in children and adolescents.[58] Approaching patients closer to the time of injury/ED visit could increase the response rate. The sample size of this study was relatively small, with some patients deciding not to participate because of a lack of symptoms. It is conceivable that those patients were relatively active and/or did not have high levels of fatigue, so that both the proportions of inactive patients as well as the difference between the mTBI and OI groups may be overestimated. Further, there were relatively more girls than boys, both in the mTBI and OI groups, hampering the generalizability of the results. In addition, there were some differences between the general and injury characteristics between the mTBI and the OI groups, the latter having a significantly lower age and BMI, whereas it is known from the literature that PA levels decrease with age.[23] Although we adjusted for age and BMI in the multivariable analysis, confounding cannot be

completely ruled out. Moreover, BMI data were obtained by means of self-report, where clinical measurement would have yielded more reliable results. There was also a significant difference regarding the mechanism of the injury, with sports injuries most common in the mTBI group and street/traffic related injuries in the OI group. The mechanism of injury can have secondary influences on functioning due to potential symptoms related to, e.g. a post-traumatic stress disorder, which were not taken into account in this study. Moreover, this study was performed in only one region of the Netherlands which limits the generalizability of the results to all Dutch AYA with TBI, or similar patients in other countries. Regarding the assessments, measuring PA and sleep only with subjective measures, i.e. questionnaires, may have given rise to report bias. For PA, the AQuAA was used, for which it was proven that its reliability is low and its validity in comparison with an accelerometer is poor [35] while on the other hand, it is the questionnaire used in the Netherlands by the Central Bureau for Statistics to gather health data from the general population. In the literature it is indeed concluded that both adolescents and adults underestimate the time spent on sedentary behavior and overestimate the time spent on PA.[35] Therefore, the use of accelerometers in addition to self-report questionnaires to quantify PA after TBI has been suggested and implemented in adult TBI studies.[59]

In addition, both for fatigue and sleep quality we used one particular instrument (i.e. the CIS and the PSQI), and it remains to be established to what extent with other measurement instruments, including objective measurements for sleep, different results would have been obtained.

Strengths of our study include the selection of patients from hospital registries and the use of a group patients with OI from the same hospitals in the same period. In addition, in our analyses we controlled for a substantial number of potential confounders, looking further than the injury itself.

Conclusions

Adolescents and young adults with mild TBI, at least 6 months post-injury, less often meet the Dutch health enhancing physical activity recommendations and report more concentration problems related to fatigue when compared to a control group with orthopedic injuries. Further research needs to explore the relationships between physical activity, fatigue and sleep quality in adolescents and young adults with a mTBI and possible causality leading to opportunities to develop more specific rehabilitation treatment programs.

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Declaration of interests

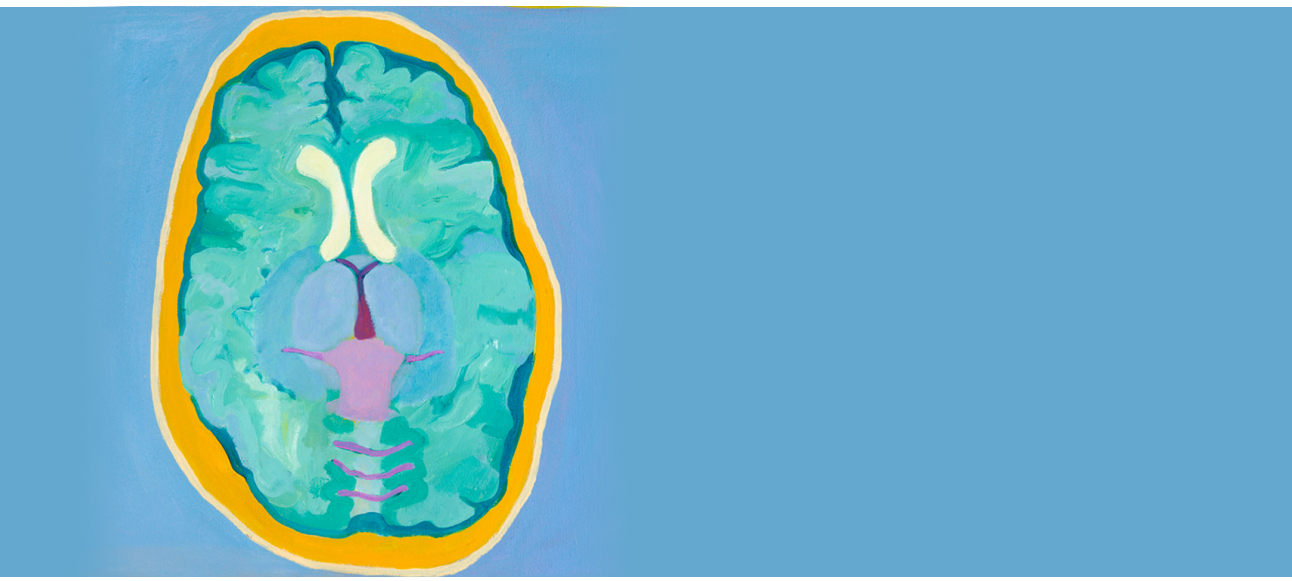
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References

1. McKinlay A, Grace R, Horwood L, et al. Prevalence of traumatic brain injury among children, adolescents and young adults: prospective evidence from a birth cohort. *Brain Inj*. 2008;Feb;22(2):175-81.
2. de Kloet A, Hilberink S, Roebroeck M, et al. Youth with acquired brain injury in the Netherlands: a multicenter study. *Brain Inj*. 2013;27:843–849.
3. Barlow K, Crawford S, Stevenson A, et al. Epidemiology of postconcussion syndrome in pediatric mild traumatic brain injury. *Pediatrics*. 2010;126;e374-e381.
4. Barlow K. Postconcussion Syndrome: A Review. *J Child Neurol*. 2014;Jan;31(1):57-67.
5. van Markus-Doornbosch F, Meesters J, Kraaij L, et al. Fatigue and its relationship with physical activity in adolescents and young adults with traumatic brain injury. *Eur J Phys Rehabil Med*. 2017;53(6)900-909.
6. Gagner C, Landry-Roy C, Lainé F, Beauchamp M. Sleep-Wake Disturbances and fatigue after pediatric traumatic brain injury: A systematic review of the literature. *J Neurotrauma*. 2015;Oct 15;32(20):1539-52.
7. Crichton A, Anderson V, Oakley E, et al. Fatigue following traumatic brain injury in children and adolescents: A longitudinal follow-up 6 to 12 months after injury. *J Head Trauma Rehabil*. 2018;33(3):200-209.
8. Norup A, Svendsen S, Doser K, et al. Prevalence and severity of fatigue in adolescents and young adults with acquired brain injury: A nationwide study. *Neuropsychol Rehabil*. 2019;29(7):1113-1128].
9. Wilkinson J, Marmol N, Godfrey C, et al. Fatigue following paediatric acquired brain injury and its impact on functional outcomes: A systematic review. *Neuropsychol Rev*. 2018;28(1):73-87.
10. Berger I, Obeid J, Timmons B, DeMatteo C. Exploring accelerometer versus self-report sleep assessment in youth with concussion. *Global Ped Health*. 2017;4:1-9.
11. Schmidt J, Rubino C, Boyd L, Virji-Babul N. The role of physical activity in recovery From concussion in youth: A neuroscience perspective. *J Neurol Phys Ther*. 2018;Jul;42(3):155-162.
12. Theadom A, Starkey N, Jones K, et al. Sleep difficulties and their impact on recovery following mild traumatic brain injury in children. *Brain Inj*. 2016;30:10, 1243-1248.
13. Botchway E, Godfrey C, Anderson V, Catroppa C. A Systematic Review of Sleep-Wake Disturbances in Childhood Traumatic Brain Injury: Relationship with Fatigue, Depression, and Quality of Life. 2019;34(4):241-256..
14. Jiménex-Pavón D, Kelly J, Reilly J. Associations between objectively measured habitual physical activity and adiposity in children and adolescents: Systematic review. *Int J Pediatr Obes*. 2010;5(1):3-18.
15. Baque E, Barber L, Sakzewski L, et al. Characteristics associated with physical activity capacity and performance in children and adolescents with an acquired brain injury. *Brain Inj*. 2017;31(5):667-673.
16. Gordon W, Sliwinski M, Echo J, et al. The benefits of exercise in individuals with traumatic brain injury: a retrospective study. *J Head Trauma Rehabil*. 1998;13(4):58-67.
17. Fleming J, Braithwaite H, Gustafsson L, et al. Participation in leisure activities during brain injury rehabilitation. *Brain Injury*. 2011;25(9): 806-18.
18. Driver S, Ede A, Dodd Z, et al. What barriers to physical activity do individuals with a recent brain injury face? *Disabil Health J*. 2012;5(2):117-25.
19. Iverson G, Gardner A, Terry D, et al. Predictors of clinical recovery from concussion: a systematic review. *Br J Sports Med*. 2017;51(12):941-948.
20. Chan C, Iverson G, Purtzki J, et al. Safety of active rehabilitation for persistent symptoms after pediatric sport-related concussion: A randomized controlled trial. *Arch Phys Med Rehabil*. 2018;99(2):242-249.
21. Leddy JJ J, Haider M, Ellis M, Willer B. Exercise is medicine for concussion. *Curr Sports Med Rep*. 2018;17(8):262-270.
22. Ruiz J, Castro-Piñero J, Artero EG E, et al. Predictive validity of health-related fitness in youth: a systematic review. *Br J Sports Med*. 2009;43(12):909-23.
23. Dumith S, Gigante D, Domingues M, Kohl

Hr. Physical activity change during adolescence: a systematic review and a pooled analysis. *Int J Epidemiol.* 2011;40(3):685-98.
24. Ponsford J, Willmott C, Rothwell A, et al. Cognitive and behavioral outcome following mild traumatic head injury in children. *Head Trauma Rehabil*. 1999;14(4):360-372.
25. Overweg-Plandsoen WCG KA, van Straaten M. et al. Mild closed head injury in children compared to traumatic fractured bone; neurobehavioural sequelae in daily life 2 years after the accident. *Eur J Pediatr*. 1999;158: 249-252.
26. Nacajauskaite O, Endziniene M, Jureniene K, Schrader H. The validity of post-concussion syndrome in children: a controlled historical cohort study. *Brain Dev*. 2006;28(8):507-14.
27. Maher C, Crettenden A, Evans K, et al. Fatigue is a major issue for children and adolescents with physical disabilities. *Dev Med Child Neurol*. 2015;57(8):742-7.
28. Saunders T, Gray C, Poitras V, et al. Combinations of physical activity, sedentary behaviour and sleep: relationships with health indicators in school-aged children and youth. *Appl Physiol Nutr Metab*. 2016;41: S283–S293.
29. Crichton A, Babl F, Oakley E, et al. Prediction of multidimensional fatigue after childhood brain injury. *J Head Trauma Rehabil*. 2017;Mar/Apr;32(2):107-116.
30. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet*. 1974;13:81–4.
31. Cole T, Flegal K, Nicholls D, Jackson A. Body mass index cut offs to define thinness in children and adolescents: International survey. *BMJ 2007*. 2007;335(7612):19.
32. van Buuren S. [Body mass index cut-off values for underweight in Dutch children]. *Ned Tijdschr Geneeskd* 2004;148(40):1967-72.
33. World Health Organization: World Database on Body Mass Index. http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi. [last accessed 18 August 2019].
34. Wendel-Vos G, Schuit A, Saris W, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. *J Clin Epidemiol*. 2003;56(12):1163-9.
35. Chinapaw M, Slootmaker S, Schuit A, et al. Reliability and validity of the Activity Questionnaire for Adults and Adolescents (AQuAA). *BMC Med Res Methodol*. 2009;9:58.
36. Ainsworth B, Haskell W, Leon A, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc*. 1993;25:71-80.
37. Kemper H, Ooijendijk W, Stiggelbout M. [Consensus over the Dutch health recommendation for healthy physical activity]. *Tijdschr Soc Gezonheidsz*. 2000;78:180-183.
38. Ooijendijk W, Hildebrandt V, Hopman-Rock M, *[Physical activity in The Netherlands 2000-2005]*, in *[Trend report Physical activity and health 2004/2005]*. 2007, TNO: Hoofdorp/Leiden.
39. Garber C, Blissmer B, Deschenes M, et al. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparantly healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. 2011 43(7):1334-59.
40. World Health Organization. Physical Activity. https://www.who.int/en/news-room/fact-sheets/detail/physical-activity. [last accessed 18 August 2019].
41. Vercoulen J, Swanink C, Fennis J, et al. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res*. 1994;383-92.
42. Stulemeijer M, van der Werf S, Bleijenberg J, et al. Recovery from mild traumatic brain injury: a focus on fatigue. *J Neurol*. 2006;253:1041-47.
43. ter Wolbeek M, van Doornen L, Kavelaars A, Heijnen C. Severe fatigue in adolescents: a common phenomenon? *Pediatrics*. 2006;117(6):e1078-86.
44. Buysse D, Reynolds Cr, Monk T, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193-213.
45. Ertan P, Yilmaz O, Caglavan M, et al. Relationship of sleep quality and quality of life in children with monosymptomatic enuresis. *Child Care Health Dev*. 2009;35(4):469-74.
46. Ponsford J, Parcell D, Sinclair K, et al. Changes in sleep patters following trau-

matic brain injury: a case controlled study. *Neurorehabil Neural Repair*. 2013;27(7):613-21.
47. IBMCorp. SPSS Statistics for Windows, Version 22.0. 2015, Armonk, NY.
48. Cancelliere C, Hincapié C, Keightley M, et al. Systematic review of prognosis and return to play after sport concussion: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil*. 2014;Mar;95(3 Suppl):S210-29.
49. Sawyer Q, Vesci B, Valovich McLeod, TC. Physical activity and intermittent post-concussion symptoms after a period of symptom-limited physical and cognitive rest. *J Athl Train*. 2016;51(9):739–742.
50. Law M, Anaby D, Dematteo C, Hanna S. Participation patterns of children with acquired brain injury. *Brain Inj*. 2011;25(6):587-95.
51. Farooq M, Parkinson K, Adamson A, et al. Timing of the decline in physical activity in childhood and adolescence: Gateshead Millennium Cohort Study. *Br J Sports Med* 2018;52(15):1002-1006.
52. Necajauskaite O, Endziniene M, Jureniene K. The prevalence, course and clinical features of post-concussion syndrome in children. *Medicina (Kaunas)*. 2005;41(6):457-64.
53. Resnick H, Carter E, Aloia M, and Phillips B. Cross-sectional relationship of reported fatigue to obesity, diet, and physical activity: results from the third national health and nutrition examination survey. J Clin Sleep Med 2006;2(2):163-9.
54. Tham S, Palermo T, Vavilala M, et al. The longitudinal course, risk factors, and impact of sleep disturbances in children with traumatic brain injury. *J Neurotrauma*. 2012;Jan 1;29(1):154-61.
55. Lequerica A, Botticello A, Lengenfelder J, et al. Factors associated with remission of post-traumatic brain injury fatigue in the years following traumatic brain injury (TBI): a TBI model systems module study. *Neuropsychol Rehabil*. 2017;27(7):1019-1030.
56. Ponsford J, Schönberger M, Rajaratnam S. A model of fatigue following traumatic brain injury. *J Head Trauma Rehabil*. 2015;30(4):277-282.
57. Schnieders J, Willemsen D, de Boer H. Factors contributing to chronic fatigue after traumatic brain injury. *J Head Trauma Rehabil*. 2012;27(6):404-12.
58. de Kloet A, Lambregts S, Berger M, et al. Family impact of acquired brain injury in children and youth. *J Dev Behav Pediatr*. 2015;36(5):342-51.
59. Hassett L, Moseley A, Harmer A, van der Ploeg H. The reliability, validity and feasibility of physical activity measureme15nt in adults with traumatic brin injury: an observational study. *J Head Trauma Rehab*. 2015;30(2):E55-61.



Chapter 5

Physical activity after mild traumatic brain injury: What are the relationships with fatigue and sleep quality?

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Abstract

Objectives
To determine self-reported physical activity (PA) levels and relationships with fatigue and sleep quality in adolescents and young adults after mild traumatic brain injury (mTBI).

Setting
Follow-up 6-18 months after visiting the emergency department of one of 2 general hospitals.

Participants
Forty-nine adolescents and young adults aged 12-25 years (mean 18.4 years), 22 (45%) male with mTBI.

Design
Cross-sectional survey study. Main outcome measures: The Activity Questionnaire for Adults and Adolescents (AQuAA), with results dichotomized into meeting or not meeting Dutch Health Enhancing PA recommendations (D-HEPA), the Checklist Individual Strength (CIS, 4 subscores) and the Pittsburgh Sleep Quality Index (PSQI, total score) were administered.

Results
Twenty-five participants (51%) did not meet the D-HEPA recommendations. After adjusting for sex, BMI and age, not meeting the recommendations was associated with a higher CIS Total Score (OR 1.04, 95%CI 1.01, 1.07) but not with PSQI Total Score (OR 0.99, 95% CI 0.80, 1.21).

Conclusions
In adolescents and young adults with mTBI the level of reported PA is associated with fatigue but not with sleep quality. It remains to be established whether interventions aiming to promote PA should primarily be focused on PA or fatigue or both.

Keywords
brain injuries, adolescent, fatigue, sleep, physical activity, pediatric

Introduction

Traumatic brain injury (TBI) is one of the leading causes of death and disability in adolescents and young adults (AYA), with an estimated yearly incidence of 2.25-2.96 per 100 for the age group 15-25 years in western countries.[1,2] The majority is classified as mild TBI (mTBI), with symptoms often resolving within 4 weeks. However, a significant minority reports persistent symptoms.[3,4] These longer-term consequences of mTBI in adolescents and young adults are often multiple and complex, affecting physical, emotional, cognitive and/or social functioning.[4]

Regarding the physical symptoms, lower PA levels are one of the reported consequences of mTBI in adults.[5-7] In children and adolescents studies on PA levels are often merely focussing on "return to play"[8], "sports participation"[9,10] or participation in activities[11] or concern advices on rest until symptoms resolve.[12-14] Some of these studies only include selected patients with mTBI related to sport concussions, whereas patients with traffic related injuries and injuries occurring at home or school should be considered as well, to give a complete perspective on activity levels after mTBI.

Regarding factors associated with physical activity, Baque et al. found in a mixed population of children with an acquired brain injury that older age and lower level of gross motor functioning partially explained physical performance, although no distinction was made for TBI severity.[15] In addition, in particular fatigue and sleep quality have been previously identified as relevant in pediatric populations.[16,17] In pediatric TBI populations fatigue was found at 6-12 months post-injury[18,19] and 24 months post-injury.[20] A recent study by Theadom and colleagues found in a pediatric cohort of mTBI patients sleep difficulties 12 months post-injury.[21]

Interrelationships between physical activity and respectively, fatigue or sleep have been examined in other pediatric conditions including multiple sclerosis[22] and pediatric oncology[23] and adult TBI studies[24-27] but are limited in the pediatric TBI population. One study by Tham et al. found sleep disorders to predict decreased activity participation 24 months post-injury.[28] Given the lack of knowledge on PA after mTBI in adolescents and young adults, the aim of the current study was to describe the level of physical activity after mTBI and as its relationship with fatigue symptoms and sleep quality 6-18 months post-injury. Better insight into these symptoms will allow clinicians to develop interventions suitable for the pediatric mTBI population and improve health outcomes.

Methods

Study design

This multicenter, cross-sectional study was executed at the Haaglanden Medical Center and Haga Teaching Hospital (location Leyweg and Juliana Children's Hospital), both large teaching hospitals in The Hague, The Netherlands.
The study was approved by the Medical Ethics Review Committee of the Leiden University Medical Center (P12.156) and all patients and their parents (when patient was under 18 years of age) provided written informed consent.

Participants

Patients were eligible for the study if they met all of the following criteria: a) aged 12-25 years at injury; b) registered with the diagnosis mild traumatic brain injury (Glasgow Coma Scale 13-15)[29]; c) visited the Emergency Department (ED) of one of the two hospitals between March 1, 2012 and March 1, 2013. Patients were not eligible if they: a) visited the ED for brain injuries more than once in the same year; b) underwent surgery related to the trauma; c) had other medical conditions with an impact on functioning (such as congenital disorders, rheumatic disease, chronic fatigue syndrome, epilepsy, psychiatric diagnosis); d) had an intellectual level with an IQ < 70 based on self-report in ED report or school level; e) were non-fluent in the Dutch language (based on ED report or self-report) or lived outside of The Netherlands.
Date of birth, sex, date of ED visit, and location of trauma were extracted from the medical files (all data extracted by the principle investigator, FvM-D). Medical history (reported in categories: congenital disorder, rheumatic disorder, neurologic disorder, chronic fatigue syndrome, psychiatric disorder), surgery (yes/no) or multiple ED visits for all potential participants were extracted out of the medical files. Location of trauma was categorized in home, school, work, street/traffic related, sport/field, or other.
When Glasgow Coma Scale (GCS) was not reported but the patient was fully conscious (i.e. walked into the Emergency Department, cycled to the hospital) with the diagnosis mild brain injury they were included in the mild TBI group.

Assessments

This study is part of a larger study with a one-time survey comprising five validated Patient Reported Outcome Measures (PROMs), completed by patients (if necessary with help from their parents) at home, either electronically (NetQ, www.netq.nl) or on paper. Those completing the paper version returned the questionnaire in a pre-stamped envelope. The questionnaires were coded to match the medical records and made anonymous. By providing 2 methods for completing the questionnaire the

impediment of not having a computer or having computer problems was avoided. All eligible patients and/or their parents were invited by postal mail 6-18 months post-injury and, if they agreed to participate, asked to return the signed informed consent and to state whether they preferred a paper or electronic questionnaire. Patients and/or their parents who did not respond were contacted once by postal mail 2 weeks after the first mailing, and once again by telephone after 3 months. Patients received an incentive (€10 voucher) for completing the questionnaire.

General and sociodemographic characteristics

Patients were asked to report height and weight; from which body mass index: BMI = weight (kg)/height squared (m^2) was calculated. For patients aged 12 to 17 underweight was defined as BMI under 17.0, overweight as BMI 25.1-30.0 and obesity as BMI above 30.0.[30,31] For patients 18 years and older cut-off points for underweight, overweight and obesity according to international criteria: <18.5, 25 and > 30 kg/m^2, respectively, were used.[32] Current age was determined using the date of questionnaire completion; for non-responders the mean date of completion was used (June 1, 2014).

Physical activity

Physical activity was measured using the Activity Questionnaire for Adults and Adolescents (AQuAA), a 5 category self-assessment of physical activity based on the SQUASH (Short QUestionnaire to ASsess Health enhancing physical activity). The AQuAA has been validated in the Netherlands for children and adults.[33] Patients were asked about frequency (number of days per week), duration (time spent) and intensity (low, average, or high) spent on activities in the past 7 days with examples of activities to facilitate questionnaire completion. Each activity has a MET (Metabolic Equivalent of Task) score related to the intensity of the activity, and is reported as milliliter oxygen use per kilogram bodyweight per minute. The METS compendium developed by Ainsworth[34] was used in this study. Activities were further categorized, using the METS for each activity, into low, moderate or vigorous activities,[35] with the total amount of PA being expressed as minutes spent on low, moderate and vigorous activities per week. In addition, the achievement of the Dutch Health Enhancing PA recommendations (D-HEPA) was calculated from the data. In The Netherlands, a healthy PA level has been established for children and adults.[35,36] Children (4-17 years of age) should be physically active 60 minutes with moderate to vigorous activities (minimum 5 METS), 7 days a week. Adults meet the criterion if they are physically active (minimum 4 METS) for 30 minutes, 5 days a week. This questionnaire proved to be fairly reliable and reasonably valid for the healthy Dutch population; test-retest reliability ICC (intraclass correlation) ranging from 0.30 to 0.59 for adolescents, and for adults an ICC ranging

from 0.49 to 0.60 for sedentary, light and moderate intensity activities and an ICC= -0.005 (poor) for vigorous activities. Similar guidelines have been developed by the American College of Sports Medicine,[37] and the World Health Organization.[38] To obtain a more clinically comparable situation the data was dichotomized into meeting or not-meeting the D-HEPA.

Fatigue

The Checklist Individual Strength (CIS), was used to measure fatigue. It is a 20-item self-report rating scale for assessing fatigue and associated behavior during the past two weeks. Four domains, (1) severity of fatigue (8 items, score range 8-56), (2) concentration problems (5 items, score range 5-35), (3) reduced motivation (4 items, score range 4-28), and (4) reduced physical activity (3 items, score range 3-21) are measured. Each item is scored on a seven point Likert scale. The Total Score is calculated by the sum of the 20 items (range 20-140). Higher scores indicate higher levels of fatigue, higher levels of concentration problems, decreased motivation, and lower levels of physical activity.[39] The CIS has been validated for use in the adolescent and adult Dutch population.[40]

Sleep quality

To evaluate sleep quality the Pittsburgh Sleep Quality Index (PSQI)[41] was administered. It is a self-rated questionnaire which evaluates sleep quality and disturbances over a 1 month interval. Seven items (subjective sleep quality, sleep latency (the time from lying down for sleep to the start of actual sleep), sleep duration, habitual sleep efficiency (the proportion of actual sleep time spent in bed), sleep disturbances, use of sleep medication and daytime dysfunction) are scored on 4 point Likert scales (0-3, low to high), with a total score ranging from 0 to 21 with higher scores representing poorer sleep quality. The PSQI has been used in pediatric[42] and adult TBI studies.[43]

Statistical analysis

Descriptive statistics were used for the sociodemographic and injury characteristics of all eligible patients and compared between participants and non-participants by means of independent sample t-tests or Chi square test, where appropriate.

Due to non-normal distribution of the data, medians and interquartile ranges (IQR, i.e. the 25th-75th percentile) were calculated for physical activity levels (AQuAA) in minutes per week, CIS total and subscores and PSQI total score. The associations between, respectively fatigue (CIS) and sleep quality (PSQI) scores of participants (independent variables) and meeting or not meeting the Dutch norm for healthy PA (yes/no; dependent variable) were calculated by unadjusted logistic regression analyses.

Subsequently, adjusted regression analyses were performed with the same dependent and independent variables while adjusting for sex, BMI and age. Results are reported as Odds ratios and 95% confidence intervals (95%CI).
For the comparison of characteristics the level of statistical significance was defined as $p < 0.05$.
All analyses were performed using SPSS 22.0 for Windows.[44]

Results

Of the 406 patients identified from the registry, 100 were excluded based on the information in the medical records; 7 had a GCS below 13, 12 had multiple visits to the ED in the same year, 18 underwent surgery for their injuries, 35 had a congenital, neurological or psychiatric condition, 7 had an IQ below 70, 11 did not speak the Dutch language or lived outside of The Netherlands and 10 envelopes were returned by the postal service. Of the 306 invited patients, 133 responded with 49 returning a complete questionnaire (37%) (Figure 1).
Baseline characteristics of the patients who did (n=49) and did not participate in the study (n=257), were significantly different regarding sex (p=0.04), with more female patients among participants (55%, 38%, respectively) and time since injury (1.6 years (SD 0.5), 1.8 years (SD 0.3), respectively, $p < 0.01$), with no significant differences in age at injury (mean 16.8 years (SD 3.6), 17.7 years (SD 3.6), respectively, p=0.10), or current age (18.4 years (SD 3.6), 19.5 years (SD 3.6), respectively, p=0.06). Forty-nine percent of participating patients had a sports injury, whereas 51% were injured at home, school, work or traffic related, compared to 56% sport related and 44% home, school, work or traffic related in the non-participant group (p=0.72).
Within the group of non-participants, sex, age at injury and current age of responders who chose not to participate (n=71) did not differ significantly from the non-responders (n=173).
Within the participant group, 24 were aged 12-17 years and 25 were 18 years or older. Participants had a mean BMI of 22.2 (SD 2.7) with 74% having a normal weight. Twenty-five out of the 49 participating patients did not meet the D-HEPA recommendations (51%); 13 of which were adolescents aged 12-17 years (54% of the adolescent group) and 12 were 18 years or older (48% of the young adult group). Nine (41%) were male and 4 (44%) had overweight with a BMI greater than 25. Age, sex and BMI were not significantly different between those meeting or not meeting the D-HEPA recommendations (Table 1).

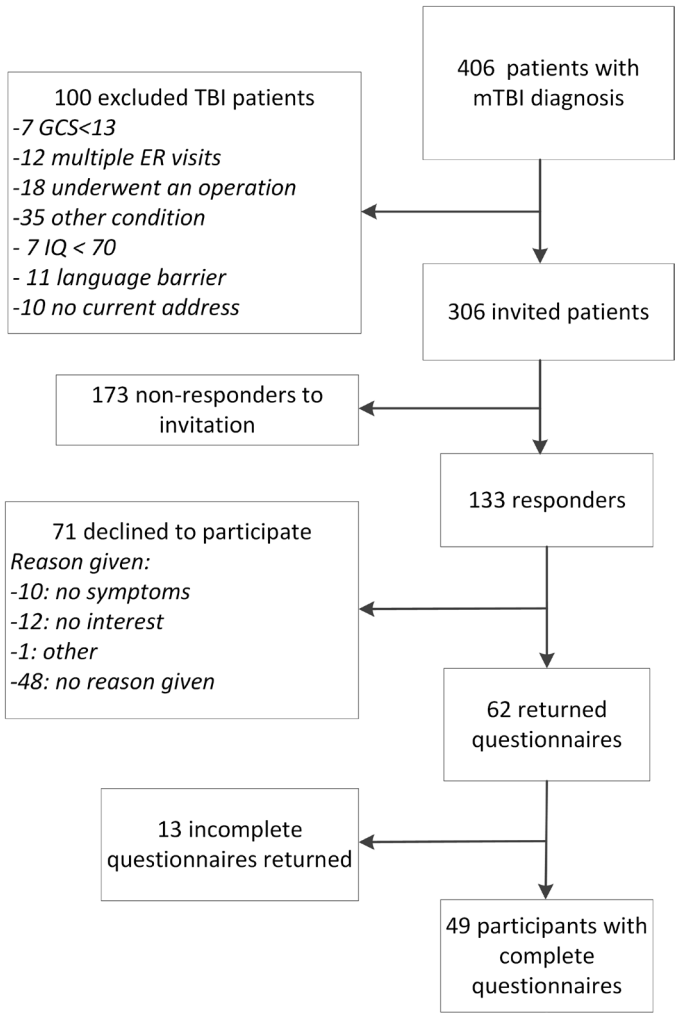


Figure 1. Flowchart of participants with mild traumatic brain injury.

Participants performed general physical activity (METS>2) on average 1350 min/week (IQR 755-2250 min/week). Moderate to vigorous activities were performed on average 793 min/ week (IQR 248-1133 min/week) and sedentary activities 2670 min/week (IQR 1750-4405 min/week). In the unadjusted analyses not meeting the D-HEPA was associated with time spent on general activities (OR 0.23, 95%CI 0.08, 0.62) but no association was found with time spent on sedentary activities (OR 0.40, 95%CI 0.15, 1.08).

Table 1. Characteristics of participants and non-participants in a cohort of adolescents and young adults (AYA) with mild traumatic brain injury (mTBI).

	Participants n=49	**Non-participants n=257**	**p value**
Sex, male; no. (%)	22 (45)	159 (62)	0.04
Age at injury, years; mean (SD)	16.8 (3.7)	17.7 (3.6)	0.10
Time since injury, years; mean (SD)	1.6 (0.5)	1.8 (0.3)	<0.01
Current age, years; mean (SD)	18.4 (3.6)	19.5 (3.6)	0.06
Under 18 years, no. (%)	24 (49)	93 (36)	
18 years and older, no. (%)	25 (51)	164 (64)	
Location of injury; no. (%)			
home	6 (12)	35 (14)	
school	1 (2)	5 (2)	
work	5 (10)	17 (7)	0.72
street/traffic related	11 (23)	39 (15)	
sport/field	24 (49)	146 (56)	
other	2 (4)	16 (6)	
BMI (kg /m²) [a]; mean (SD)	22.2 (2.7)		
Underweight, no. (%)	3 (6)		
Normal weight, no. (%)	36 (74)		
Overweight, no. (%)	9 (18)		
Obesity, no. (%)	0		
Missing	1 (2)		
Does not meet D-HEPA recommendations[b]			
No. (%)	25 (51)		
Under 18 year (n=24)	13 (54)		0.67
18 years and older (n=25)	12 (48)		
Male sex (n=22)	9 (41)		0.20
Female sex (n=27)	16 (59)		
BMI under 25 (n=39)	21 (54)		0.61
BMI boven 25 (n=9)	4 (44)		
Missing (n=1)			

***** Significance (p<0.05) between participants and non-participants were carried out by means of Independent samples t-tests for continuous variables and Chi square test for categorical variables.

[a] Body Mass Index (BMI; weight (kg) / height squared (m2)). Underweight is BMI under 18.5 above 18 years of age and under 17.0 for young adults under 18 years of age, normal weight 18.5-25.0, overweight 25.1-30.0, obesity above 30.0

[b] D-HEPA: children (≤ 17 years) meet the recommendation if they perform moderate to vigorous (minimum 5 METS) activities for a minimum of 60 minutes, 7 days a week. Adults (≥ 18years) meet the recommendation if they perform moderate to vigorous (minimum 4 METS) activities for a minimum of 30 minutes, 5 days a week.

Table 2. Physical activity, fatigue and sleep quality in adolescents and young adults with mild traumatic brain injury (mTBI), comparing those meeting the Dutch Health Enhancing Physical Activity recommendations (D-HEPA) to those not meeting the D-HEPA recommendations. Raw scores reported as medians and interquartile ranges (IQR). Unadjusted analyses reported as odds ratios (OR) and 95% confidence intervals (95%-CI).

		Total Group **n=49** **median (IQR)**	**Not meeting D-HEPA recommendations[b]** **n=25** **median (IQR)**	**Meeting D-HEPA recommendations** **n=24** **median (IQR)**	**Unadjusted OR,** **(95%-CI)**
AQuAA[a]	(minutes/week)				
	General activities >2 METS	1350 (755-2250)	920 (505-1580)	1918 (1221-3244)	0.23 (0.08, 0.62)*
	Moderate-vigorous activities > 5 METS	793 (24-133)	225 (113-438)	1065 (871-1348)	
	Sedentary activities < 2 METS	2670 (1750-4405)	2420 (1538-3438)	3413 (2010-4789)	0.40 (0.15, 1.08)
CIS[c]	Total Score (range 20-140)	64.0 (48.5-85.5)	78.0 (54.5-89.5)	57.5 (41.3-67.0)	1.03 (1.00, 1.06) *
	Fatigue (range 8-56)	26.0 (16.5-37.0)	32.0 (21.0-43.0)	22.5 (14.3-28.9)	1.07 (1.01, 1.13) *
	Concentration (range 5-35)	20.0 (13.0-24.0)	20.0 (14.0-28.0)	19.5 (12.3-22.5)	1.04 (0.97, 1.12)
	Motivation (range 4-28)	11.0 (7.5-15.0)	13.0 (9.0-16.0)	8.0 (6.3-14.8)	1.10 (0.98, 1.23)
	Physical Activity (range 3-21)	7.0 (4.0-11.5)	10.0 (5.0-12.5)	6.0 (4.0-8.8)	1.15 (1.00, 1.33) *
PSQI[d]	Total Score (range 0-21)	4.5 (4.0-6.0)	4.5 (4.0-6.0)	4.5 (4.0-7.8)	0.99 (0.82, 1.19)

[a] Activity Questionnaire for Adults and Adolescents (AQuAA): 5 category self-assessment containing questions in the domains of commuting activities, household activities, leisure time and sport activities, activities at school and/or work, and sedentary activities.
[b] D-HEPA: children (≤ 17 years) meet the recommendation if they perform moderate to vigorous (minimum 5 METS) activities for a minimum of 60 minutes, 7 days a week. Adults (≥ 18years) meet the recommendation if they perform moderate to vigorous (minimum 4 METS) activities for a minimum of 30 minutes, 5 days a week.
[c] Checklist Individual Strength (CIS): higher scores represent higher levels of fatigue.
[d] Pittsburgh Sleep Quality Index (PSQI): higher scores represent poorer sleep quality.
* $p < 0.05$

The median CIS Total Score was 64.0 (IQR 48.5-85.5); when dichotomized between those meeting the D-HEPA and those not meeting the D-HEPA, not meeting the D-HEPA was associated with a higher CIS Total Score (OR 1.03, 95%CI 1.00, 1.06). The median CIS subscore Fatigue was 26.0 (IQR 16.5-37.0) with not meeting the D-HEPA being associated with higher fatigue scores (OR 1.07, 95%CI 1.01, 1.13). The subscore Physical Activity

Table 3. Multivariate regression analysis assessing the relationship between fatigue and sleep quality (independent variables) and not meeting Dutch Health Enhancing Physical Activity recommendations (D-HEPA) (dependent variable) while correcting for sex, BMI, and age in a cohort of adolescents and young adults with mild traumatic brain injury (mTBI).

		Not meeting D-HEPA recommendations [a]
		Odds ratio, (95%-CI)
Checklist Individual Strength[b]	**Total Score (range 20-140)**	**1.04 (1.01, 1.07) ***
	Female sex	1.60 (0.41, 6.27)
	BMI	1.13 (0.86, 1.49)
	Age	0.84 (0.69, 1.03)
	Fatigue (range 8-56)	**1.09 (1.02, 1.67) ***
	Female sex	1.17 (0.27, 5.04)
	BMI	1.12 (0.84, 1.48)
	Age	0.82 (0.67, 1.02)
	Concentration (range 5-35)	**1.05 (0.97, 1.14)**
	Female sex	2.55 (0.70, 9.25)
	BMI	1.18 (0.91, 1.54)
	Age	0.89 (0.74, 1.08)
	Motivation (range 4-28)	**1.10 (0.97, 1.25)**
	Female sex	2.15 (0.58, 7.90)
	BMI	1.17 (0.90, 1.52)
	Age	0.88 (0.72 1.06)
	Physical Activity (range 3-21)	**1.17 (0.99, 1.38)**
	Female sex	1.64 (0.42, 6.31)
	BMI	1.14 (0.88, 1.48)
	Age	0.86 (0.70, 1.04)
Pittsburgh Sleep Quality Index[c]	**Total Score (range 0-21)**	**0.99 (0.80, 1.21)**
	Female sex	2.25 (0.60, 8.45)
	BMI	1.18 (0.92, 1.53)
	Age	0.89 (0.74, 1.08)

[a] D-HEPA: children (≤ 17 years) meet the recommendation if they perform moderate to vigorous (minimum 5 METS) activities for a minimum of 60 minutes, 7 days a week. Adults (≥ 18years) meet the recommendation if they perform moderate to vigorous (minimum 4 METS) activities for a minimum of 30 minutes, 5 days a week.
[b] Checklist Individual Strength (CIS): higher scores represent higher levels of fatigue.
[c] Pittsburgh Sleep Quality Index (PSQI): higher scores represent poorer sleep quality.
* $p < 0.05$

(median 7.0, IQR 4.0-11.5) was associated with not meeting the D-HEPA (OR 1.15, 95%CI 1.00, 1.33). The subscores Concentration and Motivation were not significantly associated with meeting or not meeting D-HEPA recommendations (OR 1.04, 95%CI 0.97, 1.12; OR 1.10, 95%CI 0.98, 1.23, respectively). The median PSQI Total Score was 4.5 (IQR 4.0-6.0) for the total group with no significant association with meeting or not meeting the D-HEPA recommendations (OR 0.99, 95%CI 0.82, 1.19) (Table 2).
After adjusting for potential confounders sex, BMI, and current age, the association between the CIS Total Score and subscore Fatigue on the one side and not meeting D-HEPA recommendations on the other side remained significant (OR 1.04, 95%CI 1.01, 1.07; OR 1.09, 95%CI 1.02, 1.17, respectively) (Table 3).

Discussion and conclusions

This study comparing PA, fatigue and sleep in AYA with mild TBI 6-18 months post-injury, found that 51% had activity levels lower than recommended by the D-HEPA. Not meeting public health recommendations for PA was associated with fatigue symptoms but not sleep quality.
Concerning the amount of PA and the percentage of patients meeting D-HEPA recommendations observed in the mTBI group, comparisons with the literature are difficult to make. Previous studies on pediatric TBI populations report outcomes in terms of return to play,[8] general activity patterns[11] or PA capacity[15] instead of amount of PA. A previous study, from our own research group, included AYA with TBI who had taken part in a rehabilitation program, found that 50% of the AYA with mTBI met D-HEPA recommendations[45] which is comparable to the current study with 49% of AYA with mTBI meeting the D-HEPA recommendations. Although no direct comparisons can be made, the results in the mTBI group observed in our study are similar to results found in the general Dutch population. National Dutch data, also acquired with the AQuAA during the same time period, reported the total amount of PA ranging from 966 to 1414 min/week, with 45% of adolescents and 69% of adults meeting the D-HEPA recommendations.[46]
Regarding fatigue, in the current study fatigue reported by the AYA with mTBI is similar to data collected earlier in The Netherlands in the general population where a mean CIS Total Score of 59 for school-aged female adolescents and 51 for school-aged males was reported.[40] The data in the current study support previous studies with pediatric populations showing higher fatigue scores with lower activity levels (children with mild to moderate physical disabilities,[16] pediatric multiple sclerosis[22]). Whereas in a study on cerebral palsy the relationship between fatigue and physical activity was not found.[47]

In adult TBI studies it is suggested that increasing demands on participation[24,48] and muscular deconditioning[49] contribute to post-injury fatigue symptoms. In the current study sleep quality was not associated with physical activity levels 6-18 months post-injury. PSQI Total Score was similar to the scores found by Theadom[21] at 12 months post-injury for the mTBI group. Studies on sleep problems after mTBI are contradictory, with several studies finding less sleep disturbances over time[50,51] while others studies[52] indicate sleep problems 3 years post-injury. The relationship between physical activity and sleep in adolescents and young adults is questionable. One pediatric study with healthy children found no relationship between sleep and PA[53] while in pediatric cancer patients a positive relationship between improved PA and better sleep quality was reported.[54]

Limitations and directions for future research

There are several limitations in this study. We collected only post-injury data and have no data concerning PA levels, fatigue or sleep before the trauma. In TBI research collection of pre-injury data is not possible unless registry data or similar data are available. Due to the cross-sectional design of this study no causal relationship can be established.

The response rate of 43% is moderate, but is similar to studies concerning TBI in children and adolescents.[55] Specifically, the results reflect a hospital based population and excludes those with a mild TBI that consulted only ambulance personnel, a general practitioner or sought no care at all. Many telephone numbers were disconnected or unavailable. A higher response rate can be expected when approaching patients shortly after their injury. On the other had we approached an unselected hospital population with a diversity of trauma's identifying important aspects, i.e. PA, fatigue and sleep quality, in this patient population.

Identification of patients with mild TBI was based on GCS. Due to incomplete registration in the medical files, further classification was not possible. Consequent classification and registration of individuals presenting to the ED is needed.

Regarding the assessments, measuring PA and sleep with only subjective measures, i.e. questionnaires, may have given rise to report bias. Use of accelerometers or other objective measures to quantify PA and sleep after TBI have been suggested and implemented in TBI studies[7,56,57] although exact measurements for physical activity and rest are limited. Further research should explore the use of objective measures in addition to subjective measures when studying physical activity[7] and sleep.[57]

Future research should explore other pre- and post-injury factors that can influence activities and participation in adolescents and young adults after mTBI such as deconditioning, increasing demands on participation, or psychosocial issues.

Conclusions

Six to 18 months post-injury, adolescents and young adults with mTBI report fatigue and reduced PA but not decreased sleep quality. Higher fatigue levels are associated with activity levels lower than recommended by the D-HEPA recommendations. The causal relationship between fatigue symptoms and physical activity is unknown and requires longitudinal research. Enhancing physical activity in the general youth population is an accepted principle and further specification for the adolescent and young adult population with mTBI is needed.

Conflicts of interest and source of funding
The authors declare no conflicts of interest or financial gains.

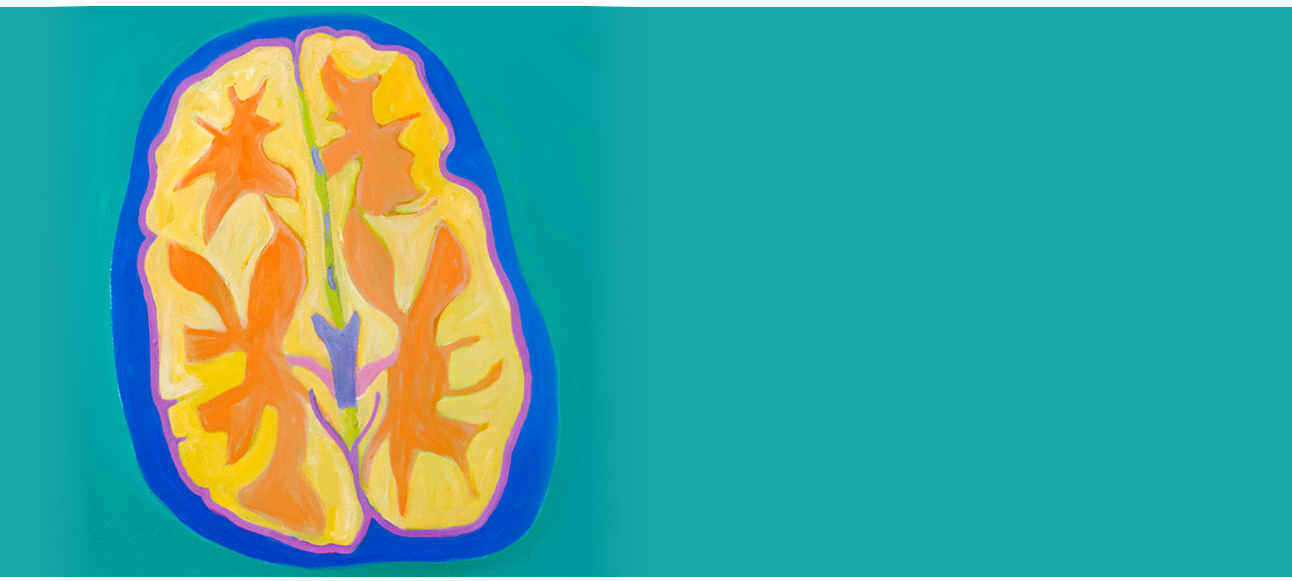
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References

1. McKinlay A, Grace R, Horwood L, Fergusson D, Ridder E, MacFarlane M. Prevalence of traumatic brain injury among children, adolescents and young adults: prospective evidence from a birth cohort. *Brain Inj* 2008:Feb;22(2):175-81.
2. Kloet A, Hilberink S, Roebroeck M, et al. Youth with acquired brain injury in The Netherlands: a multicenter study. *Brain Inj* 2013;27:843-9.
3. Barlow K, Crawford S, Stevenson A, Sandhu S, Belanger F, DeweyD. Epidemiology of postconcussion syndrome in pediatric mild traumatic brain injury. *Pediatrics* 2010;126:e374-81.
4. Barlow K. Postconcussion syndrome: a review. *J Child Neurol* 2014:Jan;31(1):57-67.
5. Fleming J, Braithwaite H, Gustafsson L, Griffin J, Collier M, Fletcher S. Participation in leisure activities during brain injury rehabilitation. *Brain Inj* 2011;25(9):806-18.
6. Driver S, Ede A, Dodd Z, Stevens L, Warren A. What barriers to physical activity do individuals with a recent brain injury face? *Disabil Health J* 2012;5(2):117-25.
7. Hassett L, Moseley A, Harmer A, van der Ploeg H. The reliability, validity and feasibility of physical activity measurement in adults with traumatic brain injury: an observational study. *J Head Trauma Rehabil* 2015;30(2):E55-61.
8. Cancelliere C, Hincapie C, Keightley M, et al. Systematic review of prognosis and return to play after sport concussion: results of the international collaboration on mild traumatic brain injury prognosis. *Arch Phys Med Rehabil* 2014:Mar;95(3 Suppl):S210-29.
9. Howell D, Osternig L, Chou L. Adolescents demonstrate greater gait balance control deficits after concussion than young adults. *Am J Sports Med* 2015;43(3):625-32.
10. Gagnon I, Swaine B, Friedman D, Forget R. Exploring children's self-efficacy related to physical activity performance after a mild traumatic brain injury. *J Head Trauma Rehabil 2005*;20(5):436-49.
11. Anaby D, Law M, Hanna S, Dematteo C. Predictors of change in participation rates following acquired brain injury: results of a longitudinal study. *Dev Med Child Neurol* 2012;54(4):339-46.
12. Sawyer Q, Vesci B, Valovich McLeod TC. Physical activity and intermittent post-concussion symptoms after a period of symptom-limited physical and cognitive rest. *J Athl Train* 2016;51(9):739-42.
13. McCrory P, Meeuwisse W, Dvorak J, et al. Consensus statement on concussion in sport -the 5th international conference on concussion in sport held in Berlin, October 2016. *Br J Sports Med* 2017;51(11):1-10.
14. Grool A, Aglipay M, Momoli F, et al. Association between early participation in physical activity following acute concussion and persistent postconcussive symptoms in children and adolescents. *JAMA* 2016;316(23):2504-14.
15. Baque E, Barber L, Sakzewski L, Ware R, Boyd R. Characteristics associated with physical activity capacity and performance in children and adolescents with an acquired brain injury. *Brain Inj* 2017;31(5):667-73.
16. Maher C, Crettenden A, Evans K, et al. Fatigue is a major issue for children and adolescents with physical disabilities. *Dev Med Child Neurol* 2015;57(8):742-7.
17. Saunders T, Gray C, Poitras V, et al. Combinations of physical activity, sedentary behaviour and sleep: relationships with health indicators in school-aged children and youth. *Appl Physiol Nutr Metabol* 2016;41:S283-93.
18. Crichton A, Anderson V, Oakley E, et al. Fatigue following traumatic brain injury in children and adolescents: a longitudinal follow-up 6 to 12 months after injury. *J Head Trauma Rehabil* 2018 May/Jun;33(3):200-9.
19. Crichton A, Babl F, Oakley E, et al. Prediction of multidimensional fatigue after childhood brain injury. *J Head Trauma Rehabil* 2017:Mar/Apr;32(2):107-16.
20. Starkey N, Jones K, Case R, Theadom A, Barker-Collo S, Feigin V. Post-concussive symptoms after a mild traumatic brain injury during childhood and adolescence. *Brain Inj* 2018;32(5):617-26.
21. Theadom A, Starkey N, Jones K, et al. Sleep

difficulties and their impact on recovery following mild traumatic brain injury in children. *Brain Inj* 2016;30(10):1243-8.
22. Yeh E, Kinnett-Hopkins D, Grover S, Motl R. Physical activity and pediatric multiple sclerosis: developing a research agenda. *Mult Scler* 2015;21(13):1618-25.
23. Braam K, van der Torre P, Takken P, Veening M, van Dulmen-den Broeder E, Kaspers G. Physical exercise training interventions for children and young adults during and after treatment for childhood cancer. *Cochrane Database Syst Rev* 2016;3, CD008796.
24. Ponsford JL, Ziino C, Parcell DL, et al. Fatigue and sleep disturbance following traumatic brain injury-their nature, causes, and potential treatments. *J Head Trauma Rehabil* 2012;27(3):224-33.
25. Ponsford J, Schonberger M, Rajaratnam S. A model of fatigue following traumatic brain injury. *J Head Trauma Rehabil* 2015;30(4):277-82.
26. Driver S, Ede A. Impact of physical activity on mood after TBI. *Brain Inj* 2009:203-12.
27. Jankowski L, Sullivan S. Aerobic and neuromuscular training: effect on the capacity, efficiency, and fatigability of patients with traumatic brain injuries. *Arch Phys Med Rehabil* 1990;71(7):500-4.
28. Tham S, Palermo T, Vavilala M, et al. The longitudinal course, risk factors, and impact of sleep disturbances in children with traumatic brain injury. *J Neurotrauma* 2012:Jan 1;29(1):154-61.
29. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet* 1974;13:81-4.
30. Cole T, Flegal K, Nicholls D, Jackson A. Body mass index cut offs to define thinness in children and adolescents: international survey. *BMJ* 2007;335(7612):19.
31. van Buuren S. Body mass index cut-off values for underweight in Dutch children. *Ned Tijdschr Geneeskd* 2004;148(40):1967-72.
32. World database on body mass index [internet]. World Health Organization; 2017. http://apps.who.int/bmi/index. jsp?introPage=intro_3.html. [cited April 13 2018].
33. Wendel-Vos G, Schuit A, Saris W, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. *J Clin Epidemiol* 2003;56(12):1163-9.
34. Ainsworth B, Haskell W, Leon A, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc* 1993;25:71-80.
35. Kemper H, Ooijendijk W, Stiggelbout M. Consensus over the Dutch health recommendation for healthy physical activity. *Tijdschr Soc Gezonheidsz* 2000;78:180-3.
36. Ooijendijk W, Hildebrandt V, Hopman-Rock M. Physical activity in The Netherlands 2000-2005. In: Trend report Physical activity and health 2004/2005. Hoofdorp/ Leiden: TNO; 2007.
37. Garber C, Blissmer B, Deschenes M, et al. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* 2011;43(7):1334-59.
38. Global recommendations on physical activity for health. Switzerland: WHO Press; 2010.
39. Vercoulen J, Swanink C, Fennis J, Galama J, van der Meer J, Bleijenberg G. Multidimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994:383-92.
40. ter Wolbeek M, van Doornen L, Kavelaars A, Heijnen C. Severe fatigue in adolescents: a common phenomenon? *Pediatrics* 2006;117(6):e1078-86.
41. Buysse D, Reynolds Cr, Monk T, Berman S, Kupfer D. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatr Res* 1989;28(2):193-213.
42. Theadom A, Starkey N, Barker-Collo S, et al. Population based cohort study of the impacts of mild traumatic brain injury in adults four years post-injury. *PLoS One* 2018;13(1):e0191655.
43. Ponsford J, Parcell D, Sinclair K, Roper M, Rajaratnam S. Changes in sleep patterns following traumatic brain injury: a case controlled study. *Neurorehabilitation Neural Repair* 2013;27(7):613-21.
44. SPSS statistics for Windows, version 22.0. 2015, IBM Corp: Armonk, NY.
45. van Markus-Doornbosch F, Meesters J, Kraaij L, Wolterbeek R, Vliet Vlieland T. Fatigue and its relationship with physical activity in adolescents and young adults with traumatic brain injury. *Eur J Phys Rehabil Med* 2017;53(6):900-9.

46. TNO monitor physical activity and health 2000-2013. Leiden: TNO; 2013.
47. Balemans A, van Wely L, Becher J, Dallmeijer A. Longitudal relationship among physical fitness, walking-related physical activity, and fatigue in children with cerebral palsy. *Phys Ther* 2015;95(7):996-1005.
48. Mollayeva T, Kendzerska T, Mollayeva S, Shapiro C, Colantonio A, Cassidy J. A systematic review of fatigue in patients with traumatic brain injury: the course, predictors and consequences. *Neurosci Biobehav Rev* 2014;47:684-716.
49. Chaudhuri A, Behan P. Fatigue in neurological disorders. *Lancet* 2004;363(9413): 978-88.
50. Hooper S, Alexander J, Moore D, et al. Caregiver reports of common symptoms in children following a traumatic brain injury. *NeuroRehabilitation* 2004;19:175-89.
51. Necajauskaite O, Endziniene M, Jureniene K. The prevalence, course and clinical features of post-concussion syndrome in children. *Medicina (Kaunas)* 2005;41(6):457-64.
52. Kaufman Y, Tzischinsky O, Epstein R, Etzioni A, Lavie P, Pillar G. Long-term sleep disturbances in adolescents after minor head injury. *Pediatr Neurol* 2001;24(2):129-34.
53. Soric M, Starc G, Borer K, et al. Associations of objectively assessed sleep and physical activity in 11-year old children. *Ann Hum Biol* 2015;42(1):31-7.
54. Orsey A, Wakefield D, Cloutier M. Physical activity (PA) and sleep among children and adolescents with cancer. *Pediatr Blood Cancer* 2013;60:1908-13.
55. de Kloet A, Lambregts S, Berger M, van Markus F, Wolterbeek R, Vliet Vlieland T. Family impact of acquired brain injury in children and youth. *J Dev Behav Pediatr* 2015;36(5):342-51.
56. Baque E, Barber L, Sakzewski L, Boyd R. Randomized controlled trial of web-based multimodal therapy for children with acquired brain injury to improve gross motor capacity and performance. *Clin Rehabil* 2017;31(6):722-32.
57. Berger I, Obeid J, Timmons B, DeMatteo C. Exploring accelerometer versus self-report sleep assessment in youth with concussion. *Global Pediatr Health* 2017;4:1-9.



Chapter 6

Fatigue, participation and quality of life in adolescents and young adults with acquired brain injury in an outpatient rehabilitation cohort

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Abstract

Purpose

To study the association between fatigue and participation and QoL after acquired brain injury (ABI) in adolescents and young adults (AYAs).

Materials and Methods

Cross-sectional study with AYAs aged 14-25 years, diagnosed with ABI. The PedsQL™Multidimensional Fatigue Scale, Child&Adolescent Scale of Participation, and PedsQL™4.0 Generic Core Scales were administered.

Results

Sixty-four AYAs participated in the study, 47 with traumatic brain injury (TBI). Median age at admission was 17.6 yrs, 0.8 yrs since injury. High levels of fatigue (median 44.4 (IQR 34.7-59.7)), limited participation (median 82.5 (IQR 68.8-92.3)), and diminished QoL (median 63.0 (IQR 47.8-78.3)) were reported. More fatigue was significantly associated with more participation restrictions (β 0.64, 95%CI 0.44, 0.85) and diminished QoL (β 0.87, 95%CI 0.72, 1.02).

Conclusions

AYAs with ABI reported high levels of fatigue, limited participation and diminished quality of life with a significant association between fatigue and both participation and QoL. Targeting fatigue in rehabilitation treatment could potentially improve participation and QoL.

Key words

fatigue, participation, quality of life, acquired brain injury, adolescents and young adults.

Introduction

Acquired brain injury (ABI) refers to any damage to the brain that occurs after birth, due to a traumatic (TBI) or non-traumatic (NTBI) cause.[1] Like in children and older patients, the sequelae of ABI in adolescents and young adults (AYAs) may have a considerable negative impact on functioning, participation and health-related quality of life (HRQoL) of AYAs during their development to adulthood.[1-7]

Fatigue is one of the most common physical symptoms occurring after pediatric ABI, irrespective of the severity of TBI[8, 9] or NTBI (brain tumors[10]; stroke[11]), and may persist long after injury[12]. Although fatigue is difficult to define due to complex interactions between biological, behavioural and psychosocial processes, it can be seen as a multidimensional symptom with physical, mental and emotional components.[13]

Fatigue was found to be associated with poorer psychosocial, physical, and (school) participation in childhood stroke[14] and brain tumors[10], as well as other childhood conditions (multiple sclerosis[15]; cerebral palsy[16]; leukemia[17, 18]; chronic pain[19]) as well as the adult stroke population[20, 21]. Furthermore, it was found to be related to diminished HRQoL, but this was studied only in adults with TBI.[22]

Participation is defined as involvement in life situations[23] and is vital for the development of physical, psychological and social emotional skills. These skills, specifically in the age group of AYAs, subsequently determine future healthy living and participation.[24] However, in studies on determinants of participation of youth (up to 18 years old) after ABI, fatigue was not taken into account. These studies did find that severity of ABI, motor, cognitive, behaviour and sensory functioning were determinants of participation restrictions.[25-27] The possible mutual relationship between fatigue and participation remains unknown in AYAs with ABI.

Health-related quality of life (HRQoL) could also possibly be affected by fatigue. HRQoL is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning.[28] Pediatric and adult patients with TBI may experience decreased HRQoL during and after the first year of TBI[3, 29, 30], with mental HRQoL more affected than physical HRQoL.[31] Reduced HRQoL has also been found in children with a stroke[6] and brain tumors.[32] The relationship between fatigue and HRQoL however, has not been studied yet in AYAs in the ABI population.

Knowledge on fatigue in AYAs with ABI is scarce and it is not known whether targeting fatigue in rehabilitation treatment may improve outcomes on participation and HRQoL. To be able to determine this the first step is to investigate the relation between fatigue, participation and HRQoL. The aim of the present study was therefore to explore multidimensional fatigue symptoms, participation and HRQoL in AYAs with ABI, and to study the association of fatigue and both participation and HRQoL.

Methods

Study design

This study is part of a larger multi-center longitudinal prospective cohort study on ABI in children and young adolescents (4 to 25 years old) referred for rehabilitation treatment to one of eight participating rehabilitation centers in The Netherlands. This longitudinal study was started, integrated in regular care, in June 2014 and is still ongoing. Data were collected at time of admission (T0), as part of the routine assesssment, and patients and their parents were asked to complete the same questionnaires 1 year (T1) and 2 years (T2) thereafter. For the present study only admission data collected at one center, Basalt Rehabilitation in The Hague, were used. This study was approved by the Medical Ethics Committee of the Leiden University Medical Center (P15.165). The Committee approved the study and provided an exempt from full medical ethical review since data were collected as part of regular care (assessing possible problems and restrictions for discussion during rehabilitation intake). All local research committees of the participating centers approved the study.

Patients

Patients were included in the current study if they were referred to the AYA (14-25 years) outpatient clinic (Basalt Rehabilitation in The Hague) with a diagnosis of ABI. All eligible patients and their parents were asked to fill in a set of questionnaires prior to their first appointment at the outpatient clinic. Patients were included in this study if either the patient or the parent or both completed the questionnaires.

General and sociodemographic characteristics

Patient and injury characteristics were obtained from the patients' medical record by the primary investigator (FvM-D) and included date of birth, sex, date of injury and description of ABI (categorized in NTBI (stroke, asfyxia, brain tumor, meningitis or encephalitis, hypoxia-ischemia) or TBI). The severity of TBI was determined by means of the Glasgow Coma Scale (GCS) at hospital admission (mild when GCS 13–15, moderate when 9–12 and severe when ≤8).[33] Age at admission was calculated using the date of the first appointment at the outpatient clinic.

Assessments

Assessments included a survey comprising three validated Patient Reported Outcome Measures (PROMs), which had to be completed by patients and parents (electronically www.QuestBack.nl, or on paper). The questionnaires were administered as part of the regular care. Patients were sent an email link to the patient version of the questionnaires

and were also requested to forward a link to their parents/caregivers to fill out the parent version of the questionnaires. Those not responding to the electronic questionnaire were given the opportunity to complete the questionnaire on paper prior to the first appointment at the outpatient clinic. If a patient came without parents to the clinic, parents were asked to complete the questionnaires on paper or electronically within 1 week after the first appointment. For patients 16 years and older this was only done after permission of the patient.

Fatigue

The PedsQL™ Multidimensional Fatigue Scale (MFS)[34], Dutch language version[35, 36], was used to measure fatigue. This 18-item questionnaire yields a Total Scale Score, and 3 subscale scores: general fatigue (6 items), sleep/rest fatigue (6 items), and cognitive fatigue (6 items). The items are reversely scored using a 5-point Likert scale. Subsequently scores are linearly transformed to a 0–100 scale (0 (never) = 100, 1 = 75, 2 = 50, 3 = 25, 4 (always) = 0), with lower scores indicating more fatigue. Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). If more than 50% of the items in a subscale were missing, the subscale score is not computed. Normative data have been collected in several cohorts of adolescents[35] and young adults[34,36] making a comparison between healthy and chronically ill individuals possible. The average scores of healthy AYAs in the Netherlands is 71.8-77.4 (SD 10.1-14.6).[35, 36] Panepinto[37] defined severe fatigue as a score more than 2SD from the norm on the MFS Total Score.

Participation

The Child and Adolescent Scale of Participation (CASP), part of the Child & Family Follow-up Survey (CFFS), was administered to measure participation restrictions. The CFFS is a parent reported questionnaire developed and validated for children and youth with ABI[38] and has been been validated in the Dutch language[39]. A child and youth self-reported version of the CASP is available[40] and was used next to the parent-reported version in the present study.

The CASP consists of 20 items in 4 subdomains measuring the child's home participation (6 items), community participation (4 items), school participation (5 items) and home & community living activities (5 items). Activities are rated on a four-point ordinal scale: age expected (full participation), somewhat limited, very limited and unable. Items marked as not applicable do not receive a score. Scores for each item are summed and divided by the maximum possible score based on the number of items rated, multiplied by 100 to give a final score between 0-100. Higher scores are considered to be participating closer to age-expected levels. A score below 97.5 is defined as restricted participation (unpublished correspondence with author GM Bedell).

Health-related Quality of Life (HRQoL)

For HRQoL, the Pediatric Quality of Life Inventory™ Generic Core Scales (PedsQL) Dutch language version[41], assessing 5 dimensions of QoL (physical functioning (8 items), emotional functioning (5), social functioning (5), school functioning (5), and total HRQoL) was used.[42] In this study the parent- and child reported versions for children 13-18 years old was applied. The scoring system is similar to that of the MFS. Varni[43] defined impaired quality of life as more than 1 SD below the population mean. Normative scores for 13-18 year olds in The Netherlands is a mean of 83.1 (SD 9.0) [44] and for 18-25 year olds 85.9 (SD 11.5) [41] for the PedsQL Total Score. The PedsQL has been validated for the pediatric TBI population[45] as well as the young adult population.[41]

Data analysis

Sociodemographic and injury characteristics as well as all clinical outcome variables were described and reported as medians with interquartile ranges based on the distribution of the data (Kolmogorov-Smirnov test). Comparisons between patients' and parents' scores of the MFS, CASP, and PedsQL were done using the paired samples Wilcoxon signed rank tests and by calculating the Intraclass Correlation coefficient ($ICC_{2,1}$, absolute agreement, single measures). Linear regression was performed with participation (CASP total and subscales) and quality of life (PedsQL total and subscales) as dependent variables and fatigue (MFS) as the independent variable, adjusted for sex, age at admission (<18 or >18), and type of injury (TBI/NTBI). The level of statistical significance was defined as $p<0.05$ and ICC scores rated according to Bartko[46]: below 0.40: poor; between 0.41 and 0.60: moderate; between 0.61 and 0.80 good; above 0.81: excellent. All analyses were performed using SPSS 22 for Windows.[47]

Results

Sixty-four patients and/or their parents participated in this study. Median age of the AYA at admission was 17.6 years (IQR 16.2-20.0), with 38 (59%) under 18 years. Thirty-two (50%) were male and 47 (73%) patients had a TBI. All other clinical characteristics are presented in Table 1.

In Table 2, outcomes regarding fatigue, participation and HRQoL as perceived by patients and parents are presented. Patients and parents reported considerable fatigue (MFS median total score 44.4, respectively, 56.9) and diminished HRQol scores (PedsQL median total score 59.8, respectively, 69.6). Participation restrictions were reported as well (CASP median total score 79.7, respectively, 91.1). When comparing patient- to

Table 1. Patient characteristics of AYAs with ABI referred for outpatient rehabilitation treatment.

	Patients n=64	TBI n=47	NTBI n=17
Sex, male, n (%)	32 (50)	21 (45)	11 (65)
Age at injury, years; median (IQR)	16.3 (14.6-18.3)	17.2 (15.6-18.7)	15.0 (9.3-17.0)
Time since injury, years; median (IQR)	0.8 (0.2-2.3)	0.6 (0.2-1.4)	2.4 (0.3-7.0)
Age at admission, years; median (IQR)	17.6 (16.2-20.0)	17.7 (16.0-20.8)	17.4 (16.1-18.4)
under 18 years, n (%)	38 (59)	26 (55)	12 (70)
18 years and older, n (%)	26 (41)	21 (45)	5 (30)
Severity of injury, n (%)			
mild		37 (79)	
moderate/severe		8 (17)	
unknown		2 (4)	

TBI=traumatic brain injury, NTBI=non-traumatic brain injury
IQR= Inter Quartile Range
Severity of injury based on Glasgow Coma Scale, 13-15 is mild, 9-12 is moderate, 8 and under is severe injury.

parent-reported outcomes, only a few significant differences were found; with parents reporting signficantly more general fatigue than patients and patients reporting significantly more restrictions than their parents in participation at home, in the community and at school. Correlations between patient- and parent-reported outcomes were moderate to good (ICC 0.52-0.66, 49-50 pairs) for fatigue (MFS), moderate to poor (ICC 0.30-0.55, 38-49 pairs) for participation (CASP), and moderate to good (ICC 0.60-0.78, 49-50 pairs) for HRQoL (PedsQL).

In Table 3 the association between patient-reported fatigue and participation and HRQoL is shown. The linear regression analyses, adjusted for sex, age and type of injury, clearly showed that more fatigue is associated with more participation restrictions in all subdomains of the CASP and diminished HRQoL in all subscales of functioning in the PedsQL (all $p<0.001$).

In the parent-reported data (Table 4), similar relationships were found between fatigue and participation restrictions and HRQoL (almost all $p<0.05$). However, no significant associations between sleep/rest fatigue and home participation and home and community activities were found. Furthermore, parent-reported fatigue was not significantly associated with social functioning according to the PedsQL.

Table 2. Patient- and parent-reported fatigue, participation and quality of life outcomes in a cohort of AYAs with ABI referred to an outpatient rehabilitation clinic.

		median (IQR)			
		Patients, n=59	**Parents, n=54**	**number of pairs**	**$ICC_{2,1}$**
PedsQL™ MFS	Total Score	44.4 (34.7-59.7)	47.9 (36.1-63.9)	50	0.64
	General fatigue	45.8 (29.2-66.7)	44.4 (25.0-62.5)*	50	0.66
	Score sleep/rest fatigue	50.0 (41.7-62.5)	54.2 (39.6-68.8)	49	0.52
	Cognitive fatigue	41.7 (25.0-58.3)	43.8 (25.0-70.8)	50	0.64
CASP	Total Score	82.5 (68.8-92.3)	91.1 (80.0-96.9)*	49	0.54
	Home participation	87.5 (75.0-100.0)	93.8 (86.9-100.0)*	49	0.44
	Community participation	75.0 (50.0-100.0)	89.6 (75.0-100.0)**	49	0.55
	School participation	85.0 (65.0-95.0)	90.0 (80.0-100.0)*	38	0.40
	Home & community living activities	85.0 (69.7-94.1)	88.8 (78.8-100.0)*	48	0.30
PedsQL™ Generic Core Scales	Total Score	63.0 (47.8-78.3)	63.6 (46.7-75.3)	50	0.78
	Physical functioning	62.5 (50.0-90.6)	64.1 (43.8-82.0)	50	0.75
	Emotional functioning	60.0 (45.0-85.0	60.0 (40.0-81.3)	50	0.68
	Social functioning	80.0 (60.0-95.0)	75.0 (60.0-100.0)	50	0.60
	School functioning	45.0 (30.0-65.0)	45.0 (27.5-67.5)	49	0.72

* p<0.05, **p<0.001; Wilcoxon signed-rank test for nonparametric data outcomes, for differences between patient- and parent reported outcomes.
50 patient-parent pairs (37 traumatic brain injury and 13 non-traumatic brain injury) were used for this analysis.
PedsQL™ Multidimensional Fatigue Scale (MFS), 0-100, with lower scores indicating more fatigue.
Child and Adolescent Scale of Participation (CASP), 0-100 with lower scores indicating more participation restrictions.
PedsQL™ Generic Core Scales (0-100), with lower scores indicating diminished health-related quality of life.
$ICC_{2,1}$; Intraclass Correlation Coefficients, absolute agreement, single measures.

Table 3. Patient-reported outcomes: the association between fatigue and participation and quality of life in AYAs with ABI, adjusted for sex, age at admission and type of injury.

		CASP				
		Total Score	**Home participation**	**Community participation**	**School participation**	**Home & Community activities**
		β (95%CI)				
PedsQL™ MFS	Total Score	0.64 (0.44, 0.85)**	0.52 (0.33, 0.72)**	0.73 (0.43, 1.04)**	0.65 (0.34, 0.96)**	0.68 (0.43, 0.92)**
	General fatigue	0.51 (0.35, 0.68)**	0.45 (0.30, 0.60)**	0.63 (0.39, 0.87)**	0.58 (0.33, 0.83)**	0.49 (0.29, 0.70)**
	Sleep/rest fatigue	0.46 (0.21, 0.71)**	0.37 (0.14, 0.60)**	0.44 (0.08, 0.80)*	0.53 (0.20, 0.86)*	0.51 (0.23, 0.80)**
	Cognitive fatigue	0.36 (0.19, 0.53)**	0.27 (0.11, 0.43)**	0.42 (0.18, 0.66)**	0.31 (0.05, 0.56)*	0.41 (0.22, 0.61)**

		PedsQL™ Generic Core Scales				
		Total Score	**Physical functioning**	**Emotional functioning**	**Social functioning**	**School functioning**
		β (95%CI)				
PedsQL™ MFS	Total Score	0.87 (0.72, 1.02)**	0.90 (0.65, 1.14)**	0.90 (0.61, 1.18)**	0.63 (0.39, 0.87)**	1.05 (0.82, 1.29)**
	General fatigue	0.69 (0.56, 0.81)**	0.76 (0.58, 0.94)**	0.72 (0.50, 0.95)**	0.48 (0.29, 0.67)**	0.75 (0.53, 0.96)**
	Sleep/rest fatigue	0.65 (0.42, 0.88)**	0.76 (0.47, 1.05)**	0.52 (0.16, 0.88)*	0.46 (0.19, 0.74)**	0.80 (0.48, 1.11)**
	Cognitive fatigue	0.49 (0.33, 0.64)**	0.41 (0.19, 0.64)**	0.56 (0.33, 0.79)**	0.37 (0.18, 0.55)**	0.65 (0.45, 0.86)**

Linear regression analyses with data represented as β-estimates (95% confidence interval, 95%CI) with CASP and PedsQL™ Generic Core Scales (dependent variables) and MFS (independent variables) adjusted for sex, age at admission (18 or >18) and type of injury (TBI/NTBI).
* p<0.05; ** p<0.001
PedsQL™ Multidimensional Fatigue Scale (MFS), 0-100, with lower scores indicating more fatigue
Child and Adolescent Scale of Participation (CASP), 0-100 with lower scores indicating more participation restrictions
PedsQL™ Generic Core Scales, 0-100, with lower scores indicating diminished health-related quality of life.

Table 4. Parent-reported outcomes: the association between fatigue and participation and quality of life in AYAs with ABI, adjusted for sex, age at admission and type of injury.

		CASP				
		Total Score	**Home participation**	**Community participation**	**School participation**	**Home & Community activities**
		β (95%CI)				
PedsQL™ MFS	Total Score	0.32 (0.14, 0.50)**	0.22 (0.06, 0.38)*	0.39 (0.15, 0.64)*	0.51 (0.24, 0.79)*	0.28 (0.06, 0.50)*
	General fatigue	0.25 (0.10, 0.41)*	0.15 (0.02, 0.29)*	0.37 (0.17, 0.57)**	0.37 (0.13, 0.60)*	0.20 (0.01, 0.39)*
	Sleep/rest fatigue	0.19 (0.03, 0.34)*	0.09 (-0.04, 0.23)	0.30 (0.11, 0.49)*	0.32 (0.07, 0.57)*	0.14 (-0.04, 0.33)
	Cognitive fatigue	0.17 (0.03, 0.31)*	0.16 (0.04, 0.28)*	0.12 (-0.04, 0.31)	0.29 (0.07, 0.50)*	0.17 (0.01, 0.34)*
		PedsQL™ Generic Core Scales				
		Total Score	**Physical functioning**	**Emotional functioning**	**Social functioning**	**School functioning**
		β (95%CI)				
PedsQL™ MFS	Total Score	0.62 (0.43, 0.82)**	0.66 (0.39, 0.94)**	0.77 (0.49, 1.05)**	0.25 (-0.07, 0.57)	0.79 (0.46, 1.12)**
	General fatigue	0.46 (0.28, 0.63)**	0.50 (0.26, 0.74)**	0.50 (0.24, 0.76)**	0.18 (-0.09, 0.44)	0.62 (0.34, 0.90)**
	Sleep/rest fatigue	0.38 (0.20, 0.56)**	0.53 (0.31, 0.75)**	0.45 (0.19, 0.71)**	-0.01 (-0.28, 0.25)	0.48 (0.19, 0.77)*
	Cognitive fatigue	0.32 (0.15, 0.49)**	0.23 (-0.001, 0.46)	0.46 (0.24, 0.68)**	0.27 (0.05, 0.50)*	0.38 (0.11, 0.64)*

Linear regression analyses with data represented as β-estimates (95% confidence interval, 95%CI); CASP Total Score and subdomains (dependent variables) and MFS (independent variables) adjusted for sex, age at admission (<18 or >18) and type of injury (TBI/NTBI). * p<0.05; ** p<0.001
PedsQL™ Multidimensional Fatigue Scale (MFS), 0-100, with lower scores indicating more fatigue.
Child and Adolescent Scale of Participation (CASP), 0-100 with lower scores indicating more participation restrictions.
PedsQL™ Generic Core Scales, 0-100, with lower scores indicating diminished health-related quality of life.

Discussion

This study in a cohort of AYAs with ABI referred for outpatient rehabilitation treatment found that AYAs and their parents reported high levels of fatigue, limited participation in school and society, and diminished quality of life. Higher levels of fatigue were found to be associated with both participation restrictions and diminished HRQoL. Fatigue may be a modifiable symptom to be targeted in rehabilitation treatment to possibly decrease participation restrictions and improve HRQoL.

Patient characteristics

The distribution of severity of TBI in our cohort is similar to published incidence data.[48] Based on the literature, it is expected that 90% of mild injuries resolve within 4-6 weeks[49, 50] with no need for rehabilitation treatment. The high percentage of mild injuries in our cohort reflect the subgroup of patients in the generally 'mild injury' group with persisting symptoms. The question remains whether an initial mild classification can always be properly made early after injury and if the classification is suitable for outcomes.

Fatigue

AYAs and their parents in this study report high levels of fatigue, comparable to previous studies.[9, 13] The median fatigue score of the AYAs in our cohort (44.4) is considerably lower than the average scores of healthy AYAs in the Netherlands (71.8-77.4).[35, 36] With a definition of severe fatigue as a score more than 2SD from the norm on the MFS Total Score,[37] using the normative data collected by Haverman,[36] our patients, on average, can be considered severely fatigued.

In the subscales sleep/rest and cognitive fatigue patients reported more fatigue than their parents, similar to other studies using the PedsQL™ MFS,[35, 51] however these differences in our study were not statistically significant. Parents did report significantly more general fatigue than their children but the actual median difference was rather small (1.4 points on a 0-100 scale) and it is to be determined whether this difference is clinically meaningful. Moreover, there was moderate to good agreement between patient- and parent- reported data, also in the general fatigue scale (ICC 0.66, 50 pairs). Therefore, the question remains whether it is necessary to measure both patient- and parent-reported fatigue as was suggested in other studies.[15, 51, 52]

Participation

Patients and their parents in this study reported participation restrictions in all domains of participation (median total score 82.5 (IQR 68.8-92.3), 91.1 (IQR 80.0-96.9),

respectively), supporting earlier studies in this patient population (pediatric ABI[27, 53]; adult mTBI[54]; stroke[55]). In the current study, AYAs reported significantly more participation restrictions than their parents, in home, community and school activities. Previous research on patient- and parent-reported participation with the CASP have found patients reporting less participation restrictions than their parents.[40] The question remains whether the differences found (patient median 82.5 versus parent median 91.1) are actually clinically meaningful, since the minimal clinical important differences are unavailable for this instrument. Agreement between patient- and parent-reported data is poor to moderate, supporting studies that use both patient- and parent-reported data. By using both perspectives a broad view on overall functioning is attained[40] and give professionals the opportunity to address both patient and parent rehabilitation goals. Therefore, both patients' and parents' perspectives on participation should be measured in ABI studies.

Health-related quality of life (HRQoL)

HRQoL is impaired in children, adolescents and adults with ABI[30, 31, 56] which concurs with the findings in our study. In our study a median patient Total Score of 63.0 was found; using Varni's definition of impaired QoL as a value greater than 1 SD from the population norm,[43] compared to the Dutch population norm of 83.1-85.9,[41, 44] our patients have an impaired quality of life. In the current study there was no difference between patient- and parent-reported HRQoL with a good agreement between patient and parent data. In previous literature a difference was found where parents tended to underestimate their child's HRQoL.[57]

Although the patient perspective is considered more important in evaluating quality of life, the parent perspective reflects the utilization of health care services, including rehabilitation treatment[42] and possibly a reflection of their own HRQoL[58] and should therefore also be taken into account.

Relationship between fatigue, participation and HRQoL

Regarding the relationship between fatigue and participation and HRQoL, this is the first study which shows relationship between these important aspects in life in AYAs with ABI. In other pediatric (chronic fatigue syndrome[59]; stroke[14]; juvenile idiopathic arthritis[60]) and adult (stroke[21]; TBI[61]) cohorts a relationship between fatigue and participation was found as well. The relationship between fatigue and quality of life has also been shown in other patient populations (pediatric brain tumors[10]; chronic disorders[62]; adult stroke[20]) and these findings support the results found in this study. We found that more patient-reported fatigue was associated with diminished HRQoL on all subscales, while the association between parent-reported fatigue was significant

for specific subscales. These results underline the need to explore fatigue as a multidimensional symptom influencing quality of life in specific domains and should be addressed in rehabilitation treatment.

Limitations and directions for future research

The current study had a number of limitations. The small size of the cohort as well as collecting data was from only one rehabilitation center limits the generalizability of the results. The cohort included only patients with symptoms, and/or restrictions in activities and participation and therefore outcomes may not be generalizable for all patients with ABI. However, we were specifically interested in outcomes in patients treated in rehabilitation which automatically leads to confounding by indication. The study also limited itself to the symptoms of fatigue and does not take into account the effect of other symptoms (e.g. pain, sleep) on participation or HRQoL. The latter has however been the subject of research in previous studies[63] concluding that sleep-wake disturbances were associated with poor quality of life following pediatric TBI. Finally, this study only used questionnaires filled out by patients and parents. Answers within these questionnaires could be influenced by several factors e.g., bad mood, stress within the family, amongst others.

Future rehabilitation research should include a prospective cohort study of ABI patients with an emphasis on intervention programs focussing on fatigue and other common symptoms after ABI while promoting participation. The associations between fatigue, participation and QoL deem to be further explored in a larger cohort where all potential mutual associations and their directions are explored, preferably based on a conceptual theoretical model.

Conclusions

Fatigue is an often reported symptom after ABI which significantly affects activities, participation and health-related quality of life in adolescence and young adulthood. Fatigue is possibly a modifiable multidimensional symptom which, when targeted during rehabilitation treatment, could potentially improve participation and HRQoL. When reporting fatigue, the patient perspective is sufficient while for participation and HRQoL the patient and parent viewpoint give a complete perspective of functioning.

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Declaration of interests
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References

1. Greenwald BD, Burnett DM, Miller MA. Congenital and acquired brain injury. 1. Brain injury: epidemiology and pathophysiology. *Arch Phys Med Rehabil* 2003;84:S3-S7.
2. Catroppa A, Anderson VA, Morse SA, Haritou D, Rosenfeld JV. Outcome and predictors of functional recovery 5 years following pediatric traumatic brain injury. *J Pediatr Psychol* 2008;33:707–718.
3. Di Battista A, Soo C, Catroppa C, Anderson V. Quality of life in children and adolescents post-TBI: a systematic review and meta-analysis. *J Neurotrauma* 2012; 29:1717–1727.
4. Green L, Godfrey C, Soo S, Anderson V, Catroppa C. A preliminary investigation into psychosocial outcome and quality-of-life in adolescents following childhood traumatic brain injury. *Brain Inj* 2013;7–8:872–877.
5. Anderson V, Brown S, Newitt H, Hoile H. Educational, vocational, psychosocial, and quality-of-life outcomes for adult survivors of childhood traumatic brain injury. *J Head Trauma Rehabil* 2009;Sep-Oct;24(5):303-12.
6. Neuner B, von Mackensen S, Krümpel A, Manner D, Friefeld S, Nixdorf S, Frühwald M, deVeber G, Nowak-Göttl U. Health-related quality of life in children and adolescents with stroke, self-reports, and parent/proxies reports: cross-sectional investigation. *A. Ann Neurol* 2011;70:70–78.
7. Kristiansen I, Strinnholm M, Strömberg B, Frisk P. Clinical characteristics, long-term complications and health-related quality of life (HRQoL) in children and young adults treated for low-grade astrocytoma in the posterior fossa in childhood. *J Neurooncol* 2019;Mar;142(1):203-210.
8. Gagner C, Landry-Roy C, Lainé F, Beauchamp MH. Sleep-Wake Disturbances and fatigue after pediatric traumatic brain injury: A systematic review of the literature. *J Neurotrauma* 2015;Oct 15;32(20):1539-52.
9. Crichton A, Anderson V, Oakley E, Greenham M, Hearps S, Delzoppo C, Beauchamp MH, Hutchison JS, Guerguerian AM, Boutis K, Babl FE, group Biomarker & QoL in Children with TBI. Fatigue following traumatic brain injury in children and adolescents: A longitudinal follow-up 6 to 12 months after injury. *J Head Trauma Rehabil* 2018;May/Jun;33(3):200-209.
10. Meeske K, Katz ER, Palmer SN, Burwinkle T, Varni JVV. Parent proxy-reported health-related quality of life and fatigue in pediatric patients diagnosed with brain tumors and acute lymphoblastic leukemia. *Cancer* 2004;Nov 1;101(9):2116-25.
11. Goeggel Simonetti B, Ritter B, Gautschi M, Wehrli E, Boltshauser E, Schmitt-Mechelke T, Weber P, Weissert M, El-Koussy M, Steinlin M. Basilar artery stroke in childhood. *Dev Med Child Neurol* 2013;Jan;55(1):65-70.
12. Aaro Jonsson CC, Emanuelson IM, Smedler AC. Variability in quality of life 13 years after traumatic brain injury in childhood. *Int J Rehabil Res* 2014;Dec;37(4):317-22.
13. Wilkinson J, Marmol NL, Godfrey C, Wills H, van Eijndhoven Q, Botchway EN, Sood N, Anderson V, Catroppa C. Fatigue following paediatric acquired brain injury and its impact on functional outcomes: A systematic review. *Neuropsychol Rev* 2018;28(1):73-87.
14. Greenham M, Gordon AL, Cooper A, Ditchfield M, Coleman L, Hunt RW, Mackay MT, Monagle, Monagle P, Anderson V. Social functioning following pediatric stroke: contribution of neurobehavioral impairment. *Dev Neuropsychol* 2018;43(4):312-328.
15. MacAllister WS, Christodoulou C, Troxell R, Milazzo M, Block P, Preston TE, Bender HA, Belman A, Krupp LB. Fatigue and quality of life in pediatric multiple sclerosis. *Mult Scler* 2009;Dec;15(12):1502-8.
16. Berrin SJ, Malcarne VL, Varni JW, Burwinkle TM, Sherman SA, Artavia K, Chambers HG. Pain, fatigue, and school functioning in children with cerebral palsy: a path-analytic model. *J Pediatr Psychol* 2007;Apr;32(3):330-7.
17. Gedaly-Duff V, Lee KA, Nail L, Nicholson HS, Johnson KP. Pain, sleep disturbance, and fatigue in children with leukemia and their parents: a pilot study. *Oncol Nurs Forum* 2006;May 3;33(3):641-6.

18. Gordijn MS, van Litsenburg RR, Gemke RJ, Huisman J, Bierings MB, Hoogerbrugge PM, Kaspers GJ. Sleep, fatigue fatigue, depression, and quality of life in survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2013;Mar;60(3):479-85.
19. Gold JI, Mahrer NE, Yee J, Palermo TM. Pain, fatigue, and health-related quality of life in children and adolescents with chronic pain. *Clin J Pain* 2009;Jun;25(5):407-12.
20. van de Port IG, Kwakkel G, Schepers VP, Heinemans CT, Lindeman E. Is fatigue an independent factor associated with activities of daily living, instrumental activities of daily living and health-related quality of life in chronic stroke? *Cerebrovasc Dis* 2007;23(1):40-5.
21. Ezekiel L, Collett J, Mayo NE, Pang L, Field L, Dawes H. Factors Associated With Participation in Life Situations for Adults With Stroke: A Systematic Review. *Arch Phys Med Rehabil* 2019;May;100(5):945-955.
22. Cantor JB, Ashman T, Gordon W, Ginsberg A, Engmann C, Egan M, Spielman L, Dijkers M, Flanagan S. Fatigue after traumatic brain injury and its impact on participation and quality of life. *J Head Trauma Rehabil* 2008;23(1):41-51.
23. Imms C, Adair B, Keen D, Ullenhag A, Rosenbaum P, Granlund M. 'Participation': a systematic review of language, definitions, and constructs used in intervention research with children with disabilities. *Dev Med Child Neurol* 2016;Jan;58(1):29-38.
24. Scales PC, Benson PL, Oesterle S, Hill KG, Hawkins JD, Pashak TJ. The dimensions of successful young adult development: a conceptual and measurement framework. *Appl Dev Sci* 2016;20(3):150-174.
25. Lambregts SAM, Smetsers JEM, Verhoeven IMAJ, de Kloet AJ, van de Port IGL, Ribbers GM, Catsman-Berrevoets CE. Cognitive function and participation in children and youth with mild traumatic brain injury two years after injury. *Brain Inj* 2018;32(2):230-241.
26. de Kloet AJ, Gijzen R, Braga LW, Meesters JJL, Schoones JW, Vliet Vlieland TPM. Determinants of participation of youth with acquired brain injury: A systematic review. *Brain Inj* 2015;Sep;29(10):1135-1145.
27. Anaby D, Law M, Hanna S, Dematteo C. Predictors of change in particpation rates following acquired brain injury: results of a longitudinal study. *Dev Med Child Neurol* 2012;54(4):339-46.
28. Calman K, Definitions and dimensions of quality of life, in The quality of life of cancer patients. 1987, Raven: New York. p. 81-87.
29. Stancin T, Drotar D, Taylor HG, Yeates KO, Wade SL, Minich NM. Health-related quality of life of children and adolescents after traumatic brain injury. *Pediatrics* 2002;Feb;109(2):E34.
30. Limond J, Dorris L, McMillan TM. Quality of life in children with acquired brain injury: parent perspectives 1-5 years after injury. *Brain Inj* 2009;Jul;23(7):617-22.
31. Polinder S, Haagsma JA, van Klaveren D, Steyerberg EW, van Beeck EF. Health-related quality of life after TBI: a systematic review of study design, instruments, measurement properties, and outcome. *Popul Health Metr* 2015;Feb 17;13:4.
32. Gupta P, Jalali R. Long-term Survivors of Childhood Brain Tumors: Impact on General Health and Quality of Life. *Curr Neurol Neurosci Rep* 2017;Nov 8;17(12):99.
33. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet* 1974;13:81–4.
34. Varni JW, Limbers CA. The PedsQL Multidimensional Fatigue Scale in young adults: feasibility, reliability and validity in a University student population. *Qual Life Res* 2008;Feb;17(1):105-14.
35. Gordijn M, Cremers EM, Kaspers GJ, Gemke RJ. Fatigue in children: reliability and validity of the Dutch PedsQL™ Multidimensional Fatigue Scale. *Qual Life Res* 2011;Sep;20(7):1103-8.
36. Haverman L, Limperg PF, van Oers HA, van Rossum MA, Maurice-Stam H, Grootenhuis MA. Psychometric properties and Dutch norm data of the PedsQL Multidimensional Fatigue Scale for Young Adults. *Qual Life Res* 2014;Dec;23(10):2841-7.
37. Panepinto JA, Torres S, Bendo CB, McCavit TL, Dinu B, Sherman-Bien S, Bemrich-Stolz C, Varni JW. PedsQL™ Multidimensional Fatigue Scale in sickle cell disease: feasibility, reliability, and validity. *Pediatr Blood Cancer* 2014;Jan;61(1):171-7.
38. Bedell GM. Further validation of the

Child and Adolescent Scale of Participation (CASP). *Dev Neurorehabil* 2009;12(5):342-51.
39. de Kloet AJ, Berger MA, Bedell GM, Catsman-Berrevoets CE, van Markus-Doornbosch F, Vliet Vlieland TP. Psychometric evaluation of the Dutch language version of the Child and Family Follow-up Survey. *Dev Neurorehabil* 2015;18(6):357-64.
40. McDougall J, Bedell G, Wright V. The youth report version of the Child and Adolescent Scale of Participation (CASP): Assessment of psychometric properties and comparison with parent report. *Child Care Health Dev* 2013;Jul;39(4):512-22.
41. Limperg PF, Haverman L, van Oers HA, van Rossum MA, Maurice-Stam H, Grootenhuis MA. Health related quality of life in Dutch young adults: psychometric properties of the PedsQL generic core scales young adult version. *Health Qual Life Outcomes* 2014;Jan 18;12:9.
42. Varni JW, Limbers CA, Burwinkle TM. Parent proxy-report of their children's health-related quality of life: an analysis of 13,878 parents' reliability and validity across age subgroups using the PedsQL 4.0 Generic Core Scales. *Health Qual Life Outcomes* 2007;Jan 3;5:2.
43. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr* 2003;Nov-Dec;3(6):329-41.
44. Engelen V, Haentjens MM, Detmar SB, Koopman HM, Grootenhuis MA. Health related quality of life of Dutch children: psychometric properties of the PedsQL in the Netherlands. *BMC Pediatr* 2009;Nov 3;9:68.
45. McCarthy ML, MacKenzie EJ, Durbin DR, Aitken Me, Jaffe KM, Paidas CN, Slomine BS, Dorsch AM, Berk RA, Christensen JR, Ding R R, Group CHAT Study. The Pediatric Quality of Life Inventory: an evaluation of its reliability and validity for children with traumatic brain injury. *Arch Phys Med Rehabil* 2005;Oct;86(10):1901-9.
46. Bartko JJ. The intraclass correlation coefficients as a measure of reliability. *Psychol Rep* 1966;19(1):3-11.
47. SPSS Statistics for Windows, Version 22.0. 2016, Armonk, NY: IBM Corp.
48. de Kloet AJ, Hilberink SR, Roebroeck ME, Catsman-Berrevoets CE, Peeters EAJ, Lambregts SAM, van Markus-Doornbosch F, Vliet Vlieland TPM. Youth with acquired brain injury in the Netherlands: a multicenter study. *Brain Inj* 2013;27:843–849.
49. Barlow KM. Postconcussion Syndrome: A Review. *J Child Neurol* 2014;Jan;31(1):57-67.
50. Barlow KM, Crawford S, Stevenson A, Sandhu SS, Belanger F, Dewey D. Epidemiology of postconcussion syndrome in pediatric mild traumatic brain injury. *Pediatrics* 2010 2010;126;e374-e381.
51. Crichton AJ, Babl F, Oakley E, Greenham M, Hearps S, Delzoppo C, Hutchison J, Beauchamp M, Anderson V. Prediction of multidimensional fatigue after childhood brain injury. *J Head Trauma Rehabil* 2017;Mar/Apr;32(2):107-116.
52. Yeh CH, Chiang YC, Lin L, Yang CP, Chien LC, Weaver MA, Chuang HL. Clinical factors associated with fatigue over time in paediatric oncology patients receiving chemotherapy. *Br J Cancer* 2008;Jul 8;99(1):23-9.
53. van Tol E, Gorter JW, DeMatteo C, Meester-Delver A. Participation outcomes for children with acquired brain injury: a narrative review. *Brain Inj* 2011;25(13-14):1279-87.
54. Theadom A, Starkey N, Barker-Collo S, Jones K, Ameratunga S, Feigin V, Group BIONIC4you Research. Population-based cohort study of the impacts of mild traumatic brain injury in adults four years post-injury. *PLoS One* 2018;13(1):e0191655.
55. Engel-Yeger B, Tse T, Josman, Baum C, Carey LM. Scoping Review: The Trajectory of Recovery of Participation Outcomes following Stroke. *Behav Neurol* 2018;Sep 9;2018:5472018.
56. Rivara FP, Vavilala MS, Durbin D, Temkin N, Wang J, O'Connor SS, Koepsell TD, Dorsch A, Jaffe KM. Persistence of disability 24 to 36 months after pediatric traumatic brain injury: a cohort study. *J Neurotrauma* 2012;29(15):2499-504.
57. Upton P, Lawford J, Eiser C. Parent-child agreement across child health-related quality of life instruments: a review of the literature. *Qual Life Res* 2008;Aug;17(6):895-913.
58. Eiser C, Varni JW. Health-related qual-

ity of life and symptom reporting: similarities and differences between children and their parents. *Eur J Pediatr* 2013;Oct;172(10):1299-304.
59. Knight SJ, Politis J, Garnham C, Scheinberg A, Tollit MA. School Functioning in Adolescents With Chronic Fatigue Syndrome. *Front Pediatr* 2018;Oct 16;6:302.
60. Cavallo S, April KT, Grandpierre V, Majnemer A, Feldman DE. Leisure in children and adolescents with juvenile idiopathic arthritis: a systematic review. *PLoS One* 2014;Oct 20;9(10):e104642.
61. Lequerica AH, Botticello AL, Lengenfelder J, Chiaravalloti N, Bushnik T, Dijkers MP, Hammond FM, Kolakowsky-Hayner SA, Rosenthal J. Factors associated with remission of post-traumatic brain injury fatigue in the years following traumatic brain injury (TBI): a TBI model systems module study. *Neuropsychol Rehabil* 2017;27(7):1019-1030.
62. Eddy L, Cruz M. The relationship between fatigue and quality of life in children with chronic health problems: a systematic review. *J Spec Pediatr Nurs* 2007;Apr;12(2):105-14.
63. Botchway EN, Godfrey C, Anderson V, Catroppa C. A systematic review of sleepwak disturbances in childhood traumatic brain injury: relationship with fatigue, depression and quality of life. *J Head Trauma Rehabil* 2018;Jul/Aug; 34(4):241-256.



Chapter 7

The outcomes of a vocational rehabilitation program in unemployed adults with acquired brain injury

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Abstract

Background and aim

Favorable results of rehabilitation programs have been described in working patients with acquired brain injury, but knowledge on their effectiveness in patients who were not working at the time of injury is limited. Therefore, this study aimed to explore the process and outcomes of a novel vocational rehabilitation program based on the concept of buddy-support in unemployed young adults with non-recent acquired brain injury.

Methods

This observational, retrospective study included unemployed adults with acquired brain injury who were taking part in a vocational rehabilitation program between 2012 and 2017. The vocational rehabilitation program included a comprehensive assessment, the training of specific skills, group and individual counselling by a job coach and the provision of 'buddy' support from volunteering managers from the corporate or public sector. Adherence to the program and work status were registered during rehabilitation, whereas at follow-up in 2017 all patients were invited to complete a questionnaire on their work status and the EuroQol 5-dimensions-5 Levels. Patients' clinical characteristics were extracted from the medical records.

Results

49 patients started the program, of whom 41 completed the follow-up. Their median age was 31 years (interquartile range 25-37 years) and 19 (46%) were male. The median duration of the vocational rehabilitation program was 8 months (interquartile range 5-12 months).Thirty-one patients (76%) took part in the (group) training with a job coach, 23 (56%) used the services of a 'buddy' and 19 (46%) had individual job coaching. At follow-up, 4 patients were still in the program, whereas 9 patients left the program prematurely, with insufficient financial support for continuation being the primary reason for withdrawal (n=6). Nine patients had acquired paid employment (22%), 7 of whom used a buddy; 6 of whom were bothered by health problems at work. Patients who had found paid employment did not differ from those who did not with respect to sociodemographic characteristics, but did have a significantly higher EuroQol score at follow-up (0.84 versus 0.69, p=0.012).

Conclusion

With a success rate of 22% in paid employment, a vocational rehabilitation program including a 'buddy' for a subgroup of patients may be a promising program for patients

who were unemployed at the time of acquired brain injury. Lack of financial support to complete the program and concurrent health problems were found to hamper the process and outcomes of the program, respectively.

Introduction

Acquired brain damage (ABI) is a common condition, including both traumatic brain injury (TBI) and non-traumatic brain injury (NTBI). The consequences of ABI are considerable for many patients, and may include, apart from physical, cognitive, and emotional impairments, also restrictions in societal participation. Although the rates vary per condition, for many working patients, returning to work after ABI is difficult. A systematic review of return to work (RTW) reported success percentages between 30 and 65%, without substantial differences between a traumatic or non-traumatic cause of ABI.[1] The large variety in RTW percentages was probably due to different definitions of RTW, variation in severity of injury and time since onset of ABI.
Concerning the prognostic factors related to RTW, high education level is positively associated with RTW while a low education level, unemployment and length of stay in rehabilitation are negatively associated with RTW[2] and sex and localisation of lesion after NTBI and for those with TBI, injury severity, depression or anxiety, not associated with RTW[3]. Van Velzen et al.[3] looked specifically at trainable/treatable factors after ABI and found 'ability to perform activities of daily living', 'residual physical deficits/higher disability level', and 'number of associated injuries' positively associated with RTW.
Vocational rehabilitation (VR) programs are instituted to decrease work disability in patients with ABI. Their effectiveness has been demonstrated in multiple studies,[2, 4-12] with success rates of 47-80% in RTW after interventions implemented in an individualized rehabilitation plan,[8-10] and 41-70% in interventions according to a model with a rapid RTW after injury followed by individual support.[11, 12]
Most of the studies on VR in patients with ABI were so far aimed at patients who were working at the time of injury, with regaining employment as the main outcome measure. The literature on VR programs (mainly) including patients who were not working at the time of the injury, with attainment of employment being the main outcome measure, are scarce. The expected outcomes in this patient group would probably less favorable, as it has been demonstrated that unemployment at the onset of brain injury may be a negative predictor for VR outcomes.[2] This could be due to the fact that if patients are not working they lack e.g. the support of the employer and colleagues, available occupational health services and a professional network.
Putting efforts in the attainment of paid employment in this particular population may,

however, be very worthwhile. From the perspective of the individual, work is very important for one's overall well-being and self-esteem. From the societal perspective, the achievement of financial independence of every unemployed patient implies considerable savings of costs associated with long-lasting disability pensions or unemployment benefits.

Regarding the optimal composition of the intervention program, from the literature on VR in patients with ABI in general, it can be concluded that reported components of the most effective programs were tailored approach, early intervention, involvement of patient and employer, work or workplace accommodations, work practice and training of social and work-related skills, including coping and emotional support.[2] Regarding the composition of VR interventions in general, work-directed activities, education and coaching, skills training, cognitive rehabilitation, and/or supported employment have been identified as active components of the interventions.[13,14] Several studies have shown that the success rates of interventions for working patients with ABI significantly increase when employers are directly involved and committed.[15,16] Indeed, a VR program for working patients with ABI provided by our own group that specifically included the employer and a co-worker,[16] resulted in 86% of the patients returning to work.

As involvement of the employer cannot be accomplished in patients who were unemployed at the time of brain injury or thereafter, we developed a VR program including provision of 'buddy' support from volunteering managers from the corporate or the public sector.

The aim of the present study was to explore the process and outcomes of a novel vocational rehabilitation program based on the concept of buddy-support in unemployed young adults with non-recent acquired brain injury.

Methods

Study Design

This observational, retrospective cohort study evaluated the process and outcomes of a VR program by means of chart review and a follow-up questionnaire. It was carried out in a rehabilitation center, i.e. Basalt Rehabilitation, The Hague, The Netherlands. The study was judged to fall outside the remit of the Medical Research Involving Human Subjects Act according to the Medical Ethical Review Board of the Leiden University Medical Center, Leiden, The Netherlands (P14.006). The study was performed in accordance with the ethical standards laid down in the 2013 World Medical Association Declaration of Helsinki amendment.[17]

Participants

All patients were recruited at the rehabilitation center between September 2012 and February 2017 and considered eligible for the program if they: were diagnosed with ABI; aged 18 -50 years; were unemployed; were motivated to attain paid employment; and had a perspective on financial support for the program from local authority. Patients who had had work and could return to their previous work or of whom their physical, cognitive or emotional condition would prohibit the possibility to take part in the program, perform work and/or travel were excluded. Patients who were considered eligible for the program were invited to participate by their treating physiatrist to participate in the VR program. The patients were approached at time of follow-up and gave informed consent after having read the Patient Information.

Program

The novel program, called Brains4You, was executed by a team including the following professionals: a rehabilitation physiatrist, psychologist, occupational therapist and social worker within the rehabilitation center, in cooperation with job coaches who were supervised by the office manager (an occupational therapist) of a commercial labor integration company (Weustink & Partners, The Hague, The Netherlands; https://weustinkenpartners.nl/) and a professional 'buddy'. The 'buddy' was a volunteering manager (n=14) from the commercial or public sector, initially recruited in the social network of rehabilitation professionals involved in the study and later on by 'the word of mouth' by the buddies themselves.

The program consisted of 4 steps:

1. The physiatrist considered the eligibility of the patients for referral to the program using the abovementioned inclusion and exclusion criteria. After referral, during a comprehensive and standardized assessment at the rehabilitation center, the rehabilitation psychologist and occupational therapist identified the patient's opportunities and goals related to the attainment of work. Based on the patient's health status, education, preferences and other personal factors, a profile regarding potentially suitable work and specific requirements was composed. Specifically regarding the assessment of the consequences of ABI, a comprehensive neuropsychological assessment was done if not recently performed. For work ability, an instrument assessing the energy costs and benefits of the performance of daily tasks was used (Activiteitenweger; http://revalidatieapps.nl/activiteitenweger.html). On average, the duration of the complete assessment was 2-4 hours. Based on its results, if deemed necessary, rehabilitation interventions such as occupational therapy or speech-language therapy were initiated, before starting step 2.

2. A second assessment was performed by a professional from the commercial labor integration company specialized in ABI focusing on the goals and interests of the patient and acquiring the necessary financial support for the VR program. Financial support was obtained from the agreed legal compensation after injury or the municipal or national disability pension bodies, where appropriate. The assessment took place at the labor integration company, with an average duration of 1 hour.
3. A vocational training led by a job coach (individual or group, depending on capacities) was instituted, tailored to the patient's individual needs. The job coach was an ABI-trained professional from the labor integration company. Empowerment, social skills and application training were the key topics, with the number of sessions being flexible. The vocational training was not offered to patients considered to have adequate competences to acquire employment, as judged by the assessing professional in step 2. The maximum number of patients in a training group was 6, the maximum number of sessions was 8, and they all took place at the labor integration company.
4. After the (group) training sessions, the patient were offered the services of a 'buddy'. If the support of a buddy was not deemed necessary by the job coach (e.g. suitable employment was already available), the service was not offered. Buddies were professionals working in the region, having a managerial position and with a strong professional network. They were recruited via the project coordinators and their professional network contacts. The director of the labor integration company screened the potential buddies regarding their motivation and availability for the project as well as their business network. Then an introductory meeting with all of the buddies took place, and subsequently patients were matched with a buddy; each individual buddy was matched with only one patient. Buddy task included judging and enhancing the readiness for work, e.g. by giving individual coaching with respect to the demands of paid employment (e.g. appearance and attitude, conduct of a job interview, promptness). They could offer internships in their own companies. Buddies acted as mediators between the patient and potential employers within their own professional networks.

If the patients acquired paid employment, further individual job coaching was provided by the labor integration company. The length of the follow-up in the program, either or not including individual coaching on the job, was dependent on the amount of financial support acquired and the patient's needs, up to a maximum of 12 months. All patients were contacted at least once by the job coach after start at work. Job coaching at the workplace included exploring and implementing adaptations such as an adapted workspace, rest moments and adjusted work hours.

In exceptional cases, where patients had recently taken part in the assessment (step 1) or in a program similar to the vocational training (step 3), or were judged to likely have adequate competences to enter the workforce (step 3), elements of the program could be omitted.
In the Netherlands, labor integration trajectories are paid by the UWV (Employee Insurance Agency), the employer, the municipality, or through legal personal injury trajectories. The UWV is an autonomous administrative authority, commissioned by the Ministry of Social Affairs and Employment (SZW) to implement employee insurances and provide labor market and data services. The Dutch employee insurances are provided for via laws such as the WIA (Work and Income according to Labor Capacity Act). The available budget for a trajectory varies, ranging from approximately € 1875-3000 for UWV trajectories to approximately € 3500-10.000 for legal personal injury trajectories.

Assessments
Patient sociodemographic and disease characteristics were extracted from the medical records by the treating physiatrist and from the records of the VR program by one of the researchers (AJK). A set of questionnaires for follow-up was administered personally during a group meeting in June 2017 or sent by mail that same month.

Sociodemographic and disease characteristics
Sociodemographic characteristics included: age (years); sex; educational level (categorized into: primary school/occupational training; high school/professional training; or higher education/university); time since start of VR (months), and having past paid employment (yes/no).
Disease characteristics comprised of: ABI characteristics (traumatic/non-traumatic injury). The severity of TBI was determined by means of the Glasgow Coma Scale (GCS) at hospital admission recorded in the patient's file. According to the GCS, the severity of TBI was considered mild if the GCS was 13–15, moderate if the GCS was 9–12 or severe if the GCS was <9. Severity of NTBI was not registered in the patient files. In addition, time since onset of ABI at start of VR (months) was recorded.

Adherence with the VR program
The patient's participation in all activities related to the VR program was recorded: initial assessments (yes/no); vocational training (yes/no, number of session(s) <4 or 4-8); contact with job coach (yes/no) and duration of program (in months); contacts with buddy (yes/no) and number of contacts with buddy <4, 4-8 or >8, and, if employment was acquired, follow up support of the job coach in 4-6 appointments

during 12 months after starting work. Patients were considered to be completers of the VR program if they had participated until they acquired paid or non-paid employment or (re)started education. If patients left the program prematurely, the reason was registered (lack of energy; lack of motivation or satisfaction; financial support for the program rejected; or switch to another labor integration organization.

Work status, Costs and Quality of Life

The program was classified as successful if the patient obtained gainful employment. The patients' work status was recorded at follow-up by means of a number of questions on work status (having (un)paid employment, yes/no), absence from work in the past month, and health problems encountered while at work in the past month.
Productivity was valued at € 35 per fully productive hour, in accordance with the Dutch guidelines for economic evaluations in healthcare.[18] The verbal questions on absenteeism were converted to 0%, 50% and 100% absenteeism (for no, up to one month, and more than one month absenteeism, respectively). The verbal questions on bother at work were converted to 0%, 25% and 50% bother (for not at all, slightly, and very much bothered, respectively). The productivity value per month was calculated for each patient as € 35 times the working hours per month, decreased by the percentages absenteeism and bother at work.

Valuation of patients' quality of life was measured using the EuroQol 5-Dimensions 5-Levels (EQ-5D-5L), comprising five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[19, 20] Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The 5 dimensions together describe the respondent's health status, and can be converted into a single valuation index anchored at 1 (perfect health) and 0 (as bad as dead), specifically for The Netherlands.[21]. As the usual activities domain includes having employment, we also assessed the EQ-5D-5L index with the usual activities domain excluded (by setting the level to no problems for all individuals).

Analysis

All statistical analyses were performed using SPSS 22.0 software package.[22] Descriptive statistics were used for both categorical (numbers and percentages) and continuous data (median, range). The characteristics of patients (sex, age, educational level, type of ABI, time since onset of ABI, and having or not having previous employment) were compared using Bootstrap statistics, Mann-Whitney U tests or Fisher Exact tests, where appropriate, for patients who had paid employment and patients who had not acquired paid employment at the time of follow-up.

Results

Participants

Between 2012 and 2017, 49 patients were considered eligible by their treating rehabilitation specialist, referred to the VR program and able to take part in the program after financial resources were acquired. Of these patients, 41 (84%) took part in the evaluation in 2017 and were included in the present analysis. At the follow up evaluation, the time since the start of the program ranged from 6 to 58 months.

The characteristics of the patients are shown in Table 1. Their median age was 31 years (range 20-49 years), about half of them were male, and 80% had a medium or high educational level. About half of the patients had a TBI, with time since onset being more than two years in all but one patient. Nearly half of the patients had previously had paid employment.

Table 1. Characteristics of patients who were unemployed at the time of acquired brain injury (ABI) taking part in a vocational rehabilitation program

	Total, n=41	**Employed after program, n=9**	**Not employed after program, n=32**
Age, years; Median (range)	31 (20-49)	32 (27-35)	30 (24-38)
Age, categories; No. (%)			
18-25 years	11 (27%)	1 (11%)	10 (31%)
26-35 years	16 (39%)	7 (78%)	9 (28%)
36-50 years	14 (34%)	1 (11%)	13 (41%)
Sex, male; No. (%)	19 (46%)	3 (33%)	16 (50%)
Highest educational level; No. (%)			
Primary School/Occupational training	8 (20%)	0	8 (25%)
High School/Professional training	23 (56%)	6 (67%)	17 (53%)
Higher education /University	10 (24%)	3 (33%)	7 (22%)
Type of injury; No. (%)			
Traumatic (TBI)	21 (51%)	4 (44%)	17 (53%)
Non-Traumatic (NTBI)	20 (49%)	5 (56%)	15 (47%)
Time since onset of injury; No. (%)			
< 24 months	1 (2%)	0	1 (3%)
≥ 24 months	40 (98%)	9 (100%)	21 (97%)
Previously having paid employment; No. (%)	19 (46%)	4 (44%)	15 (47%)
Time since start vocational program; No. (%)			
6-18 months	6 (15%)		
18-42 months	23 (56%)		
42-58 months	12 (29%)		
EuroQol EQ-5D-5L; Median (range)	0.73 (0.65-0.79)	0.84 (0.79-0.90)	0.69 (0.61-0.77)

Participation in the components of the VR program

Table 2 describes the patients' participation in the various components of the VR program. After the initial assessments, two-thirds of the patients took part in the training sessions, whereas 23 (56%) patients used the services of a 'buddy' (in total 23 different buddies were involved between 2012 and 2017), with the majority of patients having had more than 4 contacts with their buddy. In total 9 (22%) patients ended their participation in the program prematurely, because financial support for the program ceased (n=6), the patient did not have enough energy (n=1) or other reasons (n=2). Four patients were still in the program at the time of follow-up.

Work status at follow-up and costs

Table 3 shows the work status of the 9 patients (22% of the total group; 24% if the 4 patients who were still in the program were not taken into account) who had acquired paid employment. The other 32 patients designated their main occupation as follows: not able to work (n=17; 41%), student (n=3; 7%), unpaid work (n=10, 27%) and other (n=2; 5%). Of the 32 patients who did not have paid employment, 10 designated their usual activities as satisfying.

Seven out of the 9 patients (78%) who acquired a job used a buddy during the program, and 16 of the 32 (50%) patients without paid employment did not. As shown in Table 3, of the 9 patients with paid employment, 3 had work for 8-16 hours, 3 for 17-24 hours and 3 for more than 25 hours per week. In the month preceding the evaluation, six of the working patients had been absent from work or were bothered at work by health

Table 2. Use of the various components of a vocational rehabilitation program in 41 patients who were unemployed at time of acquired brain injury (ABI)

Duration of participation in the program, months; Median (range)	8 (5-12)
Number of patients still in the program at follow-up, No. (%)	4 (10%)

Participation in the different program phases, No. (%)					
Step 1 Work related assessment	**Step 2 Assessment Labor Integration Company**	**Step 3 Training sessions with job coach**		**Step 4 Services of a 'buddy'**	**Individual coaching on the job**
37 (90%)	41 (100%)	31 (76%)		23 (56%)	19 (46%)
		Number of sessions		**Number of contacts**	
		< 4	15 (48%)	< 4	7 (30%)
		4-8	16 (52%)	4-8	4 (17%)
				>8	12 (52%)

Table 3. Work status of patients (n=9) with acquired brain injury (ABI) with paid employment after participation in a vocational rehabilitation program

	No. of patients
Number of working hours per week	
8-16	3
17-24	3
25-32	3
Absence from work due to health problems in past month	6
Absence from work for longer than 1 month	2
Bothered by health problems in the past month	
No, not at all	3
Yes, slightly	5
Yes, very much	1
Type of health problems often or always bothering work in the past month*	
Concentration problems	4
Work at a slower pace	5
Work in seclusion	3
Difficulty making decisions	1
Postpone work	1
Others having to take over work	1
Other	0

* Patients were able to report more than 1 health problem

problems in the past month. Three patients reported problems with concentration and/or working at a slower pace. These problems were addressed in the coaching on the job, if applicable, yet the contents of the coaching on the job or the individual number of sessions were not recorded.

With the observed weekly working hours, absenteeism and bother by health problems in our study (averages 24 hours, 44%, and 22%, respectively), the productivity value for our patients with paid employment was about € 2000 per month. In the general Dutch population, the productivity value is about € 6000 per month.

Costs for vocational rehabilitation programs in the Netherlands are typically around € 5000 per trajectory: € 2900 for the comprehensive rehabilitation assessment ((https://www.werkenmethersenletsel.nl/src/frontoffice/uploads/files/Participatiemeter%20Sophia%20Revalidatie%20Den%20Haag.pdf; accessed November 6, 2019) and € 2100 for the job coach trajectory (25 hours, 80 euro per hour; https://www.uwv.nl/particulieren/Images/normbedragen-voorzieningen-2019.pdf; accessed November 6, 2019) with a total program cost for all 41 patients in our study approximately € 205,000.

As 9 patients found paid employment, these costs come down to € 23,000 per patient that successfully found paid employment. Thus, for a productivity value of € 2000 per month, the intervention costs are more than recovered if patients that find employment on average maintain their employment for at least a year.

Comparison of patients who did and who did not acquire paid employment

The 9 patients who had acquired paid employment did not differ from the 32 patients who did not acquire paid employment regarding sex, age, educational level, type of ABI, time since ABI and or whether or not they previously had paid employment (results not shown). However, at follow-up, the EQ-5D-5L index score of those with paid employment was statistically significantly higher than of patients without paid employment (0.84 versus 0.69, p=0.012). The difference remained statistically significant when the usual activities domain was excluded from the EQ-5D-5L (0.88 versus 0.76, p=0.019).

Discussion

A vocational rehabilitation program including a proved to be a promising program for patients with ABI who were not gainfully employed at the time of injury. The majority of patients completed the program, with a success rate of 22% in paid employment. Ensuring sufficient financial support to complete the program is necessary, as this was the main reason for premature termination. In addition, if paid employment was acquired, health problems hindering work ability were relatively common among working patients (6/9 absent from work or bothered by health problems and up to 5/9 patients reporting one of 6 symptoms in past month) all constituting a risk of permanent work disability.

The success rate in finding new employment after ABI is relatively low in comparison with overall return to work (RTW) rates after vocational rehabilitation programs in patients with ABI as reported in the literature. In the mostly non-controlled studies RTW rates after VR were varying from 41-80%.[8-12] However, given the fact that not having paid employment at the time of ABI is a risk factor for not returning to work, the results observed in the present study are quite favourable. In particular because the study population concerned relatively young people, who could potentially benefit from the intervention for many years. Unfortunately, we could not observe how long our patients actually maintained their employment. Costs for vocational rehabilitation programs in the Netherlands are typically around € 5000 per trajectory, which would be more than recovered if patients are able to maintain their employment for at least a year. We consider this very plausible.

Lack of significant differences in characteristics between the groups with and without success in our study prevents us from making assumptions about determinants of success or risk factors. Previous paid employment before ABI did not appear to increase the chance of acquiring paid employment, but it must be noted that our sample size was very small. It remains to be established whether the observed significantly better EQ-5D-5L health index in the 9 persons with paid employment as compared to the unemployed patients is a result or a cause of acquired work and/or is influenced by other factors such as a better EQ-5D-5L score before the start of the intervention.

Six out of the 9 patients who acquired paid employment indicated that they had been absent from work due to health problems in the past month, and/or were bothered by health problems. They experienced deficits in speed of information processing, not being able to cope with work demands and a lack of understanding and support of employer and/or colleagues as major obstacle, in line with Dutch RTW studies in adults after ABI: in 96% working tasks were adjusted,[16] due to sensory overload at the workplace, condition-related factors like fatigue, lack of guidance and support.[2] These findings give an indication that patients may need extra guidance or support in order to maintain their work. As the VR program had a limited duration, it needs to be established how and by whom these patients can best be helped, e.g. by specific and repeated education and support, buddies at work or empowerment of working young people with ABI during the VR program.

The assignment of a buddy (managers deploying their business network) constituted a distinctive element in our VR program. It appeared to work as a catalyst in efficient and effective job-finding, with a more positive mind set of managers and their network regarding working capacity of young people with a disability as positive side effect.

Limitations of this study were that the sample size of the study was relatively small, no control group was used for comparison, the number of assessments was limited, time since start of the VR program varied, and the VR program was highly individualized with varying duration and intensity. Another limitation was that we did not record disease characteristics of the patients, including their level of daily activities, although these include factors that may have an impact on the outcome of vocational rehabilitation.[3] In future effect studies, all patient and disease characteristics must be comprehensively recorded. The assessments focussed mainly on the VR program and the acquisition of paid employment, whereas participation in unpaid work was not used as a primary outcome measure. This is arbitrary, as being satisfied with participation in unpaid labor may well be a successful result of a VR program.

It remains to be established to what extent our results are generalizable to other countries. However, as the composition of the program was based on elements that were proven effective in multiple studies on VR in ABI in general,[2] it is likely that the

results are applicable across countries worldwide. Regarding the financial aspects of VR, there may be large differences among countries, due to variation of health care and social security systems.

Strengths of this study are that it is unique in the sense that so far no studies have been performed in this age group of patients with ABI, in particular among those who had no paid employment at the time of ABI, thus having a relatively high risk of not finding work post-injury. Moreover, as our data were collected as part of usual care, the results are likely to be generalizable to daily practice.

An important element of the program, concerned the inclusion of volunteering buddies. More research is needed in order to determine their added value, but given the relatively high use of buddy services in our program, it is imaginable that their efforts contribute to the results observed with the evaluation of the program, with tailored provision of the various elements of the program.

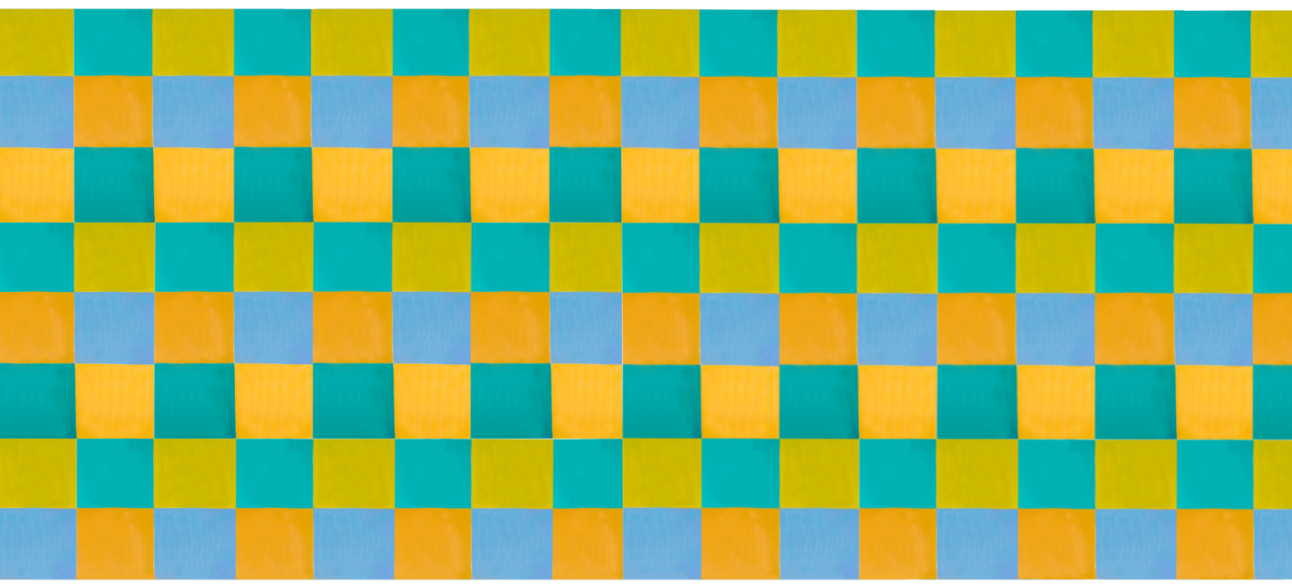
Given the results, the program will be further improved. More attention must be paid to ensure sufficient financial support to complete the program. In addition, if paid employment is acquired, attention must be paid to health problems hindering work ability.

In a next step, the program must be evaluated by means of an appropriate study design, taking into account the effectiveness, the costs and the satisfaction of patients. In a future study, more attention will be paid to the evaluation of the effectiveness regarding unpaid employment.

In conclusion, the VR program including a buddy as one of the elements in the program for a subgroup of patients is promising, and may increase the chance to acquire paid employment. It may also positively affect employers' viewpoint on people with an occupational disability.

References

1. van Velzen J, van Bennekom C, Edelaar M, et al. How many people return to work after acquired brain injury?: A systematic review. *Brain Inj*. 2009;23:473–488.
2. Donker-Cools B, Daams J, Frings-Dresen M. Effective return-to-work interventions after acquired brain injury: A systematic review. *Brain Inj*. 2016;30(2):113–131.
3. van Velzen J, van Bennekom C, Edelaar M, et al. Prognostic factors of return to work after acquired brain injury; a systematic review. *Brain Inj*. 2009;23:385-395.
4. Tibæk M, Kammersgaard L, Johnsen S, et al. Long-term return to work after acquired brain injury in young danish adults: A nation-wide registry-based cohort study. *Front Neurol*. 2019;9:1180.
5. Westerlind E, Persson H, Sunnerhagen K. Return to work after a stroke in working age persons; a six-year follow up. *PLoS ONE*. 2017;12(1):1–14.
6. Tyerman A. Vocational rehabilitation after traumatic brain injury: models and services. *Neurorehabilitation*. 2012;31(1):51–62.
7. Fadyl J, McPherson K. Approaches to vocational rehabilitation after traumatic brain injury: A review of the evidence. *J Head Trauma Rehabil*. 2009;24(3):195–212.
8. Bonneterre V, Pérennou D, Trovatello v, et al. Interest of workplace support for returning to work after a traumatic brain injury: A retrospective study. *Ann Phys Rehabil Med*. 2013;56(9-10):652-662.
9. Buffington A, Malec J. The vocational rehabilitation continuum: Maximizing outcomes through bridging the gap from hospital to community-based services. *Jnl of Head Trauma Rehabilitation*. 1997;12(5): 1-13.
10. Malec J, Moessner A. Replicated positive results for the VCC model of vocational intervention after ABI within the social model of disability. *Brain Inj*. 2006; 20(3):227-236.
11. Murphy L, Chamberlain E, Weir J, et al. Effectiveness of vocational rehabilitation following acquired brain injury: Preliminary evaluation of a UK specialist rehabilitation programme. *Brain Inj*. 2006;20(11):1119–1129.
12. Wehman P, Kreutzer J, West M, et al. Return to work for persons with trau matic brain injury: A supported employment approach. *Arch Phys Med Rehabil*. 1990;71:1047–1052.
13. Trexler L, Trexler L, Malec J, et al. Prospective randomized controlled trial of resource facilitation on community participation and vocational outcome following brain injury. *J Head Trauma Rehabil*. 2010;25(6):440–446.
14. Trexler L, Parrott D, Malec J. Replication of a prospective randomized controlled trial of resource facilitation to improve return to work and school after brain injury. *Arch Phys Med Rehabil*. 2016;97(2):204–210.
15. Machamer J, Temkin N, Fraser R, et al. Stability of employment after traumatic brain injury. *J Int Neuropsychol Soc*. 2005;11(7):807–816.
16. van Dongen C, Goossens P, van Zee I, et al. Short-term and long-term outcomes of a vocational rehabilitation program for patients with acquired brain injury in The Netherlands. *J Occup Rehabil*. 2018;28(3):523-530.
17. WMA Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects. *JAMA*. 2013;310(20): 2191-2194.
18. Hakkaart-van Roijen L, van der Linden N, Bouwmans C, et al., Costing manual: Methodology of costing research and reference prices for economic evaluations in healthcare [Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. 2016, Diemen: Zorginstituut Nederland.
19. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727-1736.
20. Janssen M, Pickard A, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res*. 2013;22(7):1717-1727.
21. Versteegh M, Vermeulen K, Evers S, et al. Dutch tariff for the five-level version of EQ-5D. *Value in Health*. 2016;19:343-352.
22. SPSS Statistics for Windows, Version 22.0. 2016, Armonk, NY: IBM Corp.



Chapter 8

Summary and General discussion

Summary

Acquired Brain Injury (ABI), being either traumatic (TBI) or non-traumatic brain injury (NTBI), is a common condition in children and adolescents and young adults (AYAs). It often results in neuropsychological problems and limitations in activities (including physical activity) and participation throughout the lifespan, particularly when compared to healthy peers. There is relatively little research on physical activity and participation in AYAs with ABI. Furthermore, fatigue is an invisible, multidimensional consequence of ABI, yet underexposed in research in this age group.

In **Chapter 1,** definitions, epidemiology and etiology of ABI, in particular in AYAs, are outlined. An overview of the literature on fatigue, physical activity and participation in this patient group is presented, and the general aims of the thesis are formulated:

1. To describe the occurrence of fatigue, physical inactivity and participation restrictions and their mutual relationships in hospital and rehabilitation based cohorts of children and AYAs with ABI.
2. To describe the work status of unemployed AYAs with ABI who took part in an age-specific vocational rehabilitation program.

In **Chapter 2,** the degree of fatigue and related factors after pediatric ABI (TBI and NTBI) were examined. This hospital-based multicenter follow-up study included patients with a diagnosis of ABI, aged 4-20 years at onset and their parents. Parents and children aged 8 years and older completed, on average 24 months after their diagnosis of ABI, among other questionnaires, the Pediatric Quality of Life Inventory™ Multidimensional Fatigue Scale (PedsQL™ MFS, 0-100, more-less fatigue), with subscales for general, sleep/rest and cognitive fatigue. Sociodemographic and diagnosis-related data were registered. Eighty-eight patients were included with a median age of 11 years, (interquartile range (IQR) 7); 69 with TBI and 19 with NTBI). Forty-nine out of the 88 patients (56%) completed the PedsQL™ MFS child version and 88 parents completed the PedsQL™ MFS parent version. The median patient-reported and parent-reported PedsQL™ MFS Total Scale Scores were 79.2 (IQR 18.1) en 77.8 (IQR 25.0), respectively. In a multivariable linear regression analysis, in addition to NTBI, increasing age and a single-parent household were significantly associated with more fatigue according to the parent-reported PedsQL™ MFS Total Score and/or one or more subscale scores.

In **Chapter 3,** fatigue and its relationship to physical activity (PA) in adolescents and young adults with TBI was assessed in the rehabilitation setting. It concerned a cross-

sectional study in patients aged 12–39 years with a diagnosis of TBI >6 months ago who had been treated in an outpatient rehabilitation center. Participants completed the Activity Questionnaire for Adults and Adolescents (AQuAA, results dichotomized into meeting Dutch recommendations for health enhancing physical activity (D-HEPA) or not) and the Checklist Individual Strength (CIS): subscales fatigue (8 items, score range 8 to 56, higher scores indicating more fatigue; 40 is the cut-off for severe fatigue), motivation (4 items, score range 4 to 28, higher scores indicating less motivation), concentration (5 items, score range 5 to 35, higher scores indicating more concentration problems) and physical activity (3 items, score range 3 to 21, higher scores indicating lower levels of physical activity) and a Total score (range 20-140, higher scores indicating more fatigue (related) problems).
Fifty patients were included with a mean age of 25.0 years (SD 7.2); 18 (36%) had a mild injury, 13 (26%) a moderate injury and 19 (38%) a severe injury. The median time spent on moderate–vigorous physical activity was 518 minutes/week (IQR 236-1725), with males spending significantly more minutes on moderate–vigorous physical activity than women, and time spent on sedentary activity 2728 minutes/week (IQR 1637-3994). Thirty-two (64%) participants met the D-HEPA. According to the fatigue subscale of the CIS, 19 participants (38%) were severely fatigued. In the univariate analyses where the group meeting the D-HEPA was compared to the group not meeting the D-HEPA, both the CIS total score and the subscales motivation and physical activity, but not the subscales fatigue and concentration, were significantly higher in the group not meeting the D-HEPA. In the multivariable logistic regression analysis, correcting for potential confounders sex, age and Body Mass Index (BMI), higher scores (i.e. more problems) on the subscales motivation and physical activity were significantly associated with not meeting the D-HEPA.

With observational studies including only patients with ABI, the impact of a trauma cannot be distinguished from the consequences of head injury specifically. For this reason, **Chapter 4** describes a study comparing physical activity, fatigue and sleep quality after mild TBI (mTBI) in AYAs as compared to orthopedic injury controls (OI) with a clavicular, arm or leg fracture. In this follow-up study patients, aged 12 to 25 years with either mTBI or orthopedic injury at least 6 months after visiting the emergency department of a general hospital, were invited to complete an electronic survey including sociodemographic data, the AQuAA (results dichotomized into meeting D-HEPA or not), the CIS (subscales fatigue, motivation, concentration and physical activity, range 20-140, higher scores indicating more fatigue (related) problems) and the Pittsburgh Sleep Quality Index (PSQI, range 0-21, higher scores indicating poorer sleep quality).

Forty-nine patients aged 12-25 years (mean 18.4 years, SD 3.6) diagnosed with mTBI and 54 patients aged 12-25 years (mean 15.8 years, SD 3.2) with OI were included. The average time since injury was 1.6 years (SD 0.5) in the mTBI group and 1.5 years (SD 0.4) in the OI group. In logistic regression analyses, where corrected for potential confounders sex, age, BMI and time since injury, patients with mTBI less frequently met D-HEPA recommendations than patients with OI (49% vs. 70%; Odds ratio (OR) 2.87, 95% confidence interval (CI) 1.07, 7.72) and reported more concentration-related fatigue problems (mean 19.1 (SD) 8.0, mean 13.9 (SD 7.8), respectively). Multivariable linear regression analysis, adjusting for potential confounders, sex, BMI, age and time since injury, showed that having a mTBI versus an OI was significantly associated with more concentration related fatigue (β 3.98, 95%CI 0.39, 7.56). There were no statistically significant differences between the mTBI and OI groups regarding sleep quality.

In **Chapter 5**, the relationships of physical activity with fatigue and sleep quality were examined within the hospital-based cohort of 49 AYAs with mTBI as described in Chapter 4. By means of an electronic survey, participants, on average 1.6 years (SD 0.5) after injury completed the AQuAA, the CIS and the PSQI.
As reported in Chapter 4, 24 participants (49%) met the D-HEPA recommendations and 25 (51%) did not. In multivariable logistic regression analysis, adjusting for sex, BMI and age, not meeting the recommendations was associated with a higher fatigue score (CIS Total Score; OR 1.04, 95%CI 1.01, 1.07) but not with poorer sleep quality (PSQI Total Score; OR 0.99, 95%CI 0.80, 1.21).

Chapter 6 describes fatigue, participation and health-related quality of life (HRQoL) in AYAs (aged 14-25 years) with ABI as reported by AYAs and/or parents in an outpatient, prospective multicenter rehabilitation cohort. Moreover, differences between patient- and parent-reported outcomes and the relationship between fatigue and both participation and quality of life were investigated. The survey included the PedsQL™ MFS, Child and Adolescent Scale of Participation (CASP; 0-100, higher scores indicating better participation), and PedsQL™ Generic Core Scales (0-100, higher scores indicating higher HRQoL). Data was used from one rehabilitation center with 64 patients participating in the study (47 with TBI and 17 with NTBI); median age was 17.6 years (IQR 16.2-20.0), and time since injury 0.8 years (IQR 0.2-2.3). Patients reported high levels of fatigue (median PedsQL™ MFS Total score 44.4 (IQR 34.7-59.7)), limited participation (median CASP Total score 82.5 (IQR 68.8, 92.3)), and diminished HRQoL (median PedsQL™ Generic Core Scales Total score 63.0 (IQR 47.8-78.3)). Multivariable linear regression analyses, adjusted for sex, age at admission (<18 or >18) and type of

injury (TBI/NTBI) showed that more fatigue was significantly associated with more participation restrictions (β 0.64, 95%CI 0.44, 0.85) and diminished HRQoL (β 0.87, 95%CI 0.72, 1.02).

Chapter 7 describes the outcomes of a vocational rehabilitation (VR) program between 2012 and 2017 in unemployed young adults with ABI. Unemployment at the time of injury can be a risk factor for employment after injury. The VR program included a comprehensive assessment, the training of specific skills, counselling by a job coach and the provision of 'buddy' support from volunteering managers from the business or public sector. Adherence to the program and work status were registered during rehabilitation. In 2017 patients received a follow-up questionnaire. Patients' clinical characteristics were extracted from the medical records.
Forty-nine patients started the intervention, of whom 41 completed the follow-up questionnaire. Nineteen (46%) were male, with a median age of 31 years (range 20-49). The median duration of the VR intervention was eight months (IQR 5-12 months). Thirty-one patients (76%) took part in the training with a job coach, whereas 23 (56%) used the services of a buddy. At follow-up, four patients were still in the program, whereas nine patients left the program prematurely, with insufficient financial support for continuation being the main reason (n=6). At follow-up, nine out of the 41 (22%) patients had acquired a paid job of whom seven out of those nine had used a buddy. Six of the patients with paid employment were restricted at work by health problems.

General discussion

Fatigue in children and AYAs with ABI

The occurrence of fatigue in children and AYAs with ABI is common and is reported by patients as well as by their parents, both after TBI and NTBI. We found that the reported levels of fatigue were higher in patients with mild TBI (mTBI) compared to orthopedic controls, but only for the dimension concentration (Chapter 4). Furthermore, the reported levels of fatigue were higher in the cohorts recruited in the rehabilitation centers (Chapters 3 and 6) than the cohorts recruited in the hospitals (Chapters 2, 4 and 5).
Fatigue can be experienced as a physical or mental problem, or a combination of both. Therefore, in this thesis multidimensional aspects of fatigue were evaluated, with either the PedsQL™ MFS (Chapters 2 and 6) or the CIS (Chapters 3, 4 and 5).
Regarding determinants of fatigue in AYAs with ABI, in this thesis older age was significantly associated with higher fatigue levels in one study (Chapter 2). Fatigue was found to be independent of severity of injury (Chapters 2 and 3) as well as sex (Chapter 2).

These results regarding occurrence and determinants of fatigue are in line with other studies[1-4] with the risk of ongoing fatigue in children and AYAs with ABI,[5-7] specifically in females.[3] However, other studies found fatigue to be related to more severe injuries,[8] but not age.[3] These discrepancies are possibly due to differences in included injuries, such as mild TBI, the population (hospital versus rehabilitation setting) as well as age (including very young children or young adults). The association between higher fatigue levels and decreased HRQoL found in this thesis (Chapters 2 and 6) is in line with findings of a study in an adult TBI population.[9]
The added value of the current thesis is the inclusion of various cohorts from different settings that were assessed in a similar way. This enables comparisons of different age groups from different settings with different levels of ABI severity. Ideally, to optimize comparison, data should be collected prospectively in an identical manner in all age groups with ABI and in all settings.

Fatigue in relation to physical activity and participation in AYAs with ABI

The results of the studies included in this thesis suggest that the physical activity (PA) level of AYAs with ABI, measured with the Activity Questionnaire for Adults and Adolescents (AQuAA), is relatively low, and many AYAs do not meet the Dutch Health Enhancing Physical Activity recommendations (D-HEPA) (Chapters 3, 4 and 5). The proportions of inactive patients were however similar to the general population of AYAs. PA levels were lower in the rehabilitation cohort (Chapter 3) compared to the hospital-based cohort (Chapters 4 and 5).
Comparisons to the literature are difficult to make since the focus of outcome measures used to assess physical (in)activity is based on different aspects of activity and participation. Some studies focus on the time needed to return to sport activities,[10] others on participation in activities[11] and use of exercise interventions[12] to improve outcomes but relatively few studies focus on the actual time spent on activities. This study used a questionnaire to measure physical activity levels. Ideally, questionnaires and objective measurements, such as accelerometers, should be used to get the most thorough results.
The studies in this thesis show that dimensions of fatigue are related to PA levels in AYAs with ABI. Higher scores on the CIS subscales motivation and physical activity were associated with not meeting the D-HEPA recommendations in a rehabilitation cohort (Chapter 3) while higher scores on the CIS subscale general fatigue were associated with not meeting the D-HEPA recommendations in a hospital-based cohort (Chapter 5). The CIS subscale concentration was not associated with meeting or not meeting the D-HEPA recommendations in either cohort. The relationship between sleep and PA is questionable. Our study (Chapter 5) found, similar to a study with healthy

children[13], no relationship, while a pediatric oncology study found that higher PA levels were associated with better sleep.[14]
In the general population, attention for creating a lifelong active lifestyle is growing. The results of this thesis support what is known about physical activity in adolescence and young adulthood. However, it can be concluded that the rehabilitation patient group in particular may have an increased risk for reduced PA and that fatigue and PA may be inter-related. Findings of which clinicians should be aware.

Participation in children and AYAs with ABI

This thesis demonstrated that children and AYAs with ABI reported participation restrictions at home, school and in the community. More patient-reported fatigue was associated with more participation restrictions in an outpatient rehabilitation cohort (Chapter 6) as well as parent-reported participation restrictions in a hospital cohort (Chapter 2). Participation restrictions were more severe in the cohort recruited in the rehabilitation center (Chapter 6) than the cohort recruited in the hospitals (Chapter 2). Overall in research, it has been found that significantly more children and adolescents with ABI have limitations in social relations, peer social-play at school and engagement in organized community, social and civic areas of life than their healthy peers.[11, 15] These participation problems are persistent[16] and do not decrease over time.[17] Relationships between fatigue and participation as explicit outcomes in AYAs have not been studied before, in contrast to general problems in movement or sensory functioning.[18, 19]

Work in AYAs with ABI

In the current thesis the vocational rehabilitation (VR) program Brains4U, including a comprehensive assessment followed by training of specific skills and counselling by a "buddy" and job coach, proved to be a promising program for AYAs who were unemployed at onset of ABI. In our study, 22% were employed in paid work after the program, compared to return to work rates after VR interventions in adults with ABI of 41-80%.[20-24] Given the fact that not having paid employment at the time of ABI is a risk factor for not returning to work,[25] the results observed in the present study are quite favorable. Acquiring paid employment is also important as it can result in the reduction in the number of years receiving social benefits. The assignment of a buddy (managers deploying their business network), constituted a distinctive element in our VR program, of which the added value must be further examined.

Methodological considerations

Measuring health status and quality of life in children and AYAs with ABI over time

Since the consequences of ABI may last over time, it is important to use outcome measures that can be used continuously throughout the lifespan. By doing so, it is possible to compare outcomes between and across ages and monitor outcomes longitudinally. In this respect, the PedsQL™ is a suitable outcome measure, as child and adolescent (2-18 years) and young adult (18-25 years) versions are available for the various modules. These versions were created to provide continuity of HRQOL measurement over time. The items within the age-appropriate versions are essentially identical, but are differing primarily in developmental appropriate language or wording (e.g. adolescents vs. young adults or school vs. study).[26] In the studies described in Chapters 2 and 6 we used the child version (2-18 years) of the PedsQL™ Generic Core Scales for all patients older than 18 years, including young adults. In hindsight we should have used the young adult version for patients older than 18 years, as the Dutch young adult version of this scale was already available[27] at the time we started our research. It can be argued that by not using age-appropriate versions of the PedsQL™ the results of studies including patients outside the age-appropriate range may not be valid. However, the impact of not using the age-appropriate version may be limited for several reasons. First, as clearly described by the developers Varni and Limbers,[26] differences between the various versions are minor, concerning only small differences in language, while the number of items and the concept of their contents are identical. Second, in the literature, including recent publications, the use of age-appropriate versions of the PedsQL™ Generic Core Scales is not explicitly stated in relatively many studies, with the specific references to the translated versions for the different age groups lacking.[28-30] Thirdly, whereas in the study described in Chapter 6, 41% of patients were over 18, in Chapter 2 the effect of not using an age-appropriate version is likely to be very small since only two out of the 88 patients were 18 years or older. Nevertheless, it is concluded that the use of the right translated and age-appropriate versions of the PedsQL™ is recommended for use in future research by our and other research groups.

Recruitment

As shown in the results in our studies, it is difficult to recruit children and AYAs with ABI for research purposes. This may be due to the fact that it is a very heterogeneous group, often restricted in energy levels, with impaired neurocognitive competencies (e.g., planning, memory) and psycho-social problems (e.g., post-traumatic stress disorder, family situations, or stress in general). This can explain the difficulty to include patients and retain their participation in a research project. In particular, collecting

data from a hospital population proved to be difficult when patients and/or parents were approached months after injury.

Implications for future research

Although this thesis has increased the knowledge on AYAs with ABI, future research is required to further decrease the knowledge gap regarding fatigue, PA, and participation outcomes in children and AYAs with ABI. Selecting the appropriate measurement instruments for these outcomes and comparing the results with the literature proved to be difficult in our studies. International consensus on outcome measures that are relevant for this patient group would help to compare and merge data from different (international) cohorts. Future studies should collect longitudinal data from the moment of injury with longer follow-up periods for patients with persisting symptoms; pre-injury data should be collected shortly after injury.

In addition, more innovative research methods may suit this age and diagnose group better, such as using social media for the administration of questionnaires. Since cohorts of patients with specific types of ABI (e.g., brain tumors) are relatively small it is recommended to initiate research in close collaboration with other specialists and (inter)national consortia to increase cohort sizes.

In addition, regarding the measurement instruments to be used in longitudinal research for fatigue, PA and participation, the use of instruments with validated, age-appropriate versions is highly recommended. The PedsQL™ Generic Core Scales and Multidimensional Fatigue Scale are such instruments and therefore very suitable to monitor health-related quality of life and fatigue over time.[26, 31-33]

With respect to interventions to increase PA and/or decrease fatigue, it remains to be established which aspect should be the primary target for treatment. In addition, objective measures to assess PA (e.g., accelerometers, wearables) in a valid and reliable manner are recommended.[34] Also systematically identifying specific barriers and facilitators for PA in this specific patient group and identifying triggers for enhancing PA, such as motivation, self-regulation skills, sensitivity to rewards, social support and other environmental facilitators is necessary.[35] The patient perspective should also be included in the development of such interventions.

Regarding possible interventions to decrease participation restrictions, we focused on a work-related rehabilitation program in a group of young patients without work at time of injury. In a next step, the program (Brains4U) must be evaluated by means of an appropriate study design, taking into account the effectiveness, the costs and the satisfaction of patients, but also paying attention to the evaluation of unpaid employment. Furthermore, research focusing on AYAs with paid employment at time of injury and return to work after ABI is necessary.

Implications for clinical practice

This thesis shows that children and AYAs with ABI have considerable problems within several domains of functioning. Therefore, tailored and structured care is needed for AYAs with ABI. The Dutch Health Care Standard [In Dutch: Zorgstandaard],[36] developed by Dutch pediatric neurologists and physiatrists, describes the recommended care for the pediatric and adolescent TBI patient in a structured manner and can be used as a clinical guideline in optimizing (rehabilitation) care for the target population. Moreover, this standard advocates structural attention for follow-up of the consequences of TBI regardless of its severity and to refer children and AYAs to the most appropriate health professional.

Furthermore, this thesis demonstrates that structured assessment and follow-up of fatigue is vital and thereby supports the goals of the 'Zorgstandaard'. Different cohorts in this thesis (age, severity of injury and clinical setting) present fatigue as a multidimensional symptom with various intensities and impact within individuals as well as the whole ABI group and support the use of structured assessment and follow-up of multiple dimensions of fatigue in all patients with ABI irrespective of severity, setting or time since injury. An appropriate instrument to assess multiple dimensions of fatigue is the PedsQL™ MFS, differentiating between general/physical fatigue, sleep/rest fatigue and cognitive fatigue. The PedsQL™ MFS will be implemented for AYAs in the Netherlands through the Brain Injury and Youth Taskforce (HeJ). It is important that clinical choices and care pathways are linked to assessment results.

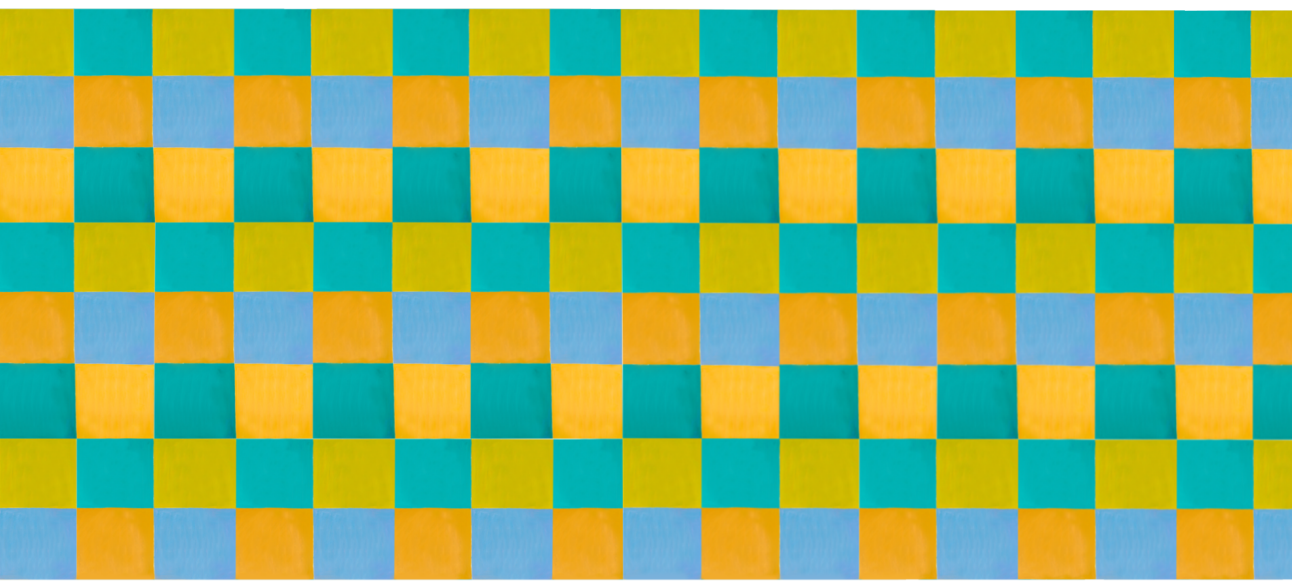
In hospital-based as well as rehabilitation-based cohorts, this thesis has found higher fatigue levels associated with lower physical activity levels, more participation restrictions and diminished HRQoL. Targeting fatigue during rehabilitation treatment can thus potentially improve participation and HRQoL. Developing a model of fatigue after ABI in the AYA population, distinguishing between physical and mental fatigue, as well including relationships with PA and participation, is recommended as an important future step. This model can be used to tailor rehabilitation treatment to either provide a physical program such as graded activity or sub-threshold training[37] and/or a mental/psychological approach such cognitive behaviour therapy[38] or Acceptance and Commitment Therapy.[39]

The results of this thesis show that vocational rehabilitation (VR) programs are promising and relevant for the AYA population. In the clinical follow-up of AYAs with ABI more attention should be given to employment, for those with paid work and those without work at the time of injury. Furthermore, improvement and implementation of evidence based VR programs for the AYA population with ABI including those with mild TBI, is needed.

References

1. Gagner C, Landry-Roy C, Lainé F, Beauchamp M. Sleep-wake disturbances and fatigue after pediatric traumatic brain injury: A systematic review of the literature. *J Neurotrauma*. 2015;Oct 15;32(20):1539-52.
2. Crichton A, Oakley E, Babl F, et al. Predicting fatigue 12 months after child traumatic brain injury: child factors and postinjury symptoms. *J Int Neuropsychol Soc*. 2017;23:1-13.
3. Norup A, Svendsen S, Doser K, et al. Prevalence and severity of fatigue in adolescents and young adults with acquired brain injury: A nationwide study. *Neuropsychol Rehabil*. 2019;29(7):1113-1128.
4. Wilkinson J, Marmol N, Godfrey C, et al. Fatigue following paediatric acquired brain injury and its impact on functional outcomes: A systematic review. *Neuropsychol Rev*. 2018;28(1):73-87.
5. Sumpter R, Brunklaus A, McWilliam R, Dorris L. Health-related quality-of-life and behavioural outcome in survivors of childhood meningitis. *Brain Inj*. 2011; 25(13-14):1288-95.
6. Falk A. A nurse-led paediatric head injury follow-up service. *Scand J Caring Sci*. 2013;Mar;27(1):51-6.
7. Aaro Jonsson C, Emanuelson I, Smedler A. Variability in quality of life 13 years after traumatic brain injury in childhood. *Int J Rehabil Res*. 2014;Dec;37(4):317-22.
8. Crichton A, Anderson V, Oakley E, et al. Fatigue following traumatic brain injury in children and adolescents: A longitudinal follow-up 6 to 12 months after injury. *J Head Trauma Rehabil*. 2018;33(3):200-209.
9. Cantor J, Ashman T, Gordon W, et al. Fatigue after traumatic brain injury and its impact on participation and quality of life. *J Head Trauma Rehabil*. 2008;23(1):41-51.
10. Cancelliere C, Hincapié C, Keightley M, et al. Systematic review of prognosis and return to play after sport concussion: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil*. 2014;Mar;95(3 Suppl):S210-29.
11. Anaby D, Law M, Hanna S, Dematteo C. Predictors of change in participation rates following acquired brain injury: results of a longitudinal study. *Dev Med Child Neurol*. 2012;54(4):339-46.
12. Baque E, Barber L, Sakzewski L, Boyd R. Randomized controlled trial of web-based multimodal therapy for children with acquired brain injury to improve gross motorcapacity and performance. *Clin Rehabil*. 2017;31(6):722-732.
13. Sorić M, Starc G, Borer K, et al. Associations of objectively assessed sleep and physical activity in 11-year old children. *Ann Hum Biol*. 2015;42(1):31-7.
14. Orsey A, Wakefield D, Cloutier M. Physical activity (PA) and sleep among children and adolescents with cancer. *Pediatr Blood Cancer*. 2013;60:1908-1913.
15. van Tol E, Gorter J, DeMatteo C, Meester-Delver A. Participation outcomes for children with acquired brain injury: a narrative review. *Brain Inj*. 2011;25(13-14):1279-87.
16. Catroppa A, Anderson V, Morse S, et al. Outcome and predictors of functional recovery 5 years following pediatric traumatic brain injury. *J Pediatr Psychol*. 2008;33:707–718.
17. Rivara F, Vavilala M, Durbin D, et al. Persistence of disability 24 to 36 months after pediatric traumatic brain injury: a cohort study. *J Neurotrauma*. 2012; 29(15):2499-504.
18. Bedell G, Dumas H. Social participation of children and youth with acquired brain injuries discharged from inpatient rehabilitation: a follow-up study. *Brain Inj*. 2004;18(1):65-82.
19. Galvin J, Froude E, McAleer J. Children's participation in home, school and community life after acquired brain injury. *Aust Occup Ther J*. 2010;57(2):118-26.
20. Bonneterre V, Pérennou D, Trovatello V, et al. Interest of workplace support for returning to work after a traumatic brain injury: a retrospective study. *Ann Phys Rehabil Med*. 2013;56(9-10):652-662.
21. Buffington A, Malec J. The vocational rehabilitation continuum: maximizing outcomes through bridging the gap from hospital to community-based services. *Jnl of Head Trauma Rehabilitation*. 1997;12(5): 1-13.

22. Malec J, Moessner A. Replicated positive results for the VCC model of vocational intervention after ABI within the social model of disability. *Brain Inj*. 2006;20(3):227-236.
23. Chamberlain E, Weir J, Berry A, et al. Effectiveness of vocational rehabilitation following acquired brain injury: preliminary evaluation of a UK specialist rehabilitation programme. *Brain Inj*. 2006;20(11):1119–1129.
24. Wehman P, Kreutzer J, West M, et al. Return to work for persons with traumatic brain injury: a supported employment approach. *Arch Phys Med Rehabil*. 1990;71(13):1047-52.
25. Donker-Cools B, Daams J, Frings-Dresen M. Effective return-to-work interventions after acquired brain injury: A systematic review. *Brain Inj*. 2016;30(2):113–131.
26. Varni J, Limbers C. The PedsQL 4.0 Generic Core Scales Young Adult Version: feasibility, reliability and validity in a university student population. *J Health Psychol*. 2009;May;14(4):611-22.
27. Limperg P, Haverman L, van Oers H, et al. Health related quality of life in Dutch young adults: psychometric properties of the PedsQL generic core scales young adult version. *Health Qual Life Outcomes*. 2014;Jan 18;12:9.
28. Daskas N, Sharples P, Likeman M, et al. Growth hormone secretion, fatigue and quality of life after childhood traumatic brain injury. *Eur J Endocrinol. 2019*. 2019; Jul 1. pii: EJE-19-0166.R3.
29. Recklitis C, Liptak C, Footer D, et al. Prevalence and Correlates of Pain in Adolescent and Young Adult Survivors of Pediatric Brain Tumors. *J Adolesc Young Adult Oncol*. 2019; Dec;8(6):641-648.
30. Sinoo C, de Lange I, Westers P, et al. Behavior problems and health-related quality of life in Dravet syndrome. *Epilepsy Behav*. 2019;Jan;90:217-227.
31. Varni J, Burwinkle T, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr*. 2003;Nov-Dec;3(6):329-41.
32. Varni J, Burwinkle T, Szer I. The PedsQLMultidimensional Fatigue Scale in pediatric rheumatology: Reliability and validity. *Journal of Rheumatology*. 2004;31:2494-2500.
33. Varni J, Limbers C. The PedsQL Multidimensional Fatigue Scale in young adults: feasibility, reliability and validity in a University student population. *Qual Life Res*. 2008;Feb;17(1):105-14.
34. Baque E, Sakzewski L, Trost S, et al. Validity of accelerometry to measure physical activity intensity in children with an acquired brain injury. *Pediatr Phys Ther*. 2017;29(4):322-329.
35. Driver S, Ede A, Dodd Z, et al. What barriers to physical activity do individuals with a recent brain injury face? *Disabil Health J*. 2012;5(2):117-25.
36. Gijzen R, Zadoks J. [*Zorgstandaard Traumatisch Hersenletsel Kinderen & Jongeren*]. 2016, Hersenstichting: The Hague, The Netherlands.
37. Leddy J, Haider M, Ellis M, Willer B. Exercise is medicine for concussion. *Curr Sports Med Rep*. 2018;17(8):262-270.
38. Zedlitz A, Rietveld T, Geurts A, Fasotti L. Cognitive and graded activity training can alleviate persistent fatigue after stroke: a randomized, controlled trial. *Stroke*. 2012;43(4):1046-51.
39. Gómez-de-Regil l, Estrella-Castillo D, Vega-Cauich J. Psychological intervention in traumatic brain injury patients. *Behav Neurol*. 2019;6937832.



Chapter 9

Nederlandse samenvatting en discussie

Vermoeidheid, fysieke activiteit en participatie van adolescenten en jongvolwassenen met niet-aangeboren hersenletsel

Samenvatting

Niet-aangeboren hersenletsel (NAH), traumatisch of niet-traumatisch, komt relatief vaak voor bij zowel kinderen als adolescenten en jong volwassenen (AYAs: Adolescents and Young Adults). Vaak leidt NAH tot beperkingen in neuropsychologische functies, activiteiten (inclusief algehele fysieke activiteit) en participatie, vooral in vergelijking met gezonde leeftijdsgenoten. Er is relatief weinig wetenschappelijk onderzoek gedaan naar fysieke activiteit en participatie van AYAs met NAH. Daarnaast is vermoeidheid een onzichtbaar, multidimensionaal gevolg van NAH dat nog onderbelicht is in wetenschappelijk onderzoek in deze leeftijdsgroep.

In **Hoofdstuk 1** worden definities, epidemiologie en etiologie van NAH, in het bijzonder bij AYAs, beschreven. Vervolgens wordt een overzicht van de literatuur over vermoeidheid, fysieke activiteit en participatie voor deze doelgroep gepresenteerd. De hieruit voortkomende doelstellingen van het onderzoek in dit proefschrift worden in dit hoofdstuk als volgt beschreven:

1. Beschrijven van vermoeidheid, fysieke inactiviteit en participatierestricties en hun onderlinge relaties in ziekenhuis- en revalidatiecohorten van kinderen en AYAs met NAH.
2. Beschrijven van een arbeidsrevalidatieprogramma en de resultaten hiervan bij AYAs met NAH die (nog) geen betaald werk hebben.

Hoofdstuk 2 betreft een multicenter studie waarin de ernst van vermoeidheid en aan vermoeidheid gerelateerde factoren bij kinderen en AYAs met NAH werden onderzocht. Dit onderzoek werd verricht in een ziekenhuiscohort van patiënten in de leeftijd van 4-20 jaar die in het ziekenhuis de diagnose NAH kregen (traumatisch of niet-traumatisch) en hun ouders. Alle ouders en patiënten vanaf 8 jaar vulden, gemiddeld 24 maanden na ontstaan van het NAH, meerdere vragenlijsten in, waaronder de Pediatric Quality of Life Inventory™ Multidimensional Fatigue Scale (PedsQL™ MFS, score 0-100, hoe lager de score hoe meer vermoeid), met subschalen voor algemene-, slaap/rust- en cognitieve vermoeidheid. Daarnaast werden diverse sociodemografische kenmerken en ziektekenmerken geregistreerd.
Achtentachtig patiënten werden geïncludeerd, met een mediane leeftijd van 11 jaar (Inter Quartile Range (IQR) 7), waarvan 69 met traumatisch en 19 met niet-traumatisch

hersenletsel. Negenenveertig van de 88 patiënten (56%) vulden de PedsQL™ MFS kinderversie in, en 88 ouders de ouderversie. De gemiddelde PedsQL™ MFS totaalscores waren respectievelijk 79.2 (IQR 18.1) en 77.8 (IQR 25.0) voor respectievelijk kinderen/AYAs of ouders. Uit een multivariabele lineaire regressieanalyse bleek dat er een statistisch significante associatie was tussen meer vermoeidheid (lagere ouder gerapporteerde PedsQL™ MFS Totaal Score en/of één of meer subschaal scores) en een niet-traumatische oorzaak van het hersenletsel, hogere leeftijd van het kind en het deel uitmaken van een één ouder gezin.

In **Hoofdstuk 3** wordt een onderzoek naar vermoeidheid en de relatie tussen vermoeidheid en de hoeveelheid fysieke activiteit beschreven, dat plaatsvond in een poliklinisch revalidatiecohort van AYAs met traumatisch hersenletsel. Deze dwarsdoorsnedestudie werd verricht onder patiënten met een leeftijd van 12-39 jaar, met een minimale duur van 6 maanden sinds het hersenletsel, die in het revalidatiecentrum onder behandeling waren (geweest). Deelnemers vulden de Activity Questionnaire for Adults and Adolescents (AQuAA, resultaten gedichotomiseerd voor wel of niet voldoen aan de Nederlandse Norm voor Gezond Bewegen (NNGB)) en de Checklist Individual Strength (CIS, subschalen vermoeidheid (8 vragen, score 8 tot 56, hoe hoger de score hoe meer vermoeid; 40 is de grens voor ernstige vermoeidheid), motivatie (4 vragen, score 4 tot 28, hoe hoger de score hoe minder gemotiveerd), concentratie (5 vragen, score 5 tot 35, hoe hoger de score hoe meer concentratie problemen) en fysieke activiteit (3 vragen, score 3 tot 21, hoe hoger de score hoe minder fysiek actief), Totaal Score (door optelling van de subschalen, score 20 tot 140, hoe hoger de score hoe meer vermoeidheid (gerelateerde) problemen).
Vijftig patiënten werden geïncludeerd, met een gemiddelde leeftijd van 25.0 jaar (SD 7.2): 18 van hen (36%) hadden licht hersenletsel, 13 (26%) matig ernstig hersenletsel en 19 (38%) ernstig hersenletsel. De mediane tijd besteed aan matig tot zwaar intensieve fysieke activiteit was 518 minuten/week (IQR 236-1725) en de mediane tijd besteed aan zittende activiteiten 2728 minuten/week (IQR 1637-3994). Tweeëndertig (64%) van de deelnemers voldeden aan de NNGB. Op basis van de subschaal vermoeidheid van de CIS werden 19 (38%) van de deelnemers geclassificeerd als ernstig vermoeid. In de univariate analyses waar de groep die voldeed aan de NNGB werd vergeleken met de groep die niet voldeed aan de NNGB waren de CIS Total Score en subschalen motivatie en fysieke activiteit significant hoger dan in de groep patiënten die niet voldeed aan de NNGB. In een multivariabele logistische regressieanalyse, waarbij leeftijd, geslacht en Body Mass Index (BMI) werden meegenomen als mogelijke confounding variabelen, waren hogere scores op de subschalen motivatie (minder gemotiveerd) en fysieke activiteit (minder fysiek actief) geassocieerd met het niet voldoen aan de NNGB.

In hoeverre fysieke inactiviteit, beperkingen in participatie of vermoeidheid na traumatisch hersenletsel het gevolg zijn van het trauma op zich, of specifiek van het hersenletsel, is moeilijk vast te stellen. Daarom wordt in **Hoofdstuk 4** een studie beschreven waarin fysieke activiteit, vermoeidheid, en kwaliteit van slaap bij AYAs met licht traumatisch hersenletsel (LTHL) werden vergeleken met een controlegroep van patiënten met een traumatisch orthopedisch letsel (gebroken sleutelbeen, arm of been). In dit onderzoek werden patiënten tussen de 12 en 25 jaar oud, met ofwel een licht-traumatisch hersenletsel of een orthopedisch letsel minimaal 6 maanden na bezoek aan de Spoedeisende Hulp van twee perifere ziekenhuizen gevraagd een set digitale vragenlijsten in te vullen. Naast vragen over sociodemografische gegevens werden de AQuAA (resultaten gedichotomiseerd voor wel of niet voldoen aan de NNGB), CIS (subschalen vermoeidheid, motivatie, concentratie en fysieke activiteit, totaal score 20-140, hoe hoger de score hoe meer vermoeid) en de Pittsburgh Sleep Quality Index (PSQI, score 0-21, hoe hoger de score hoe slechter de slaapkwaliteit) afgenomen.
Negenenveertig patiënten met LTHL (gemiddelde leeftijd 18.4 jaar, SD 3.6) en 54 patiënten met orthopedisch letsel (gemiddelde leeftijd 15.8 jaar, SD 3.2) werden geïncludeerd. De gemiddelde tijd sinds het letsel was 1.6 jaar (SD 0.5) in de LTHL-groep en 1.5 jaar (SD 0.4) in de orthopedische groep. Logistische regressieanalyse, waarin gecorrigeerd werd voor mogelijk confounding variabelen (geslacht, BMI, leeftijd en tijd sinds letsel), toonde aan dat patiënten met LTHL statistisch significant minder vaak aan de NNGB voldeden dan patiënten met orthopedisch letsel (49% vs. 70%, odds ratio (OR) 2.87, 95% betrouwbaarheidsinterval (CI) 1.07, 7.72). Patiënten met LTHL rapporteerden ook meer concentratie-gerelateerde vermoeidheid dan de orthopedische controles (respectievelijk, gemiddeld 19.1 (SD 8.0) en, 13.9 (SD 7.8)). Multivariabele lineaire regressieanalyse, met correctie voor geslacht, BMI, leeftijd en tijd sinds letsel, liet zien dat het hebben van LTHL versus orthopedisch letsel geassocieerd was met aan concentratie gerelateerde vermoeidheid (β 3.98, 95%CI 0.39, 7.56), terwijl de aard van het traumatisch letsel niet met slaapkwaliteit samenhing.

In **Hoofdstuk 5** worden de relaties tussen fysiek activiteitenniveau enerzijds en vermoeidheid en slaapkwaliteit anderzijds onderzocht in hetzelfde ziekenhuiscohort dat beschreven is in Hoofdstuk 4. Deze patiëntenpopulatie bestond uit 49 AYAs met licht-traumatisch hersenletsel, die gemiddeld 1.6 jaar (SD 0.5) na het letsel de vragenlijsten AQuAA, CIS en PSQI invulden.
Vierentwintig en 25 van de 49 deelnemers (49% en 51%) voldeden respectievelijk wel en niet aan de NNGB. Multivariabele logistische regressie waarbij gecorrigeerd werd voor geslacht, BMI en leeftijd toonde dat een hogere vermoeidheidscore (CIS Totaal

Score) geassocieerd was met niet voldoen aan de NNGB (OR 1.04, 95%CI 1.01, 1.07). Een verminderde slaapkwaliteit (PSQI Totaal Score) bleek dat niet te zijn (OR 0.99, 95%CI 0.80, 1.21).

Hoofdstuk 6 beschrijft vermoeidheid, participatie en kwaliteit van leven van AYAs (14-25 jaar) met NAH, zoals ervaren door henzelf en/of hun ouders, gebruikmakend van gegevens die verzameld werden in het kader van een prospectieve multicenter studie. Ook worden de relaties tussen vermoeidheid en participatie, en vermoeidheid en kwaliteit van leven beschreven. In het dwarsdoorsnede onderzoek werden de volgende vragenlijsten afgenomen: de PedsQL™ MFS, Child and Adolescent Scale of Participation (CASP, score 0-100, hoe hoger de score hoe beter de participatie), en de PedsQL™ Generic Core Scales (score 0-100, hoe hoger de score hoe beter de kwaliteit van leven). Voor deze studie naar vermoeidheid, participatie en kwaliteit van leven werden gegevens van 64 patiënten uit één revalidatiecentrum geanalyseerd. Zevenenveertig van hen hadden traumatisch en 17 niet-traumatisch hersenletsel, de mediane leeftijd was 17.6 jaar (IQR 16.2-20.0) en de mediane tijd sinds letsel 0.8 jaar (IQR 0.2-2.3). Patiënten rapporteerde hoge niveaus van vermoeidheid (mediane PedsQL™ MFS Totaal score 44.4 (IQR 34.7-59.7)), evenals beperkingen in participatie (mediane CASP Totaal score 82.5 (IQR 68.8-92.3)) en verminderde kwaliteit van leven (mediane PedsQL™ Generic Core Scales Totaal score 63.0 (IQR 47.8-78.3)). Multivariabele lineaire regressieanalyse, waarbij gecorrigeerd werd voor geslacht, leeftijd (<18 of >18) en type letsel (traumatisch of niet-traumatisch letsel), toonde een associatie aan tussen een hogere vermoeidheidsscore en meer participatie restricties (β 0.64, 95%CI 0.44, 0.85) en tussen een hogere vermoeidheidsscore en verminderde kwaliteit van leven (β 0.87, 95%CI 0.72, 1.02).

Hoofdstuk 7 beschrijft de uitkomsten van een arbeidsrevalidatie programma dat tussen 2012 en 2017 aangeboden werd aan jongvolwassenen met NAH die gerevalideerd hadden en geen betaald werk hadden. Juist het ontbreken van een relatie met de arbeidsmarkt kan na NAH het verkrijgen of herkrijgen van betaald werk bemoeilijken. Het arbeidsrevalidatie-programma omvatte een uitgebreide assessment, het zo nodig inzetten van revalidatie-interventies, het oefenen van specifieke vaardigheden gericht op het ver- of herkrijgen van betaald werk, gesprekken met een jobcoach en ondersteuning door een vrijwilliger (manager uit het bedrijfsleven of overheid die als “buddy” functioneerde). Zowel het voltooien van het programma als het verkrijgen van werk werden geregistreerd tijdens de deelname aan het programma. Daarnaast ontvingen deelnemers in 2017 een follow-up vragenlijst. Relevante patiëntkenmerken werden uit de medische dossiers gehaald.

Negenenveertig patiënten startten met het programma waarvan 41 de follow-up vragenlijsten hebben ingevuld. Hun mediane leeftijd was 31 jaar (range 20-49), 19 (46%) waren man. De mediane duur van het programma was 8 maanden (IQR 5-12 maanden). Eénendertig patiënten (76%) maakten gebruik van een jobcoach en 23 (56%) van een buddy. Op het moment van follow-up hadden vier patiënten het programma nog niet afgerond en negen patiënten hadden het programma vroegtijdig verlaten, waarbij onvoldoende financiële middelen de voornaamste oorzaak vormde (n=6). Ten tijde van de follow-up hadden negen van de 41 patiënten (22%) betaald werk, waarbij zeven van die negen gebruik hadden gemaakt van een buddy. Zes van hen ervaarden gezondheidsproblemen bij de uitvoering van hun werk.

Algemene discussie

Vermoeidheid bij kinderen en AYAs met NAH

Bij kinderen en AYAs met NAH (traumatisch of niet-traumatisch) komt vermoeidheid veel voor, en wordt dit gerapporteerd door zowel patiënten zelf als hun ouders. Onderzoek beschreven in dit proefschrift liet zien dat bij AYAs met licht-traumatisch hersenletsel met name concentratie-gerelateerde vermoeidheid vaker voorkwam dan bij vergelijkbare patiënten met orthopedisch letsel (Hoofdstuk 4). Verder bleek dat gemiddelde zelf-gerapporteerde vermoeidheidsscores hoger waren in de cohorten van patiënten die gerekruteerd waren in revalidatiecentra (Hoofdstukken 3 en 6) dan in de ziekenhuiscohorten (Hoofdstukken 2, 4 en 5).

Vermoeidheid kan worden ervaren als een fysiek of mentaal probleem, of een combinatie daarvan. Daarom is in dit proefschrift gekozen voor het gebruik van multidimensionale uitkomstmaten voor vermoeidheid, namelijk de PedsQL™ MFS (Hoofdstukken 2 en 6) en de CIS (Hoofdstukken 3, 4, en 5).

Ten aanzien van de determinanten van vermoeidheid *binnen* de groep patiënten met NAH werd naast de setting (ziekenhuis of revalidatiecentrum) in dit proefschrift een associatie gevonden tussen hogere leeftijd en meer ervaren vermoeidheid in één studie (Hoofdstuk 2). De mate van ervaren vermoeidheid bleek niet samen te hangen met de ernst van het letsel (Hoofdstukken 2 en 3) noch geslacht (Hoofdstuk 2).

Bovengenoemde resultaten over het voorkomen en de determinanten van vermoeidheid zijn grotendeels vergelijkbaar met de literatuur,[1-4] waarin op de lange termijn een verhoogd risico op vermoeidheid wordt gerapporteerd bij kinderen en AYAs met NAH,[5-7] met name bij meisjes.[3] In tegenstelling tot onze uitkomsten werden in andere studies relaties tussen vermoeidheid en ernst van het hersenletsel[8] gevonden, maar niet met leeftijd[3]. Deze verschillen zijn mogelijk te verklaren door verschillen in

inclusiecriteria tussen de studies, bijvoorbeeld ten aanzien van de ernst van het hersenletsel, de setting (ziekenhuis versus revalidatiecentrum), de leeftijd of de tijd sinds het ontstaan van het letsel. De in dit proefschrift gevonden relatie tussen ernstiger vermoeidheid en mindere kwaliteit van leven (Hoofdstukken 2 en 6) is vergelijkbaar met de resultaten van een studie onder volwassen patiënten met traumatisch hersenletsel.[9]

De toegevoegde waarde van de resultaten van de studies beschreven in dit proefschrift betreft met name de bevindingen die specifiek zijn voor de leeftijdsgroep AYAs en het betrekken van patiënten uit verschillende settings (ziekenhuis, revalidatie), gebruikmakend van zoveel mogelijk dezelfde meetinstrumenten. Hierdoor kunnen resultaten van verschillende leeftijdsgroepen in verschillende settings en met verschillende ernst van letsel tot op zekere hoogte met elkaar worden vergeleken. Idealiter zouden voor een dergelijke vergelijking prospectief en op identieke wijze in alle leeftijdsgroepen en in alle settings bij kinderen en AYAs met NAH gegevens moeten worden geregistreerd.

Vermoeidheid in relatie tot fysieke activiteit en participatie bij AYAs met NAH

De resultaten van de studies in dit proefschrift suggereren dat de hoeveelheid fysieke activiteit van AYAs met NAH, gemeten met de AQuAA, relatief laag is en dat een aanzienlijk deel van hen niet voldoet aan de NNGB (Hoofdstukken 3, 4 en 5). Het aandeel inactieve patiënten is echter wel vergelijkbaar met gezonde leeftijdsgenoten in de algemene Nederlandse bevolking. Wel lieten de onderzoeken in dit proefschrift zien dat de hoeveelheid fysieke activiteit lager was in het revalidatiecohort (Hoofdstuk 3) dan in het ziekenhuiscohort (Hoofdstukken 4 en 5).

Vergelijkingen met de literatuur zijn moeilijk te maken omdat in onderzoek naar fysieke activiteit veel verschillende uitkomstmaten gebruikt worden om fysieke (in)activiteit te meten, en omdat studies uiteenlopen ten aanzien van hun focus op functies, activiteiten en/of participatie. Zo legde een aantal studies bijvoorbeeld de nadruk op sporthervatting,[10] terwijl ander onderzoek vooral gericht was op participatie in activiteiten[11] en nog een andere studie op oefeninterventies.[12] Weinig studies hebben echter de daadwerkelijke tijd die besteed wordt aan het uitvoeren van fysieke activiteiten gemeten. In ons onderzoek werd daartoe gebruik gemaakt van een vragenlijst. Idealiter worden vragenlijsten gecombineerd met een objectief meetinstrument, zoals accelerometrie, om een compleet beeld te krijgen van het activiteitenniveau.

De studies in dit proefschrift laten zien dat de verschillende dimensies van vermoeidheid gerelateerd zijn aan de hoeveelheid fysieke activiteit van AYAs met NAH. Hogere scores op de subschalen motivatie en fysieke activiteit van de CIS bleken geassocieerd te zijn

met het niet voldoen aan de NNGB in een revalidatiecohort (Hoofdstuk 3) terwijl hogere scores op de subschaal algemene vermoeidheid van de CIS waren geassocieerd met het niet voldoen aan de NNGB in een ziekenhuiscohort (Hoofdstuk 5). De subschaal concentratie van de CIS was niet geassocieerd met al dan niet voldoen aan de NNGB in beide cohorten. Ten aanzien van de relatie tussen slaap en fysieke activiteit waren de resultaten van de studie beschreven in hoofdstuk 5 vergelijkbaar met een studie onder gezonde kinderen[13] waarin geen relatie tussen slaap en fysieke activiteit werd aangetoond, terwijl een kinderoncologische studie wel een associatie vond tussen betere slaap en meer fysieke activiteit.[14]
In de algemene bevolking wordt veel aandacht besteed aan het belang van een actieve leefstijl. Dit proefschrift laat zien dat het belangrijk is te beseffen dat een aanzienlijk deel van de patiënten die revalideren of gerevalideerd hebben na NAH onvoldoende fysiek actief is, waarbij de mate van vermoeidheid en de hoeveelheid fysieke activiteit enigszins samenhangen. Met deze bevinding dient rekening gehouden te worden bij het volgen en behandelen van deze doelgroep.

Participatie van kinderen en AYAs met NAH

Dit proefschrift beschrijft dat kinderen en AYAs met NAH thuis, op school en in hun leefomgeving zelf-gerapporteerde participatiebeperkingen ervaren. In een poliklinisch revalidatiecohort bleek méér patiënt-gerapporteerde vermoeidheid geassocieerd te zijn met méér ervaren participatierestricties (Hoofdstuk 6). In een ziekenhuis cohort bleek méér ouder-gerapporteerde vermoeidheid geassocieerd te zijn met méér ervaren participatierestricties (Hoofdstuk 2). Tevens bleek dat meer en ernstiger participatierestricties werden ervaren door de patiënten in een poliklinisch revalidatiecohort (Hoofdstuk 6) dan in een ziekenhuiscohort (Hoofdstuk 2).
In het algemeen blijkt uit de literatuur dat kinderen en AYAs met NAH significant meer beperkingen ervaren in sociale relaties, spelen met leeftijdsgenoten op school, en participeren in gemeenschapsactiviteiten dan gezonde leeftijdsgenoten.[11, 15] Deze beperkingen zijn chronisch[16] en verminderen niet met de tijd.[17] De relaties tussen participatie en vermoeidheid als expliciete uitkomsten bij AYAs zijn tot op heden niet bestudeerd, in tegenstelling tot motorische en sensorische problemen.[18, 19]

Arbeidsparticipatie van AYAs met NAH

In dit proefschrift is het arbeidsrevalidatieprogramma Brains4U bij AYAs met NAH die geen betaald werk hadden onderzocht. Het geobserveerde percentage van 22% van de deelnemers met betaald werk na het programma lijkt relatief laag vergeleken met de gerapporteerde werkhervattingspercentages van 41-80% na arbeidsrevalidatie van volwassenen met NAH.[20-24] Echter, onze resultaten moeten worden gezien in het licht

van het gegeven dat het niet hebben van werk ten tijde van het letsel een risicofactor is voor het niet verkrijgen van werk na letsel.[25] Daarnaast betekent het verkrijgen van werk dat er mogelijk vele jaren geen of minder een beroep op een uitkering gedaan hoeft te worden. De toegevoegde waarde van de inzet van een manager als "buddy" (manager die gebruik maakt van zijn/haar zakelijke connecties), een onderscheidend kenmerk van dit arbeidsrevalidatie programma, moet nader worden onderzocht.

Methodologische aspecten

Het over de tijd meten van gezondheid en kwaliteit van leven in kinderen en AYAs

Omdat de gevolgen van NAH jarenlang kunnen persisteren is het belangrijk om meetinstrumenten te gebruiken die gedurende het leven gebruikt kunnen worden. Door dit te doen is het mogelijk om uitkomsten tussen patiënten in verschillende leeftijdsfases en over de tijd te monitoren. De PedsQL™ is een meetinstrument dat op deze manier gebruikt kan worden, met leeftijdsspecifieke versies voor kinderen en adolescenten (2-18 jaar) en jong volwassenen (18-25 jaar). Het aantal en de inhoud van de vragen in de verschillende versies zijn identiek, er zijn echter verschillen in de toepassing van leeftijdsspecifieke terminologie en taalgebruik.[26] In de studies in Hoofdstuk 2 en 6 hebben we voor patiënten boven de 18 jaar de kinderversie (2-18 jaar) van de PedsQL™ Generic Core Scales gebruikt. Achteraf gezien hadden wij in deze leeftijdsgroep beter de jong volwassen versie van de vragenlijst kunnen gebruiken, die reeds in Nederlands beschikbaar was toen ons onderzoek van start ging.[27] Mogelijk zijn de resultaten die verkregen zijn in de groep 18 plussers daarom minder valide dan bij het gebruik van de correcte versie. Echter, de impact van het niet gebruiken van de leeftijdsspecifieke versie voor de 18 plussers lijkt om meerdere redenen beperkt. Ten eerste zijn, zoals de ontwikkelaars Varni en Limbers[26] zelf beschrijven, de verschillen tussen de PedsQL™ versies minimaal, met alleen verschillen in het taalgebruik, terwijl het aantal vragen en de inhoud van de vragen identiek zijn. Ten tweede wordt in meerdere studies, waaronder ook recente literatuur, niet expliciet vermeld of er gebruik gemaakt is van leeftijdsspecifieke versies van de PedsQL™ Generic Core Scales, waarbij ook de referenties naar de vertaalde versies van de leeftijdsspecifieke versies ontbreken.[28-30] Ten derde waar in het onderzoek beschreven in hoofdstuk 6 41% van de patiënten 18 jaar of ouder waren, was het effect van het gebruik van de onder-18 versie in hoofdstuk 2 zeer klein omdat slechts 2 van de 88 patiënten 18 jaar of ouder waren waarmee de invloed van het gebruik van de niet leeftijdsadequate versie zeker in die studie te verwaarlozen lijkt. Desalniettemin kan er geconcludeerd worden dat het gebruik van vertaalde en leeftijdsspecifieke versies van de PedsQL™ sterk aan te raden is in toekomstig onderzoek door onze en andere onderzoeksgroepen.

Rekrutering

Uit de beschrijving van de resultaten van de verschillende door ons uitgevoerde onderzoeken bij kinderen en AYAs kan worden opgemaakt hoe lastig het is om patiënten met NAH te rekruteren. Dit kan veroorzaakt worden door de diversiteit van deze groep, de leeftijdsfase, variatie in het beloop van het herstel, de beperkte belastbaarheid, neurocognitieve stoornissen (zoals geheugen en planning) en psychosociale problemen (zoals post-traumatische stress stoornis, gezinsproblemen of stress in het algemeen). Al deze aspecten kunnen de inclusie, maar ook het volhouden van deelname aan onderzoek, belemmerd hebben. Daarnaast bleek het vooral lastig om data te verzamelen van patiënten die enkele maanden na hun bezoek aan de spoedeisende hulp vanuit de ziekenhuizen geïncludeerd werden.

Implicaties voor toekomstig onderzoek

Hoewel het onderzoek beschreven in dit proefschrift nieuwe kennis heeft opgeleverd, blijft er in het algemeen relatief weinig bekend over vermoeidheid, fysieke activiteit en participatie van kinderen en AYAs met NAH. In toekomstig onderzoek zouden vanaf het eerste moment van letsel/ziekenhuisbezoek longitudinale data verzameld moeten worden gevolgd door een langdurige follow-up om ook lange termijn gevolgen in kaart te kunnen brengen. Gegevens over de gezondheidssituatie van vóór het letsel zouden kort na het ontstaan van het letsel moeten worden verzameld, om “recall bias” te verminderen.

Bij het verzamelen van de data zouden meer innovatieve onderzoeksmethoden gebruikt kunnen worden dan de digitale vragenlijsten die wij hebben toegepast. Methoden die beter bij deze doelgroep passen zijn bijvoorbeeld de inzet van social media. Omdat sommige vormen van NAH relatief zeldzaam zijn, zoals hersentumoren, is het belangrijk om samen te werken met andere onderzoekers en medisch specialisten binnen en buiten Nederland, opdat patiëntenpopulaties van een zekere omvang kunnen worden verkregen. Ook is het selecteren van de juiste meetinstrumenten voor vermoeidheid, fysieke activiteit en participatie een forse uitdaging, gezien de grote verscheidenheid aan uitkomstmaten in de voor dit proefschrift bestudeerde literatuur. Daarbij zijn niet voor alle meetinstrumenten leeftijdsspecifieke versies beschikbaar, hetgeen de vergelijkingen tussen leeftijdsgroepen of het volgen van patiënten over de tijd kan bemoeilijken. Meerdere leeftijdsspecifieke versies zijn er wel voor de PedsQL™ Generic Core Scales[26, 31] en PedsQL™ Multidimensional Fatigue Scale.[32, 33]

Met betrekking tot interventies om fysieke activiteit te bevorderen en/of vermoeidheid te verminderen moet nog onderzocht worden wat de juiste aangrijpingspunten en doelstellingen voor behandeling zijn. Om van dergelijke interventies de effecten te bestuderen is het aan te bevelen om ook objectieve meetinstrumenten voor fysieke

activiteit te gebruiken, bijvoorbeeld accelerometers.[34] Voordat een interventie kan worden ontworpen is een systematische identificatie van specifieke barrières en facilitatoren voor fysieke activiteit in deze doelgroep nodig, met daarbij identificatie van activators (triggers) voor het stimuleren van fysieke activiteit, zoals motivatie, zelfcontrole, gevoeligheid voor beloning, sociale steun en andere omgevings-facilitatoren.[35] Uiteraard moeten vertegenwoordigers van de doelgroep hierbij nauw worden betrokken.
Ook op het gebied van arbeidsrevalidatie voor AYAs met NAH is meer onderzoek nodig. Ons onderzoek richtte zich op het beschrijven en evalueren van het arbeidsrevalidatieprogramma Brains4U bij jonge patiënten die geen betaald werk hadden. In een volgende stap moet Brains4U in een gecontroleerd onderzoeksdesign worden geëvalueerd, waarbij effectiviteit, de kosten en de tevredenheid van de patiënten moeten worden gemeten. Naast betaald werk behoren vrijwilligerswerk of andere doelbewuste dagbestedingskeuzes ook als uitkomsten van een arbeidsrevalidatietraject te worden meegenomen. Ook is meer onderzoek naar terugkeer naar betaald werk voor de groep AYAs die wél werk hadden ten tijde van het ontstaan van NAH gewenst.

Klinische implicaties

Dit proefschrift laat zien dat een aanzienlijk deel van kinderen en AYAs met NAH problemen ervaart in meerdere domeinen van hun functioneren. Om de ervaren problemen en beperkingen te voorkomen of te verminderen is goed onderbouwde en georganiseerde zorg nodig. De Zorgstandaard voor kinderen en AYAs met traumatisch hersenletsel,[36] ontwikkeld in samenwerking met alle betrokkenen, beschrijft de aanbevolen zorg voor kinderen en AYAs met NAH en kan gebruikt worden als richtlijn voor het optimaliseren van zorg voor deze doelgroep. In deze Zorgstandaard wordt aandacht gevraagd voor het vervolgen van de mogelijke gevolgen van NAH, ongeacht de ernst van het letsel, en indien nodig te zorgen voor verwijzing naar de juiste zorgprofessional.
In dit proefschrift wordt bevestigd dat beoordeling en follow-up van vermoeidheidsklachten, zoals beschreven in de Zorgstandaard, van vitaal belang is. Onderzoeken in verschillende patiëntengroepen (variërend in leeftijd, ernst van letsel en klinische omgeving) lieten zien dat vermoeidheid een multidimensionale klacht is, waarvan de intensiteit en impact varieert binnen individuen en binnen de doelgroep. Daarom is een systematische beoordeling en follow-up van de verschillende dimensies van vermoeidheid bij alle patiënten met NAH belangrijk, ongeacht de ernst van letsel, zorgfase of tijd sinds letsel. Een bruikbaar meetinstrument om multidimensionale vermoeidheid te meten is de PedsQL™ MFS, waarin onderscheid wordt gemaakt tussen

algemene/fysieke vermoeidheid, slaap/rust vermoeidheid en cognitieve vermoeidheid. De PedsQL™ MFS wordt door de werkgroep Hersenletsel en Jeugd geïmplementeerd in de zorg voor AYAs. Belangrijk is daarbij wel dat er in de toekomst aan de verschillende scores die worden geobserveerd, klinische beslissingen en zorgtrajecten worden gekoppeld.

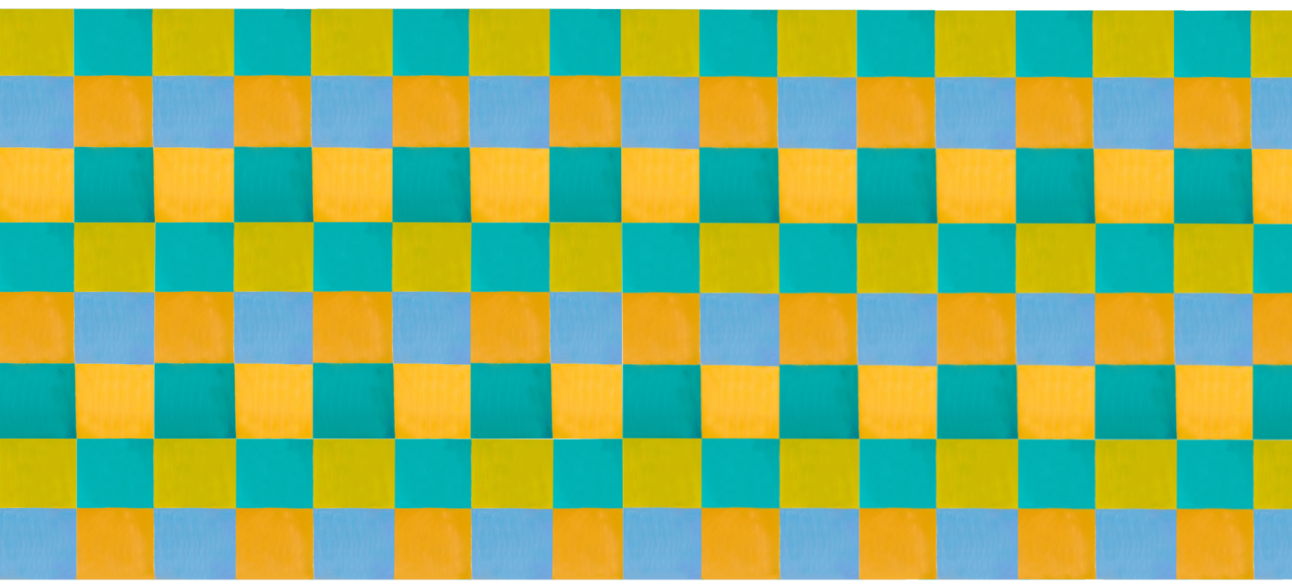
In dit proefschrift werd meermalen gevonden dat meer ervaren vermoeidheid samenhing met minder fysieke activiteit, meer participatie restricties en verminderde kwaliteit van leven. Het is lastig om causale relaties vast te stellen, maar het is denkbaar dat met een behandeling gericht op vermoeidheid ook fysieke activiteit, participatie en kwaliteit van leven zou kunnen verbeteren. Om een dergelijke interventie beter te kunnen onderbouwen is de ontwikkeling van een theoretisch model voor vermoeidheid bij AYAs met NAH noodzakelijk, waarbij onderscheid wordt gemaakt tussen fysieke en mentale vermoeidheid en waarin alle onderlinge relaties met en tussen fysieke activiteit en participatie worden aangegeven. Dit model zou verder gebruikt kunnen worden om de behandeling meer op maat te kunnen aanbieden middels een fysiek programma zoals "graded activity" of "sub-threshold training"[37] en/of een mentale/psychologische benadering zoals cognitieve gedragstherapie[38] of "Acceptance and Commitment Therapy".[39]

De resultaten in dit proefschrift laten zien dat arbeidsrevalidatieprogramma's belangrijk kunnen zijn voor AYAs met NAH. Mogelijk moet er in de klinische follow-up van AYAs met NAH meer aandacht besteed worden aan werk, zowel bij patiënten die wel als (nog) geen werk hadden ten tijde van het hersenletsel. Verder moet er aandacht zijn voor verbetering en vooral de implementatie van bewezen effectieve arbeidsrevalidatieprogramma's voor deze specifieke doelgroep.

References

1. Gagner C, Landry-Roy C, Lainé F, Beauchamp M. Sleep-wake disturbances and fatigue after pediatric traumatic brain injury: A systematic review of the literature. *J Neurotrauma*. 2015;Oct 15;32(20):1539-52.
2. Crichton A, Oakley E, Babl F, et al. Predicting fatigue 12 months after child traumatic brain injury: child factors and postinjury symptoms. *J Int Neuropsychol Soc*. 2017;23:1-13.
3. Norup A, Svendsen S, Doser K, et al. Prevalence and severity of fatigue in adolescents and young adults with acquired brain injury: A nationwide study. *Neuropsychol Rehabil*. 2019;29(7):1113-1128.
4. Wilkinson J, Marmol N, Godfrey C, et al. Fatigue following paediatric acquired brain injury and its impact on functional outcomes: A systematic review. *Neuropsychol Rev*. 2018;28(1):73-87.
5. Sumpter R, Brunklaus A, McWilliam R, Dorris L. Health-related quality-of-life and behavioural outcome in survivors of childhood meningitis. *Brain Inj*. 2011;25(13-14):1288-95.
6. Falk A. A nurse-led paediatric head injury follow-up service. *Scand J Caring Sci*. 2013;Mar;27(1):51-6.
7. Aaro Jonsson C, Emanuelson I, Smedler A. Variability in quality of life 13 years after traumatic brain injury in childhood. *Int J Rehabil Res*. 2014;Dec;37(4):317-22.
8. Crichton A, Anderson V, Oakley E, et al. Fatigue following traumatic brain injury in children and adolescents: A longitudinal follow-up 6 to 12 months after injury. *J Head Trauma Rehabil*. 2018;33(3):200-209.
9. Cantor J, Ashman T, Gordon W, et al. Fatigue after traumatic brain injury and its impact on participation and quality of life. *J Head Trauma Rehabil*. 2008;23(1):41-51.
10. Cancelliere C, Hincapié C, Keightley M, et al. Systematic review of prognosis and return to play after sport concussion: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil*. 2014;Mar;95(3 Suppl):S210-29.
11. Anaby D, Law M, Hanna S, Dematteo C. Predictors of change in participation rates following acquired brain injury: results of a longitudinal study. *Dev Med Child Neurol*. 2012;54(4):339-46.
12. Baque E, Barber L, Sakzewski L, Boyd R. Randomized controlled trial of web-based multimodal therapy for children with acquired brain injury to improve gross motorcapacity and performance. *Clin Rehabil*. 2017;31(6):722-732.
13. Sorić M, Starc G, Borer K, et al. Associations of objectively assessed sleep and physical activity in 11-year old children. *Ann Hum Biol*. 2015;42(1):31-7.
14. Orsey A, Wakefield D, Cloutier M. Physical activity (PA) and sleep among children and adolescents with cancer. *Pediatr Blood Cancer*. 2013;60:1908-1913.
15. van Tol E, Gorter J, DeMatteo C, Meester-Delver A. Participation outcomes for children with acquired brain injury: a narrative review. *Brain Inj*. 2011;25(13-14):1279-87.
16. Catroppa A, Anderson V, Morse S, et al. Outcome and predictors of functional recovery 5 years following pediatric traumatic brain injury. *J Pediatr Psychol*. 2008;33:707–718.
17. Rivara F, Vavilala M, Durbin D, et al. Persistence of disability 24 to 36 months after pediatric traumatic brain injury: a cohort study. *J Neurotrauma*. 2012;29(15):2499-504.
18. Bedell G, Dumas H. Social participation of children and youth with acquired brain injuries discharged from inpatient rehabilitation: a follow-up study. *Brain Inj*. 2004;18(1):65-82.
19. Galvin J, Froude E, McAleer J. Children's participation in home, school and community life after acquired brain injury. *Aust Occup Ther J*. 2010;57(2):118-26.
20. Bonneterre V, Pérennou D, Trovatello V, et al. Interest of workplace support for returning to work after a traumatic brain injury: a retrospective study. *Ann Phys Rehabil Med*. 2013;56(9-10):652-662.
21. Buffington A, Malec J. The vocational rehabilitation continuum: maximizing outcomes through bridging the gap from

hospital to community-based services. *Jnl of Head Trauma Rehabilitation*. 1997;12(5): 1-13.
22. Malec J, Moessner A. Replicated positive results for the VCC model of vocational intervention after ABI within the social model of disability. *Brain Inj*. 2006;20(3):227-236.
23. Chamberlain E, Weir J, Berry A, et al. Effectiveness of vocational rehabilitation following acquired brain injury: preliminary evaluation of a UK specialist rehabilitation programme. *Brain Inj*. 2006;20(11):1119–1129.
24. Wehman P, Kreutzer J, West M, et al. Return to work for persons with traumatic brain injury: a supported employment approach. *Arch Phys Med Rehabil*. 1990;71(13):1047-52.
25. Donker-Cools B, Wind H, Frings-Dresen M. Prognostic factors of return to work after traumatic or non-traumatic acquired brain injury. *Disabil Rehabil*. 2016;38(8):733-741.
26. Varni J, Limbers C. The PedsQL 4.0 Generic Core Scales Young Adult Version: feasibility, reliability and validity in a university student population. *J Health Psychol*. 2009;May;14(4):611-22.
27. Limperg P, Haverman L, van Oers H, et al. Health related quality of life in Dutch young adults: psychometric properties of the PedsQL generic core scales young adult version. *Health Qual Life Outcomes*. 2014;Jan 18;12:9.
28. Daskas N, Sharples P, Likeman M, et al. Growth hormone secretion, fatigue and quality of life after childhood traumatic brain injury. *Eur J Endocrinol. 2019*. 2019; Jul 1. pii: EJE-19-0166.R3.
29. Recklitis C, Liptak C, Footer D, et al. Prevalence and Correlates of Pain in Adolescent and Young Adult Survivors of Pediatric Brain Tumors. *J Adolesc Young Adult Oncol*. 2019; Dec;8(6):641-648.
30. Sinoo C, de Lange I, Westers P, et al. Behavior problems and health-related quality of life in Dravet syndrome. *Epilepsy Behav*. 2019;Jan;90:217-227.
31. Varni J, Burwinkle T, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr*. 2003;Nov-Dec;3(6):329-41.
32. Varni J, Burwinkle T, Szer I. The PedsQLMultidimensional Fatigue Scale in pediatric rheumatology: Reliability and validity. *Journal of Rheumatology*. 2004;31:2494-2500.
33. Varni J, Limbers C. The PedsQL Multidimensional Fatigue Scale in young adults: feasibility, reliability and validity in a University student population. *Qual Life Res*. 2008;Feb;17(1):105-14.
34. Baque E, Sakzewski L, Trost S, et al. Validity of accelerometry to measure physical activity intensity in children with an acquired brain injury. *Pediatr Phys Ther*. 2017;29(4):322-329.
35. Driver S, Ede A, Dodd Z, et al. What barriers to physical activity do individuals with a recent brain injury face? *Disabil Health J*. 2012;5(2):117-25.
36. Gijzen R, Zadoks J. [*Zorgstandaard Traumatisch Hersenletsel Kinderen & Jongeren*]. 2016, Hersenstichting: The Hague, The Netherlands.
37. Leddy J, Haider M, Ellis M, Willer B. Exercise is medicine for concussion. *Curr Sports Med Rep*. 2018;17(8):262-270.
38. Zedlitz A, Rietveld T, Geurts A, Fasotti L. Cognitive and graded activity training can alleviate persistent fatigue after stroke: a randomized, controlled trial. *Stroke*. 2012;43(4):1046-51.
39. Gómez-de-Regil l, Estrella-Castillo D, Vega-Cauich J. Psychological intervention in traumatic brain injury patients. *Behav Neurol*. 2019;6937832.



Chapter 10

List of publications
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Dankwoord

List of publications

Van Markus-Doornbosch F, van der Holst M, de Kloet AJ, Vliet Vlieland TPM, Meesters JJL. Fatigue, Participation and Quality of Life in Adolescents and Young Adults with Acquired Brain Injury in an Outpatient Rehabilitation Cohort.
Developmental Neurorehabilitation 2019 Nov 20:1-8 [Epub ahead of print].

Van Markus-Doornbosch F, Peeters E, Volker G, van der Pas S, Vliet Vlieland T, Meesters J. Physical activity, fatigue and sleep quality at least 6 months after mild traumatic brain injury in adolescents and young adults: A comparison with orthopedic injury controls.
European Journal of Pediatric Neurology 2019; 23(5):707-715.

Van Markus-Doornbosch F, Peeters E, van der Pas S, Vliet Vlieland T, Meesters J. Physical activity after mild traumatic brain injury: What are the relationships with fatigue and sleep quality?
European Journal of Pediatric Neurology 2019; 23(1):53-60.

Lambregts SAM, van Markus-Doornbosch F, Catsman-Berrevoets CE, Berger MAM, de Kloet AJ, Hilberink SR, Roebroeck ME. Neurological outcome in children and youth with acquired brain injury 2-year post-injury.
Developmental Neurorehabilitation 2018; 21(7): 465-74.

Van Markus-Doornbosch F, Meesters J, Kraaij L, Wolterbeek R, Vliet Vlieland T. Fatigue and its relationship with physical activity in adolescents and young adults with traumatic brain injury: a cross-sectional study.
European Journal of Physical and Rehabilitation Medicine 2017; 53(6):900-09.

Van Markus-Doornbosch F, de Kloet AJ, Berger MAM, Lambregts SAM, Wolterbeek R, Vliet Vlieland TPM. Factors related to fatigue after paediatric acquired brain injury (ABI).
Brain Injury 2016 30(13-14): 1533-41.

De Kloet AJ, Berger MAM, Bedell GM, Catsman-Berrevoets CE, van Markus-Doornbosch F, Vliet Vlieland TPM. Psychometric evaluation of the Dutch language version of the Child and Family Follow-up Survey.
Developmental Neurorehabilitation 2015; 18(6): 357-64.

De Kloet AJ, Lambregts SAM, Berger MAM, van Markus F, Wolterbeek R, Vliet Vlieland TPM. Family impact of acquired brain injury in children and youth.
Journal of Developmental and Behavioral Pediatrics 2015; 36(5): 342-51.

Slaman J, van den Berg-Emons HJ, van Meeteren J, Twisk J, van Markus F, Stam HJ, van der Slot WM, Roebroeck ME. A lifestyle intervention improves fatigue, mental health and social support among adolescents and young adults with cerebral palsy: focus on mediating effects.
Clinical Rehabilitation 2014; 29(7):717-27.

Russchen HA, Slaman J, Stam HJ, van Markus-Doornbosch F, van den Berg-Emons RJ, Roebroeck ME. Focus on fatigue amongst young adults with spastic cerebral palsy.
Journal of NeuroEngineering and Rehabilitation 2014; 11: 161.

De Kloet AJ, Hilberink SR, Roebroeck ME, Catsman-Berrevoets CE, Peeters E, Lambregts SAM, van Markus-Doornbosch F, Vliet Vlieland TPM. Youth with acquired brain injury in The Netherlands: A multi-centre study.
Brain Injury 2013; 27(7-8): 843-849.

Curriculum Vitae

Frederike van Markus-Doornbosch werd geboren op 5 januari 1973 in Ridgewood, New Jersey in de Verenigde Staten. In 1991 behaalde zij haar middelbare school diploma op de Nyack High School. In 1995 verkreeg zij het Bachelor diploma Mariene Biologie aan de Colgate University in Hamilton, New York.

Na een jaar als docent in het onderwijs werkzaam te zijn geweest aan de Colgate University, besloot ze in 1996 de studie Geneeskunde aan de Universiteit van Leuven te starten, om na een jaar over te stappen naar de studie Geneeskunde aan de Universiteit van Leiden/LUMC. In 2001 behaalde zij het Bachelor diploma Geneeskunde en in 2003 het Artsendiploma.

In September 2003 begon zij haar loopbaan als arts niet in opleiding (ANIOS) op de kinderafdeling van Sophia Revalidatie, waarna zij van 2004 tot 2008 de opleiding revalidatiegeneeskunde volgde. Als revalidatiearts in opleiding was Frederike betrokken bij het opzetten van een nieuwe polikliniek voor jongeren tussen de 14 en 25 jaar bij Sophia Revalidatie. Na haar registratie als revalidatiearts bleef zij werkzaam bij Sophia Revalidatie (thans: Basalt, fusieorganisatie van Sophia Revalidatie en Rijnlands Revalidatie Centrum), onder andere bij de Polikliniek Revalidatie voor Jongeren (PRJ) in Den Haag.

In 2012 is zij begonnen met onderzoek naar de gevolgen van hersenletsel bij kinderen en jongeren. In 2013 startte zij het promotietraject “Fatigue, physical activity and participation in adolescents and young adults with acquired brain injury” bij het LUMC onder leiding van prof. dr. Thea Vliet Vlieland, dr. Jorit Meesters en dr. Arend de Kloet. Naast de onderzoeken beschreven in dit proefschrift is zij betrokken bij “Meedoen”, een prospectief multicenter onderzoek in Nederland naar participatie van kinderen en jongeren met hersenletsel. Zowel als clinicus als onderzoeker is zij een actief lid van de landelijke werkgroep Hersenletsel en Jeugd (HeJ).

Naast haar klinische- en onderzoekstaken is Frederike sinds 2014 plaatsvervangend opleider revalidatiegeneeskunde en met ingang van 1 september 2016 opleider revalidatiegeneeskunde voor Basalt Den Haag binnen het Opleidings- en Onderwijsregio (OOR) Leiden. Tevens is zij betrokken bij het Lectoraat Revalidatie van Basalt en de Haagse Hogeschool en als (gast) docent in de minor Revalidatie van de Haagse Hogeschool.

Frederike is getrouwd met Martin van Markus en samen met hun kinderen Simon (2008) en Lucille (2012) genieten ze van het leven “op Scheveningen”.

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Tevens dank ik Monique Berger, Suzanne Lambregts en Menno van der Holst voor hun advies en kritische blik op de manuscripten. Laurika Kraaij heeft als Master student Gezondheidswetenschappen een grote bijdrage geleverd aan het vervaardigen van een digitale vragenlijst, en Hanneke Kranenborg heeft als AIOS geholpen met de dataverzameling en analyse in ons Brain Power cohort.

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"Slice of Life" by Donna Krim Korkes