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Towards PErsonalised PRognosis for children with traumatic brain injury: the PEPR study protocol

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ABSTRACT

Introduction Traumatic brain injury (TBI) in children can be associated with poor outcome in crucial functional domains, including motor, neurocognitive and behavioural functioning. However, outcome varies between patients and is mediated by complex interplay between demographic factors, premorbid functioning and (sub) acute clinical characteristics. At present, methods to understand let alone predict outcome on the basis of these variables are lacking, which contributes to unnecessary follow-up as well as undetected impairments in children. Therefore, this study aims to develop prognostic models for the individual outcome of children with TBI in a range of important developmental domains. In addition, the potential added value of advanced neuroimaging data and the use of machine learning algorithms in the development of prognostic models will be assessed.

Methods and analysis 210 children aged 4–18 years diagnosed with mild-to-severe TBI will be prospectively recruited from a research network of Dutch hospitals. They will be matched 2:1 to a control group of neurologically healthy children (n=105). Predictors in the model will include demographic, premorbid and clinical measures prospectively registered from the TBI hospital admission onwards as well as MRI metrics assessed at 1 month post-injury. Outcome measures of the prognostic models are (1) motor functioning, (2) intelligence, (3) behavioural functioning and (4) school performance, all assessed at 6 months post-injury.

Ethics and dissemination Ethics has been obtained from the Medical Ethical Board of the Amsterdam UMC (location AMC). Findings of our multicentre prospective study will enable clinicians to identify TBI children at risk and aim towards a personalised prognosis. Lastly, findings will be submitted for publication in open access, international and peer-reviewed journals.

Trial registration number NL71283.018.19 and NL9051.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will use a unique multidimensional approach to develop a more innovative personalised prognostic model to account for the heterogeneous outcome post paediatric traumatic brain injury (TBI).
⇒ The study design is optimised for clinical implementation by (1) selecting predictors of which the great majority is available at time of discharge from acute care, (2) aligning the timing of MRI assessment with follow-up according to clinical guidelines and (3) using outcome measures that are sensitive to impairments in a range of crucial domains of daily life functioning.
⇒ This study will test the added value of selected advanced MRI metrics that have shown promising prognostic potential for outcome in children with TBI.
⇒ This study will test the added value of machine learning approaches for the development of complex outcome prediction.
⇒ The resulting prognostic models will not be readily available for clinical practice, since external validation is required in order to assess clinical implementability in the hospital setting.

INTRODUCTION

Traumatic brain injury (TBI) has an estimated annual worldwide prevalence of 69 million cases and is the leading cause of disability in children and young adults.[1 2] The impact of TBI can have enduring effects on different aspects of daily life functioning, including motor, neurocognitive, behaviour and school functioning.[3–8] Importantly, children show large differences in the nature and extent of TBI consequences, which are likely the result of the complex interplay between injury characteristics (ie, neuroimaging findings, severity of acute symptoms, vital parameters) and environmental factors (ie, premorbid functioning, socioeconomic status (SES), interventions).[8–10] Due to the distinct heterogeneity in TBI and lack of good prognostic tools, clinicians are insufficiently able to properly inform the patient and family on expected outcome and are withheld to tailor care to the individual risk profile of the child.[2 11] Considering the considerable morbidity and wide range of potential developmental disadvantages in children with TBI, better insights on TBI prognosis in children are much needed to improve appropriate

family support, provide monitoring and intervention in a timely course, as well as effectively prevent poor outcome at the level of the individual child.[12]

In current clinical practice, widely used tools for head injuries include (1) the Glasgow Coma Scale score, (2) symptoms present in the acute phase (loss of consciousness, amnesia) and (3) if present, CT-based information that are combined and used for diagnostic purposes (stratifying into mild, moderate and severe TBI).[13 14] Unfortunately, such tools are highly insufficient to predict the multifactorial outcome differences present across the spectrum of TBI severity.[15–17] Several more advanced multivariate prognostic models for TBI outcome exist, yet suffer from important limitations for use in children.[18 19] First, the vast majority defines outcome as 'death' or 'severe disability' instead of more fine-grained outcomes of threatened daily life functions (eg, motor, neurocognitive, behavioural and school functioning). Second, existing models have almost exclusively been developed in adult patients, thereby not accounting for the developmental aspects of brain functioning that are crucial for outcome prediction in children.[20] Third, advanced multimodal MRI (ie, targeting brain volume, white matter integrity, structural and functional connectivity and neurometabolites) has not been integrated in the existing prediction models, while each of these MRI techniques has shown promising prognostic potential when studied in isolation.[17 21–23] More specifically, measures of fractional anisotropy and resting-state network connectivity are considered to be strongly implicated in the neurocognitive and behavioural impairments of children with TBI.[21 23 24]

The limitations of existing prognostic models highlight the importance of research into the development of innovative prognostic models for outcome of paediatric TBI. Such models should be developed to move towards a more personalised prognosis. Given the complexity of TBI and its outcome,[11] the development of accurate prognostic models is likely to require a rich source of multidimensional data that is brought down into a concise and clinically manageable set of predictors.[10] Existing models have traditionally been developed using conventional statistical methods (eg, logistic and linear regression) which may not harvest the full predictive potential of rich data sources in complex real-life outcome prediction.[25] Machine learning offers alternative models with high flexibility (eg, decision trees, support vector machines), allowing more accurate data modelling.[25] Indeed recent application of machine learning in the prediction of global outcome after paediatric TBI has shown to improve the accuracy of prediction as compared with conventional statistical models.[26 27] Yet to date, the value of machine learning for the development of prognosis on more fine-grained yet crucial outcome domains in multifactorial disease conditions such as TBI, remains largely unexplored.[28 29]

The current study aims to move towards personalised prognostic models for outcomes of paediatric TBI in crucial domains of child development (ie, motor, neurocognitive, behavioural and school functioning), based on multidimensional data covering premorbid and (sub) acute clinical characteristics. Furthermore, we aim to determine the added value of advanced neuroimaging metrics as well as machine learning algorithms for the development of a prognostic model. The primary result should be a prognostic model that may function as a practical tool for clinicians in daily care. Thereby, this study may contribute to a better family support, better planning of early rehabilitation and follow-up, preventing unnecessary care for children in whom good recovery is expected, and facilitate adequate monitoring and treatment of children with a high-risk of adverse outcome.

METHODS AND ANALYSIS

Study design

This controlled observational multicentre study will use a prospective longitudinal design. Children with a clinical diagnosis of TBI will be enrolled for 6 months after initial hospital admission. Data collection will take place at three time points: (1) during hospital stay, (2) 1 month post-injury (MRI assessment) and (3) 6 months post-injury (outcome assessment). The total duration of the study depends on the inclusion rate and is expected to be over 2 years (2021–2023). An overview of the study design and procedures for children with TBI is displayed in figure 1. Neurologically healthy children will be enrolled in the control group for outcome assessment only.

Study population

This study will prospectively recruit a multicentre cohort of children diagnosed with mild-to-severe TBI from a research network of hospitals. Trauma-level 1 Dutch University Medical Centres and general hospitals in the geographical area of the Amsterdam University Medical Centre (initiator site) qualify as a participating centre. Thereby, seeking to recruit a representative sample of children with TBI from primary school onwards. The inclusion and exclusion criteria for participation are displayed in box 1. We will use a clinical diagnosis of TBI instead of a research diagnosis of TBI for inclusion in the TBI group. Although this may lead to a more heterogeneous study sample of children with TBI due to practice variation in the adherence to national guidelines stipulating criteria for assessment and treatment of mild TBI,[30] this will also result in a study sample that better represents the clinical population of children with TBI. Exclusion criteria relating to very poor motor or cognitive outcome (exclusion criteria 2 and 3) will be registered as an outcome, to investigate the potential bias that may be introduced by lack of outcome assessment in a specific subsample of children with very poor outcome. Inclusion will be complete when a sample of 210 children with TBI has been included (see Sample size estimation). Demographically matched neurologically healthy children will be recruited, mainly via schools, out-of-school

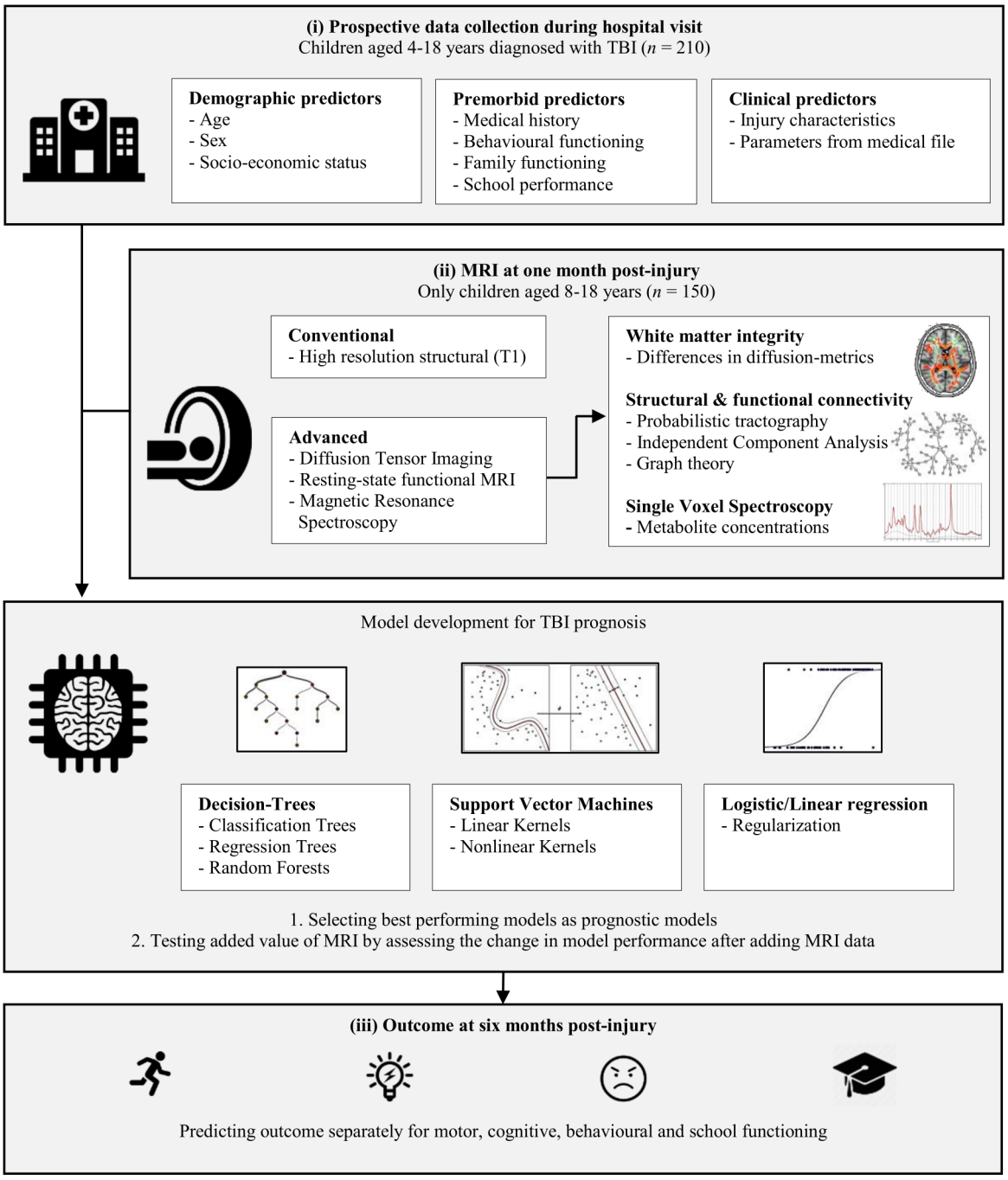

Figure 1 The study design for children with TBI. TBI, traumatic brain injury.

care facilities, sports clubs and through existing collaborations with healthcare institutions in the geographical area of the participating centres. Children in the control group will be matched to children with TBI on age, sex and SES,[31] with a 1:2 ratio requiring a control sample of 105 children.

Patient and public involvement

No patient involved.

Sample size estimation

Sample size calculation was performed according to EMGO+ guidelines,[32] which universally apply to the candidate methods that are described for model development. Consequently, 10–15 observations are required per predictor in the model (15 was chosen for a liberal calculation of the required sample size). The minimum required sample size was calculated for an advanced, yet clinically relevant and implementable prognostic model. Hence, the model complexity was set to a maximum of 10 predictors, in turn defining the minimum required sample at (10×15=) 150 children. Considering Dutch medical ethical guidelines for clinical research, children as from 8 years of age are eligible for MRI scanning in research. Therefore, we set the minimum required sample

Box 1 Inclusion and exclusion criteria for study participation

Inclusion criteria

⇒ Inhabitant of the Netherlands.
⇒ Fluent in the Dutch language.
⇒ 4–18 years old.
⇒ No documented and/or parent-reported diagnosis of a neurological disorder (other than TBI*).
⇒ A clinical diagnosis of mild-to-severe TBI according to a paediatrician or paediatric neurologist.*

Exclusion criteria

⇒ Absence or withdrawal of written informed consent.
⇒ Severe motor disability that interferes with outcome assessment at the time of assessment.
⇒ Inability to comprehend testing instructions at the time of assessment.
⇒ Somatic disorders unrelated to TBI that affect outcome assessments at the time of assessment.*

*TBI group only. TBI, traumatic brain injury.

size (150 children) as the target sample size for the MRI subsample of children (8–18 years old). Considering that we also aim to recruit an age-balanced TBI sample, we calculated the target sample of children with TBI per age year in the MRI subsample aged 8–18 years old (150/(18 years–8 years)=15 children per age year) and applied this to the age range of the whole study sample aged 4–18 years old (15×(18 years–4 years)=210 children) to arrive at the target sample size in the whole study sample of N=210. The resulting sample sizes allow detecting small-to-medium-sized group differences (f=0.18), assuming a statistical power of 80%, alpha set at 0.05 and two-sided testing using analysis of variance.[33]

Protocol

Measurements during hospital admission (TBI children only)

All children admitted to a participating hospital with the clinical diagnosis of mild-to-severe TBI will be screened for eligibility by the on-call paediatric neurologist. Children and their parents (ie, legal guardian) will be informed on the study by the researcher, potential questions will be answered and appropriate informed consent procedures will be conducted depending on age and/or incapacitation of the participant (following article 3, 4, 6 and 9 of the Medical Research Involving Human Subjects Act). Then, participants and/or parent(s) will be asked to fill out questionnaires on demographics (10 min) and premorbid functioning (15 min). Questions on premorbid functioning (assessing family[34] and behavioural[35] functioning) will be collected at the time of hospital admission to limit the contamination of assessment of premorbid functioning with potential consequences of TBI. The chosen questionnaires will lend beneficial insights in possible mediating factors of outcome, assessing the presence of a social support system and allows adjusting for SES, which is known to be important for TBI recovery.[36] SES will be defined as the average level of parental education ranging from 1 (no education) to 8 (postdoctoral education).[37] A multidisciplinary set of clinical predictors will be collected during hospital stay using standardised forms for nurses and physicians, integrated in the electronic medical record. The forms will strictly adhere to relevant care guidelines,[38–40] thereby facilitating systematic prospective data collection as well as contributing to

Table 1 Demographic, premorbid and clinical measures

Domain	Subdomain	Measures	Time point
Demographic	–	Age*, sex*, socioeconomic status†	Hospital stay
Premorbid	Medical history†	Diagnosed mental and somatic disorders	Hospital stay
	Behavioural functioning†	Strengths and Difficulties Questionnaire[35]	Day of inclusion
	Family functioning†	Questionnaire on Family Functioning for Parents[34]	Day of inclusion
Clinical	Emergency care*	Injury type, cause, GCS, medication, Advanced Trauma Life Support parameters, vital parameters according to national care guidelines[38–40]	Hospital stay
	Neurology*	Neurological examination according to national care guidelines[38 39]	Hospital stay
	Radiology*	CT findings according to clinical assessment by the attending radiologist	Hospital stay
	Neurosurgery*	Neurosurgical procedures, intracranial pressure	Hospital stay
	Intensive care*	Mechanical ventilation, medication, vital parameters, length of stay, disorder of consciousness	Hospital stay
	Nursing ward*	Mechanical ventilation, medication, vital parameters, length of stay, disorder of consciousness	Hospital stay

*Collected as part of clinical care, if applicable.
†Collected as part of the PEPR study.
GCS, Glasgow Coma Scale.

Table 2 MRI (3T) scanning protocol

Domain	Scan type	Details	Measures
High-resolution structural imaging	T1, magnetisation prepared – rapid gradient echo.	TR/TE=9.8/4.6. Flip angle=8°. 1×1×1 mm.	1. Whole brain volume. 2. Grey matter volume. 3. White matter volume. 4. Volumes of the bilateral subcortical structures (k=7).
White matter integrity (1–2) and structural connectivity (3–4)	Diffusion tensor imaging, including opposite phase scans for correction of susceptibility-induced geometric distortions.	TR/TE=9500/103. Flip angle=90°. 2×2×2 mm.	1. Average whole brain FA. 2. FA in areas with an observed spatial correlation to the outcome measures, as assessed using tract-based spatial statistics[59] and/or using voxel-based analysis after tensor-based registration.[60] 3. Probabilistic fibre tracking. 4. Organisation* assessed by global network parameters.[43]
Functional connectivity	Resting-state functional MRI, including opposite phase scans for correction of susceptibility-induced geometric distortions.	TR/TE=2000/30. Flip angle=80°. 3×3×3 mm.	1. Temporal correlation coefficients of activity between brain areas. 2. Organisation* assessed by network parameters.[43]
Spectroscopy	Single voxel magnetic resonance spectroscopy in the splenium.	TR/TE=3000/35. 2×2×2 mm.	Metabolite concentrations of *N*-acetyl aspartate, choline, myo-inositol, creatine, glutamine and glutamate.[65]

*Organisation will be assessed in terms of integration (characteristic path length), clustering (transitivity, modularity), hierarchy (assortativity), small-world organisation (small-worldness) and hubness (top 10 hubs).
FA, fractional anisotropy; mm, millimetre; TE, echo time; TR, repetition time.

clinical practice. Table 1 provides an overview of all study measures that will be recorded during hospital admission. See online supplemental appendix 1 for a full listing of clinical measures that will be collected.

MRI at 1 month post-injury (TBI children aged ≥8 years only)

According to Dutch medical ethical guidelines for scientific research, MRI will only be collected in children aged ≥8 years with negative screening for MRI contraindications. For eligible participants, one MRI session will be planned at 1 month post-injury with a 2-week time window at the Spinoza Centre for Neuroimaging, situated at the campus of the Amsterdam UMC. The chosen time point of the MRI assessment reflects a compromise between early measurement and the potentially confounding influence of brain oedema on advanced neuroimaging during the acute phase.[41] Moreover, this time window aligns with routine follow-up of children after hospital admission for TBI according to the Dutch clinical guideline[38] and enables MRI assessment of children with more severe injuries. At time of visit, actual MRI acquisition will take 40 min using a Philips 3T Achieva. The scanning protocol includes both conventional and advanced MRI scan types, all displayed in table 2 together with the accommodating predictors that will be extracted from the data. Moreover, we will compare the prognostic value of promising experimental MRI scans (ie, Diffusion Tensor Imaging, Resting-State Functional MRI, Magnetic Resonance Spectroscopy) to conventional CT and MRI (ie, T1 and Susceptible Weighted Imaging). Diffusion Tensor Imaging and Resting-State Functional MRI will be used to extract measures of structural and functional connectivity.[24 42 43] Single Voxel Magnetic Resonance Spectroscopy using Point RESolved Spectroscopy (PRESS, positioned in the Corpus Callosum) will be used as a non-invasive measure to quantify neurometabolite levels. This measure complements the assessment of structural and functional connectivity and has previously shown to be relevant for neurocognitive outcome.[44]

Functional outcome assessment

At 6 months post-injury (TBI group) or after obtaining informed consent (control group) functional outcome will be assessed in a standardised manner by research assistants in the participating hospitals with an estimated duration of 1½ hours. An overview of the measures of functional outcome is displayed in table 3. To thank children for participation they will be given a small present after being debriefed and travel expenses will be reimbursed. Participants can choose out of a small selection of age-appropriate presents (worth around €5—for children aged 4–11 years, eg, colouring books, wooden games and worth around €10—for children aged >12 years, eg, sports attributes, card games).

Motor functioning will be assessed using the Movement Assessment Battery for Children (second Dutch edition; M-ABC-2).[45] The M-ABC-2 is a standardised and widely used test battery to assess motor skills in children aged 3–16 years but also allows measurement of motor skills in adolescents.[46] Nevertheless, we will explore potential

Table 3 Measures of functional outcome

Domain	Measures	Subject
Motor skills	Movement ABC-2[45]	Child
Intelligence	Short version of the age-appropriate version of the Wechsler Intelligence Scales[47–49] (Vocabulary, Similarities, Matrix Reasoning and Block Design)	Child
Behaviour	Child Behaviour Checklist[51]	Parent
	Teacher Report Form[51]	Teacher
School	Dutch Pupil Monitoring System[52]	Teacher

ABC, Assessment Battery for Children.

ceiling effects in participants aged 17 and 18. The M-ABC-2 contains eight items measuring: (1) manual dexterity, (2) throwing and catching and (3) balance. The total score is the sum of the three components and is transformed into age-adjusted standard scores, indicative as an overall measure of motor functioning. The test has adequate psychometric properties[45] and has an estimated total duration of 20–40 min (depending on the child's age).

Intelligence will be assessed using the revised Dutch Wechsler Intelligence Scales.[47–49] Depending on the child's age either the Wechsler Preschool Primary Scale of Intelligence, Wechsler Intelligence Scale for Children or Wechsler Adult Intelligence Scale will be assessed. For all versions, age-adjusted full-scale IQ will be estimated using a short form (assessing the subtests Vocabulary, Similarities, Matrix Reasoning and Block Design), with adequate validity and reliability in estimating intelligence.[50] The short form has a duration of approximately 45 min.

Parents will fill out the Dutch version of the Child Behaviour Checklist (CBCL), which is a widely used measure for behavioural and emotional problems focusing on the past 6 months of children.[51] Either the preschool or school-age version of the CBCL will be completed depending on the age of the child. The questionnaires contain 100-items (preschool) to 113-items (school-age), providing a total score, broadband scales and small band scales. The broadband scales discriminate between externalising and internalising problems. The small bands discriminate between numerous types of behavioural problems such as somatic disorders, anxious/depressed, social problems, attentional problems and aggressive behaviour. An adaption of the Dutch preschool and school-age version of the CBCL, the Teacher Report Forms (TRFs), will be completed by teachers and allow direct comparison with outcomes from the CBCL.[51] For patients that have not returned to school and stay in an inpatient or residential programme, the TRF will be completed by the daily care medical staff, if possible. Both CBCL and TRF typically take 20 min to complete.

School functioning will be assessed in the subsample of children attending primary school. Dutch Pupil Monitoring System[52] results will be requested through primary school teachers and include information prior to the injury as well as 6 months-post injury. The Dutch Pupil Monitoring System developed by the National Institute of Educational Measurement in the Netherlands is to obtain reliable data systematically on pupil learning progress during their entire primary school career.[53] Test packages are developed for all six age groups between 6 and 12 years-old and allow seamless charting of academic development across these ages. We will assess packages developed for arithmetic's, spelling and technical reading.[54] Based on the expected age range of this group (6–12 years), this information will be available for a subsample of (3.5×30=) 105 children with TBI. The size of this subsample allows building a separate highly relevant prediction model for school outcome with a maximum of seven predictors.

Analyses

Data preprocessing and score constructions

Outliers (z-score >3.29 or z-score <−3.29) will be identified in all variables and will be assessed for measurement errors carefully. If no evidence is found for a measurement error, outliers will be rescaled using Winsorizing.[55] Variables with missing values >10% will be discarded from further analysis. Data missing at random or completely at random will be imputed using multiple imputations. Voluminous data (eg, continuous measurements of vital signs) will be reduced using principal components analysis and/or classification/regression trees to control the number of available predictors for the model.

Each age and sex standardised functional outcome score (motor development, intelligence, behavioural functioning and school performance) will first be transformed to z-scores, where the z-score describes the difference between each TBI participant's score and the mean of the demographically-matched control participant. Second, the z-scores will be adjusted for the influence of premorbid functioning (family[34] and behavioural[35] functioning) by adding these variables as predictors to the linear regression analyses on each z-score pertaining to an outcome domain. The demographic and premorbid adjusted z-scores will then be retrieved by extracting the standardised residuals of these regression analyses. Since children with high premorbid functioning and significant decrement in functioning can still perform in the average range of the general population, the demographic and premorbid adjustment procedure will increase the sensitivity of outcome prediction.

All MRI data will be preprocessed using the Functional MRI of the Brain Software Library (FSL).[56] T1 data will be assessed using volumetric analysis.[57] With regard to Diffusion Tensor Imaging data, preprocessing will involve correction for motion and eddy-currents and automated imputation of volume data.[58] White matter microstructure will be assessed by the primary diffusion measures (fractional anisotropy and mean diffusion). Spatial correlations between white matter microstructure and outcome measures will be assessed using tract-based

spatial statistics as well as voxel-based white matter parameters, using Diffusion Tensor Imaging ToolKit registration.[59 60] Structural connectivity will be assessed using probabilistic fibre tracking on the diffusion data.[61] Functional connectivity will be assessed using temporal correlations in brain activity between brain areas.[62] Global and local network parameters of structural as well as functional connectivity will be extracted from the resulting connectivity matrices using the application of graph theory.[63] All spectroscopy data will be processed using the LCModel package.[64] The spectroscopy data will be used to extract the concentrations of the following metabolites sensitive to TBI depending on quantification reliability within the population, possibly including *N*-acetyl aspartate, choline, myo-inositol, creatine, glutamine and glutamate.[44 65] Data reduction and predictor selection techniques will be used to handle the large number of MRI-derived predictors per subject (ie, ensemble averaging, independent component analysis and selective regularisation of MRI data).

Prognostic model development

Primary analyses: multivariate models for functional outcome

Statistical analyses will be performed using R and SPSS with alpha set at 0.05 (two-sided). Model development will be performed according to Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines.[66] Prognostic models will be developed for each of the four functional outcomes separately, all using predictors that were available at the moment of discharge. In addition, one prognostic model will be developed to predict the overall functional outcome (sum of z-scores) to identify children with general functional impairment.

Prediction models are anticipated to be developed using different types of candidate supervised machine learning techniques, among which decision trees and support vector machines. A reference model will be constructed using linear regression. Given the rapid developments in the field of data science, we will adapt our specific selection of candidate models to the state of the literature at the time of analysis. Model complexity will be determined using cross-validation (with a maximum of 10 predictors based on the minimum sample size calculation). Model performance will be assessed according to ABCD (ie, A calibration-in-the-large, or the model intercept; B calibration slope; C discrimination, with a concordance statistic; D and clinical usefulness, with decision-curve analysis) guidelines using measures of calibration and discrimination.[67] The entire data set will be used for model training as recommended for smaller clinical samples,[68] therefore internal validation will be performed using the bootstrap method and model performance will be corrected for optimism accordingly.[69] Ultimately, the complete methodological process will be reported in the dissemination of the data and the best performing model will be presented.

Secondary analyses: additive value of MRI metrics and machine learning

Additional analyses are aimed at assessing the additive prognostic value of innovative MRI metrics (as compared with conventional CT and MRI metrics) and the additive value of machine learning based methods (as compared with linear regression). The value of advanced MRI metrics for outcome prediction will be tested in the MRI subsample (n=150) by the change in prediction model performance after adding advanced MRI metrics to the available predictors. Differences in model performance will be analysed using bootstrap CIs created for three widely used performance measures for regression-based prediction: root mean squared error, explained variance and mean absolute error.[70] Then, the value of machine learning techniques for the development of personalised prognostic models will be compared with the reference model created with linear regression, also using the bootstrap CIs on the same performance measures as previously mentioned.[71]

Ethics and dissemination

This study poses a negligible risk to the participating children and their parents. Study participation will not restrict any received clinical care as determined by physicians (additional CT or MRI, assessments or follow-up). All study procedures will be conducted according to the principles of the Declaration of Helsinki (2013) and will follow the Medical Research Involving Human Subjects Act (WMO). Participation in the study is voluntary and participants can leave the study at any time for any reason. Leaving the study will be without any consequences for clinical care. On completion of all study measures for all participants, we will provide families interested in the results of the study with a concise report. In addition, on request, families can retrieve a report with individual outcomes for measures with readily available normative data (eg, subtest of the Wechsler Intelligence Scale). The research data including a manuscript will be published in international peer-reviewed journals, preferably open-access. Publication topics will include (1) the development of prognostic models for functional outcome 6 months post TBI in children aged 4–18 years, (2) the relevance of neuroimaging metrics for functional outcome post TBI as well as (3) the potentially added value of machine learning as compared with conventional analyses for clinical prediction models.

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Appendix 1

1. Emergency care
    - 1.1. Arrival
        1. Date and time
        2. Trauma Mechanism
        3. Suspicion of abuse
        4. Medication at the emergency department (including helicopter/ambulance)
    - 1.2. Advanced Paediatric Life Support Protocol
        1. Awareness Level (Lowest GCS Score)
        2. Loss of consciousness
        3. Behaviour
        4. Anterograde Post-Traumatic Amnesia
    - 1.3. Blood gas analysis and physiological parameters
        1. Blood gas analysis
        2. Physiological parameters
    - 1.4. Indications CT
        1. Indications CT 2-5 years
        2. CT indications from 6 years
    - 1.5. Abbreviated neurological examination
        1. Pupils
        2. Eye movements
        3. Face
        4. Motor skills
        5. Reflexes

2. Intensive Care Unit (if applicable)
    - 2.1. Admission
        1. Admitted to the intensive care unit
        2. Date
    - 2.2. Measures
        1. Mechanical ventilation
        2. Trachea cannula
        3. Device data
        4. Glasgow Coma Scale score on admission
        5. Pupil size on admission
        6. Pupil reaction on admission
        7. Intracranial Pressure
        8. Medication
    - 2.3. Discharge
        1. Date
        2. Discharge destination
        3. Discharge Condition

3. Nursing ward (if applicable)
    - 3.1. Admission
        3. Admitted to the Nursing Ward
        4. Date

- 3.2. Measures
  1. Mechanical ventilation
  2. Trachea cannula
  3. Device data
  4. Glasgow Coma Scale score on admission
  5. Pupil size on admission
  6. Pupil reaction on admission
  7. Intracranial Pressure
  8. Medication
- 3.3. Discharge
  1. Date
  2. Discharge destination
  3. Discharge Condition

4. Radiology (if present)
   - 4.1. CT scan
     1. CT scan performed
     2. Abnormalities on CT scan
     3. Rotterdam CT score
   - 4.2. MRI scan
     1. MRI scan performed
     2. Abnormalities on MRI scan

5. Neurosurgery
   - 5.1. Neurosurgical Assessment
   - 5.2. Neurosurgical Intervention (if assessed)