Title

Traumatic Brain Injury in Children and Adolescents: Psychiatric Disorders 24 Years Later

Journal

Journal of Neuropsychiatry, 34(1)

ISSN

0895-0172

Authors

Max, Jeffrey E

Troyer, Emily A

Arif, Hattan

et al.

Publication Date

2022-02-01

DOI

10.1176/appi.neuropsych.20050104

Peer reviewed

Published in final edited form as:

J Neuropsychiatry Clin Neurosci. 2022 ; 34(1): 60–67. doi:10.1176/appi.neuropsych.20050104.

Traumatic Brain Injury in Children and Adolescents: Psychiatric Disorders 24 Years Later

Jeffrey E. Max, M.B.B.Ch.,

Emily A. Troyer, M.D.,

Hattan Arif, M.D.,

Florin Vaida, Ph.D.,

Elisabeth A. Wilde, Ph.D.,

Erin D. Bigler, Ph.D.,

John R. Hesselink, M.D.,

Tony T. Yang, M.D., Ph.D.,

Olga Tymofiyeva, Ph.D.,

Owen Wade, B.S.,

Jane S. Paulsen, Ph.D.

Department of Psychiatry, University of California, San Diego (Max, Troyer, Arif); Rady Children's Hospital, San Diego (Max); Department of Psychiatry, University of Iowa, Iowa City (Max, Wade, Paulsen); Department of Family Medicine and Public Health, University of California, San Diego (Vaida); Department of Neurology, TBI and Concussion Center, University of Utah, Salt Lake City (Wilde, Bigler); Department of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston (Wilde); Department of Psychology, Brigham Young University, Provo, Utah (Bigler); Department of Radiology, University of California, San Diego (Hesselink); Department of Psychiatry, Division of Child and Adolescent Psychiatry, University of California, San Francisco (Yang); Department of Radiology and Biomedical Imaging, University of California, San Francisco (Tymofiyeva).

Abstract

Objective: The investigators aimed to extend findings regarding predictive factors of psychiatric outcomes among children and adolescents with traumatic brain injury (TBI) from 2 to 24 years postinjury.

Methods: Youths aged 6–14 years who were hospitalized following TBI from 1992 to 1994 were assessed at baseline for TBI severity and for preinjury psychiatric, adaptive, and behavioral functioning; family functioning; family psychiatric history; socioeconomic status; and intelligence within weeks of injury. Predictors of psychiatric outcomes following pediatric TBI at 3, 6, 12, and 24 months postinjury have previously been reported. In this study, repeat psychiatric assessments were completed at 24 years postinjury with the same cohort, now adults aged 29–39 years, with the outcome measure being presence of a psychiatric disorder not present before the TBI ("novel psychiatric disorder").

Send correspondence to Dr. Max (jmax@health.ucsd.edu).

Results: Fifty participants with pediatric TBI were initially enrolled, and the long-term outcome analyses focused on data from 45 individuals. Novel psychiatric disorder was present in 24 out of 45 (53%) participants. Presence of a current novel psychiatric disorder was independently predicted by the presence of a preinjury lifetime psychiatric disorder and by severity of TBI.

Conclusions: Long-term psychiatric outcome (mean=23.92 years [SD=2.17]) in children and adolescents hospitalized for TBI can be predicted at the point of the initial hospitalization encounter by the presence of a preinjury psychiatric disorder and by greater injury severity.

Pediatric traumatic brain injury (TBI) is an important public health issue, as approximately 280 per 100,000 children and adolescents incur a TBI annually worldwide (1). More than 80% of these injuries are considered to be mild TBI (1). In the United States, TBI is a leading cause of pediatric morbidity and mortality (2); post-TBI sequelae can include new-onset psychiatric disorders, neuropsychological deficits, poor school performance, and deficits in social competence and adaptive function (3–6). Long-term psychiatric outcomes for adults with a history of pediatric TBI are less well known.

Several studies have focused on psychiatric outcomes among youths with TBIs of all severities; new-onset psychiatric disorders (referred to here as “novel psychiatric disorders” [NPDs]) occur in 50%–60% of children and adolescents who have experienced severe TBI (7), 5%–9% in control subjects with orthopedic injuries, and 10%236% with mild to moderate TBI (3, 8). Because mild TBI constitutes the vast majority of all pediatric TBIs, it is worth noting the findings of a systematic review of psychiatric complications (9). In the review by Emery et al. (9), the investigators found that psychiatric problems were more common when mild TBI was associated with hospitalization, when assessment occurs earlier postinjury (suggesting that problems resolve over time), when there are recurrent previous mild TBIs, among individuals with preinjury psychiatric disorder, when outcomes are based on retrospective recall in contrast to prospective studies, and when the comparison group is uninjured children rather than injured children (e.g., with orthopedic fractures). In our prospective studies of hospitalized children with mild to severe TBI, depending on when participants were assessed, NPDs were significantly associated with the following injury and preinjury variables: lower fractional anisotropy in bilateral frontal lobe, temporal lobe, uncinate fasciculi, and centrum semiovale tracts; lifetime psychiatric disorders; family function; adaptive function; family psychiatric history; and socioeconomic status (8, 10–13).

To date and to our knowledge, there are no long-term psychiatric interview prospective studies of pediatric TBI, and the longest follow-up assessment of prospective psychiatric interview studies was 2–2.25 years (3, 11, 14). There are three published prospective investigations of long-term outcomes (at 16–23 years old) in adulthood of pediatric TBI, which examined behavioral domains of function in unselected cohorts (15–21). These studies have identified associations between severity of TBI and long-term social functioning, personality, educational, vocational, and mood-related outcomes. Besides injury severity variables, lower socioeconomic status and a less intimate family environment were associated with poorer emotional perception at the follow-up (19), and preinjury adaptive function was related to long-term internalizing problems (18). Furthermore, significant associations were found between domains of function, including social communication,

externalizing behaviors, and emotion perception (20). The aforementioned long-term studies were limited by high attrition rates (34%–69%), and other long-term outcome studies are limited due to their referral bias (22–25).

The goal of the present long-term extension of our prospective longitudinal study from 2 years (10–13) to 24 years postinjury was to fill a scientific void by examining the natural history, occurrence, phenomenology, and biological and psychosocial predictive variables for long-term psychiatric outcomes following pediatric mild to severe TBI that required acute hospital treatment. The age group that we studied (ages 29–39) is important because while follow-up to this point does not constitute an entire life course, prospective birth cohort studies suggest that individuals in this age range have reached the highest risk period for onset of many psychiatric disorders (26–29). In this study, we hypothesized that NPDs current at long-term follow-up would be significantly related to some of the following six domains examined at the baseline assessment: severity of injury and the following preinjury variables, lifetime psychiatric disorder, behavioral and adaptive function, family psychiatric history, family function, and socioeconomic class and intellectual function.

METHODS

Study Recruitment (1992–1994)

Children and adolescents ages 6–14, consecutively hospitalized between 1992 and 1994 for mild to severe TBI, were eligible for recruitment in this prospective longitudinal study, which was approved by the institutional review board at the University of Iowa. Additional eligibility criteria included having completed a head computerized tomography (CT) scan during initial hospitalization and having English as a primary language. Youths were excluded if they had a penetrating TBI, loss of consciousness greater than 3 months, prior TBI requiring hospitalization, history of child abuse, history of intellectual disability, or history of another neurologic or serious medical illness. Written informed consent was obtained from parents, and youths provided assent after they were able to demonstrate decision-making capacity to do so.

During the course of the recruitment period, 87 patients met eligibility criteria; 50 participants enrolled in the study and completed at least the psychiatric assessment component of the baseline evaluation. The most common reason provided for not enrolling in the study was that children with mild TBI and their parents believed that participation was unwarranted due to observation that the child had returned to baseline following the injury. Participating and nonparticipating youths did not differ in terms of age, sex, race, socioeconomic status, preinjury psychiatric disorder, or treatment, but they did differ in terms of TBI severity: participants were more likely to have severe TBI compared with nonparticipants. Overrepresentation of severe TBI in study participants may also be related to the main study site being a tertiary care hospital with a large catchment area (13).

We updated the severity classification of the participants to conform with current definitions for descriptive purposes. Severe injury was defined by a lowest postresuscitation Glasgow Coma Scale (GCS) score <8, moderate injury by a lowest postresuscitation GCS score of 9–12, complicated mild injury by a score of 13–15 with an intracranial lesion or depressed

skull fracture on initial CT scan, and uncomplicated mild injury was defined by a lowest postresuscitation GCS score of 13–15 unaccompanied by abnormality detected on the initial CT scan. The initial cohort of participating children (N=50) was categorized by injury severity as having experienced uncomplicated mild (N=26), complicated mild (N=5), moderate (N=4), and severe (N=15) TBI. Coma duration in subjects was as follows: no coma (N=22), <15 minutes (N=10), 1–24 hours (N=6), 1–2 days (N=2), 2–7 days (N=6), and >7 days (N=4). Subjects' posttraumatic amnesia (PTA) durations were no PTA (N=6), <15 minutes (N=1), 15–59 minutes (N=8), 1–24 hours (N=18), 1–2 days (N=3), 2–7 days (N=5), and >7 days (N=9). One subject remained in a vegetative state at all follow-up points and was therefore dropped from analyses. Causes of injury included motor vehicle accidents (N=10; 20%); bicycle or car accidents (N=6; 12%); falls from bicycles (N=9; 18%); other falls (N=10; 20%); sports and recreation (N=7; 14%); pedestrian-motor vehicle accidents (N=2; 4%); motorcycle/all-terrain vehicle accidents (N=2; 4%); and other (N=4; 8%).

Predictive Domain Models Derived From Baseline Assessments (1992–1994)

Comprehensive neurologic, psychiatric, family, and adaptive functioning assessments were conducted at baseline (mean=14 days [SD=13] postinjury) to assess severity of injury and degree of preinjury functioning. The assessments measuring distinct aspects and risk factors of NPD following pediatric TBI were grouped in six domains (severity of injury, lifetime psychiatric disorder, behavior/adaptive function, family psychiatric history, family function, and socioeconomic class and preinjury intellectual function).

The severity of injury domain consisted of three items: lowest postresuscitation GCS score (30), Traumatic Coma Data Bank (TCDB) categorization (31), and normal/abnormal initial day-of-injury CT scan. The GCS is a standard measure of acute brain injury severity; scores range from 3 (unresponsive) to 15 (normal) (30). Lowest postresuscitation score for each participant was obtained from the medical record. A pediatric radiologist and a pediatric neuroradiologist independently classified the initial day-of-injury CT scans as either showing an intracranial traumatic lesion or not. The radiologists additionally classified the CT scans according to the TCDB categorization, which incorporates the degree of brain edema and focal lesions into a single severity rating on a scale from 1 to 6 (31). Interrater reliability was excellent (13).

The lifetime psychiatric disorder domain was composed of the single variable, lifetime psychiatric disorder, and was based on baseline psychiatric assessments, which in all cases were conducted by a board-certified adult and child and adolescent psychiatrist (J.E.M.). Standardized, semistructured psychiatric interview assessments were used, including the Schedule for Affective Disorders and Schizophrenia for School-Age Children (32, 33), and psychiatric diagnoses were based on DSM-III-R criteria. The Neuropsychiatric Rating Schedule (NPRS), which is designed specifically to identify symptoms and subtypes of personality change due to TBI (34), was also administered at baseline.

The behavior/adaptive function domain included the following baseline variables: the adaptive behavior composite standard score, derived from the Vineland Adaptive Behavior Scale (VABS) interview conducted by a trained research assistant (35); and the total raw score on the parent-completed Pediatric Behavior Scale (PBS), a behavioral rating scale

designed specifically for use with pediatric neurological and other medical disorders (36). The VABS and PBS scores constituted the behavior/adaptive function variable.

The fourth domain, family psychiatric history, was based on the Family History Research Diagnostic Criteria Interview (37, 38).The interview was conducted at baseline, with parents acting as the informants. We summarized family ratings for first-degree relatives only and for a combined grouping of first- and second-degree relatives on a 4-point scale of increasing morbidity (39); both ratings comprised the family psychiatric history variable.

The fifth domain, family function, included baseline family assessment measures collected by both interview and questionnaire methods. The McMaster Structured Interview of Family Functioning is a research interview of the family and is based on the McMaster model of family functioning (40). The interviewer used the Clinical Rating Scale to rate each of six domains and global family functioning on a 7-point Likert scale, where higher scores indicated better function. In addition, the Family Assessment Device questionnaire was completed by family members at least 12 years of age (40), and the scores were used to calculate a mean global functioning dimension score for each family, where higher scores indicated worse function. The family function variable consisted of two ratings: the global family functioning score from the interview and from the questionnaire.

The socioeconomic class and preinjury intellectual function domain included four predictors. Socioeconomic class was assessed using the Four Factor Index, where higher scores indicated lower socioeconomic class (41). Measures used to assess intellectual function included teacher-report of preinjury intellectual ability and academic achievement on the PBS, along with preinjury national percentile rank for vocabulary on the Iowa Tests of Basic Skills, the latter of which is highly correlated with verbal IQ (42). Scores on the above four items made up the socioeconomic class and preinjury intellectual function variable.

Follow-Up at 24 Years (288 Months) Postinjury (2016–2018)

With approval from the institutional review boards of the University of Iowa and University of California, San Diego, participants who completed at least the baseline psychiatric assessment from 1992 to 1994 (N=50) were recontacted from 2016 to 2018 and invited to participate in a 24-year postinjury assessment that included psychiatric evaluation. At this long-term follow-up, we studied 43 (86%) participants with TBI in person, as well as the sibling of an original participant who died approximately 3 years prior to this wave of the study, and the parent of another participant who did not respond to our invitation to participate (N=45). The sibling and parent of these two original participants displayed in-depth knowledge of the probands. The study design allowed for the recruitment of a significant other (e.g., parent, partner, friend) for participants with TBI because of the possibility that awareness of deficits may be compromised after TBI; a total of 31 significant others participated. The mean interval from injury to long-term assessment was 23.92 years (SD=2.17).

Excluded participants included one original enrollee, who was still alive but who remained in a vegetative state and was therefore not eligible to participate. Four originally enrolled

participants (males, N=2; females, N=2; severe TBI, N=2; mild TBI, N=2) declined participation in the 24-year follow-up.

Psychiatric assessments were repeated at long-term follow-up by J.E.M. using the Mini-International Neuropsychiatric Interview (MINI) (43), and psychiatric diagnoses were made based on DSM-5 criteria. We used the NPRS again to diagnose personality change due to TBI (34). In cases where individuals with TBI and a significant other participated, best-estimate diagnoses were assigned based on integration of self-report and significant other report (44). An interrater reliability study was conducted by a board-certified psychiatrist (E.T.), which relied on ratings of videotaped interviews of TBI subjects, significant others when applicable, and healthy control subjects. Control subjects (N=45) were recruited and completed a single cross-sectional assessment for additional analyses (45), which are outside the scope of the current article. The board-certified psychiatrist (E.T.) was blind to group status (TBI versus control), and rated the videotaped interviews of every seventh TBI (N=7) and control participant (N=7). Interrater reliability for diagnoses was excellent (κ=0.962). There was perfect agreement on diagnoses in 12 out of 14 (86%) cases, as well as agreement on 54 out of 56 (96%) specific diagnoses that were recorded.

Current NPD (NPD-C) was the outcome variable of interest at the long-term follow-up; it was defined as a psychiatric disorder not present prior to TBI that was present at the assessment 24 years postinjury. Examples of NPD-C among participants included an individual with no preinjury psychiatric disorder who had attention deficit hyperactivity disorder (ADHD) at the 24-year assessment and an individual with only ADHD preinjury who had generalized anxiety disorder at the 24-year assessment.

Statistical Methods

To investigate the association between each of the six prespecified injury and preinjury domains (severity of injury, lifetime psychiatric disorder, behavior/adaptive function, family psychiatric history, family function, and socioeconomic class and preinjury intellectual function) and NPD-C at the 24-year follow-up, for each domain the k variables (k=1–4) were reduced to a single composite variable. The domain variable was the first principal component (PC1) from the principal component analysis (PCA) applied to the k variables in the domain, after centering and rescaling to unit variance, so that all domain variables receive equal weight in the PCA. PC1 is the projection of the rescaled k-dimensional response vectors onto the direction that captures the most variation in the data, and thus provides the best one-number summary of the k variables. The proportion of variance in the predictors explained by PC1 was reported. This dimension reduction is dictated by the low power due to the small sample size combined with a binary outcome. Logistic regression analyses were then conducted separately for each domain, with the PC1 as the predictor and NPD-C as the outcome. The association between the PC1 predictor and the outcome was evaluated using the likelihood ratio test. The strength of association was measured using R^2, the proportion of variability explained for logistic regression based on the average improvement in deviance per observation (46), and an analogous measure for variable-specific partial R^2. As a last step, a multipredictor logistic regression examined the domains associated with NPD-C at 24 years in an adjusted analysis. The final multipredictor

model was determined via stepwise backward model selection, with a threshold of a p value <0.15 of inclusion in the model. As a result of the small number of events, the starting multipredictor model only included the PC1 composite variable from domains that were associated with NPD-C at the 24-year outcome at a p value <0.15 in single-predictor analyses (47). All statistical analyses used the R statistical program, version 4.0.2 (48).

RESULTS

Demographic and injury severity data for individuals with pediatric TBI who participated in the long-term follow-up assessment and for those who were lost to follow-up are presented in Table 1. There were no significant differences in age of injury, sex, and race between those with TBI for whom data were available versus those for whom data were not available at the 24-year follow-up. The participants had a significantly higher socioeconomic status rating compared with nonparticipants (mean=2.33 [SD=0.91] versus mean=4.00 [SD=1.00]; t=3.08, df=46, p=0.004). However, one of the four nonparticipants had a missing socioeconomic status rating; it is therefore unknown if the socioeconomic status difference between participants and nonparticipants was realistic.

NPDs

NPD-C at the 24-year assessment was present in 24 out of 45 (53.3%) participants. NPD-Cs included personality change due to TBI (49), along with neurodevelopmental, depressive, anxiety, obsessive-compulsive, trauma-related, impulse-control, and substance-related disorders, as well as other specified mental disorder (Table 2).

Association of Injury and Preinjury Domains With NPDs

The logistic regression analysis of the association of each of the six domains with NPD-C revealed a significant association for preinjury lifetime psychiatric disorder (R^2=0.107, p=0.024) (Table 3). Three other domains showed association with NPD-C that fell short of statistical significance: severity of injury (R^2=0.071, p=0.072), behavior/adaptive function (R^2=0.065, p=0.100), and socioeconomic class and preinjury intellectual function (R^2=0.074, p=0.106).The factor loadings or weights of the individual tests on PC1 indicate that the association in all cases is in the expected direction.

The final multipredictor logistic regression model of NPD-C included PC1 variables for severity of injury (partial R^2=0.090, p=0.042) and for lifetime psychiatric disorder (partial R^2=0.144, p=0.009), with overall R^2=0.204, p=0.007.

The inspection of cases with regard to severity of injury (severe versus uncomplicated mild/complicated mild/moderate TBI) and presence or absence of preinjury lifetime psychiatric disorder is summarized in Table 4. Of the 12 participants with severe TBI, NPD-Cs were present in five out of six (83.3%) participants with no lifetime preinjury psychiatric disorder and in five out of six (83.3%) with a lifetime preinjury disorder. However, of the 33 participants with uncomplicated mild, complicated mild, and moderate TBI, NPD-Cs were present in three out of 16 (18.8%) participants with no lifetime preinjury psychiatric disorder and in 11 out of 17(64.7%) with a lifetime preinjury disorder (Fisher’s exact test=0.013).

DISCUSSION

The primary finding from this prospective longitudinal 24-year follow-up study of individuals who experienced a TBI requiring hospitalization at ages 6–14 years was that NPD-Cs in adulthood following pediatric TBI are independently predicted by preinjury lifetime psychiatric disorder and by greater severity of injury.

Preinjury lifetime psychiatric disorder has previously been shown to influence NPDs in the first 2 years after pediatric TBI (3), including earlier time points in the current prospective longitudinal study, particularly during the first 3 months, and in the second postinjury year (11, 13). The current finding suggests that this variable exerts its influence not only in the short term but also over more than two decades. The durability of this finding is striking, given that the participants were only aged 6–14 years when their vulnerability trait of preinjury psychiatric disorder was documented. It may be useful to think of this phenomenon as limited “behavioral reserve” increasing risk of psychiatric complications akin to the concept of limited “cognitive reserve” increasing the risk of cognitive problems after pediatric TBI (50).

The finding that severity of TBI independently significantly predicts long-term psychiatric outcome after pediatric TBI extends existing findings of a dose-response relationship from the first 2 years postinjury (3, 11, 51). This, too, is striking given that there are many intervening influences present over a span of 24 years of growth and development of children and adolescents that could mitigate the effect of injury severity.

Tying the independent significant effects of preinjury lifetime psychiatric disorder and severity of injury on NPDs may be additionally appreciated by inspection of the data. The predictive effect of preinjury lifetime psychiatric disorder is most evident in the mild to moderate TBI group, where individuals with a preinjury lifetime psychiatric disorder have significantly increased frequency of NPDs, compared with those without premorbid psychiatric history. In the severe TBI group, most individuals experienced onset of NPDs following their injury, regardless of premorbid psychiatric history. These findings suggest that severe TBI may overwhelm the protective effect of lack of preinjury lifetime psychiatric history, while mild to moderate TBI may not.

The rate of NPDs in this sample is high (53%) but consistent with other studies of shorter follow-up duration (3, 11, 52). The only disorder that is specific to TBI is personality change due to a general medical condition, which in this instance is TBI. Such heterogeneity in NPDs is typical in pediatric TBI studies (3, 11, 52). In the absence of a prospectively studied non-TBI control group, it is not possible to say conclusively which disorders occur at a significantly higher rate than expected. However, the rates of novel ADHD (30%) and novel generalized anxiety disorder (16%) appear to be higher than what might be expected in a general population sample (3.5% and 5.0%, respectively) (53, 54).

The current findings should be interpreted in light of the following limitations. First, the sample was relatively small (N=49 to N=50), and findings require replication in larger samples. However, attrition after 24 years was only 8%. Second, the longitudinal design did not include control subjects; we therefore cannot know whether the obtained model

predictive of NPD-C is unique to TBI patients. However, control subjects were recruited for the long-term assessment only and will be included in additional analyses (45). Third, most prospective longitudinal TBI studies have the limitation of requiring a retrospective assessment of preinjury variables. However, baseline assessments were completed as soon as possible after the initial injury, within a mean of 14 days (SD513). Fourth, the psychiatrist (J.E.M.) assessing the participants was not blind to group affiliation. Fifth, the psychiatric diagnoses during the first 2 years of follow-up applied DSM-III-R criteria, while the long-term follow-up diagnoses applied DSM-5 criteria. It is unclear how this may have changed the analyses, because preinjury lifetime psychiatric disorders were examined according to DSM-III-R and NPDs at long-term follow-up according to DSM-5. Sixth, in this exclusively hospitalized cohort, approximately half the participants had an uncomplicated mild TBI, a patient group that may be expected to have a low rate of NPD. However, a key finding in a systematic review on pediatric mild TBI is that a history of hospitalization for the mild TBI is associated with increased risk of psychiatric sequelae (9). Seventh, notwithstanding the in-depth knowledge displayed by the sibling of the deceased subject and the parent of the subject who did not respond to the invitation to participate, data generated directly from the probands would be preferable. Finally, consistent with the distribution of race in Iowa, all but one participant was White, which potentially limits generalizability to more diverse populations.

There were several notable strengths of the study. First, this is, to our knowledge, the only long-term prospective longitudinal psychiatric interview study of pediatric TBI. Second, the psychiatric assessment itself was a strong aspect of the study methodology. All psychiatric assessments from baseline through 24-year follow-up were completed by the same psychiatrist, who is board-certified in general psychiatry and in child and adolescent psychiatry. Diagnoses were made only in the face of true impairment, which requires clinical judgment. Assessment of most participants with TBI benefited from the input of significant others and served to address potential under-reporting due to lack of awareness of impairment in this group (55). Excellent interrater reliability was documented for psychiatric diagnoses with another board-certified psychiatrist who viewed videotapes of 16% of all interviews and who was blind to TBI versus control group affiliation. Third, attrition was only 8% at 24-year follow-up. The attrition rate was much lower than the three other long-term studies (16 to 23 years) that have examined behavioral domains of function in unselected cohorts, which had attrition rates of 34% to 69% (15–21). Fourth, the predictive models used for NPDs in the TBI cohort were based on comprehensive and clinically relevant biopsychosocial data derived from multiple sources, including the participants, parents, and teachers.

In conclusion, both preinjury lifetime psychiatric disorder and severity of injury are significant and independent predictors for long-term psychiatric complications following pediatric TBI. The results of the current study suggest that surveillance for the development of problems can be targeted in order to allow for early intervention to be delivered to affected individuals. For such intervention to be clinically meaningful, it will have to account not only for the novel disorders but also for the pre-existing disorders in this high-risk subpopulation of children with TBI constituting up to half of cases (7). Future studies involving longer term follow-up could reveal whether psychiatric disorders persist

into early and late middle age and whether the injury and preinjury risk factors change. Future analyses of data from the present study will compare adults exposed to pediatric TBI with healthy control subjects matched to age, socioeconomic status, and sex, and will also analyze cognitive function, occupational function, adaptive function, and neuroimaging correlates (6, 56) and their relationships with psychiatric disorders at long-term follow-up.

Acknowledgments

Drs. Max, Vaida, Wilde, and Hesselink receive research grant support from the National Institute of Child Health and Development (grant R-01 HD088438). Dr. Troyer receives research grant support from NIMH (grant T32MH018399). Drs. Yang and Tymofiyeva receive research grant support from the National Center for Complementary and Integrative Health (grants R21AT009173 and R61AT009864) and the National Center for Advancing Translational Sciences and NIH, through the University of California San Francisco-Clinical and Translational Science Institute (grant UL1TR001872). The other authors report no financial relationships with commercial interests.

This study was funded by a gift from Big Blue Sky Foundation.

REFERENCES

1. Dewan MC, Mummareddy N, Wellons JC 3rd, et al. : Epidemiology of global pediatric traumatic brain injury: qualitative review. World Neurosurg 2016; 91:497–509.e1 [PubMed: 27018009]
2. Shi J, Xiang H, Wheeler K, et al. : Costs, mortality likelihood and outcomes of hospitalized US children with traumatic brain injuries. Brain Inj 2009; 23:602–611 [PubMed: 19557562]
3. Brown G, Chadwick O, Shaffer D, et al. : A prospective study of children with head injuries: III. Psychiatric sequelae. Psychol Med 1981; 11:63–78 [PubMed: 7208747]
4. Fay GC, Jaffe KM, Polissar NL, et al. : Outcome of pediatric traumatic brain injury at three years: a cohort study. Arch Phys Med Rehabil 1994; 75:733–741 [PubMed: 8024416]
5. Schwartz L, Taylor HG, Drotar D, et al. : Long-term behavior problems following pediatric traumatic brain injury: prevalence, predictors, and correlates. J Pediatr Psychol 2003; 28:251–263 [PubMed: 12730282]
6. Yeates KO, Bigler ED, Dennis M, et al. : Social outcomes in childhood brain disorder: a heuristic integration of social neuroscience and developmental psychology. Psychol Bull 2007; 133:535–556 [PubMed: 17469991]
7. Max JE: Neuropsychiatry of pediatric traumatic brain injury. Psychiatr Clin North Am 2014; 37:125–140 [PubMed: 24529428]
8. Max JE, Wilde EA, Bigler ED, et al. : Neuroimaging correlates of novel psychiatric disorders after pediatric traumatic brain injury. J Am Acad Child Adolesc Psychiatry 2012; 51:1208–1217 [PubMed: 23101746]
9. Emery CA, Barlow KM, Brooks BL, et al. : A systematic review of psychiatric, psychological, and behavioural outcomes following mild traumatic brain injury in children and adolescents. Can J Psychiatry 2016; 61:259–269 [PubMed: 27254800]
10. Max JE, Lindgren SD, Robin DA, et al. : Traumatic brain injury in children and adolescents: psychiatric disorders in the second three months. J Nerv Ment Dis 1997; 185:394–401 [PubMed: 9205426]
11. Max JE, Robin DA, Lindgren SD, et al. : Traumatic brain injury in children and adolescents: psychiatric disorders at two years. J Am Acad Child Adolesc Psychiatry 1997; 36:1278–1285 [PubMed: 9291730]
12. Max JE, Robin DA, Lindgren SD, et al. : Traumatic brain injury in children and adolescents: psychiatric disorders at one year. J Neuropsychiatry Clin Neurosci 1998; 10:290–297 [PubMed: 9706536]
13. Max JE, Smith WL Jr, Sato Y, et al. : Traumatic brain injury in children and adolescents: psychiatric disorders in the first three months. J Am Acad Child Adolesc Psychiatry 1997; 36:94–102 [PubMed: 9000786]

14. Max JE, Friedman K, Wilde EA, et al. : Psychiatric disorders in children and adolescents 24 months after mild traumatic brain injury. J Neuropsychiatry Clin Neurosci 2015; 27:112–120 [PubMed: 25923850]
15. Hessen E, Anderson V, Nestvold K: MMPI-2 profiles 23 years after paediatric mild traumatic brain injury. Brain Inj 2008; 22:39–50 [PubMed: 18183508]
16. Klonoff H, Clark C, Klonoff PS: Long-term outcome of head injuries: a 23 year follow up study of children with head injuries. J Neurol Neurosurg Psychiatry 1993; 56:410–415 [PubMed: 8482963]
17. Klonoff H, Low MD, Clark C: Head injuries in children: a prospective five year follow-up. J Neurol Neurosurg Psychiatry 1977; 40: 1211–1219 [PubMed: 591990]
18. Rosema S, Muscara F, Anderson V, et al. : Agreement on and predictors of long-term psychosocial development 16 years post-childhood traumatic brain injury. J Neurotrauma 2014; 31:899–905 [PubMed: 24417184]
19. Ryan NP, Anderson V, Godfrey C, et al. : Predictors of very-long-term sociocognitive function after pediatric traumatic brain injury: evidence for the vulnerability of the immature “social brain”. J Neurotrauma 2014; 31:649–657 [PubMed: 24147615]
20. Ryan NP, Anderson V, Godfrey C, et al. : Social communication mediates the relationship between emotion perception and externalizing behaviors in young adult survivors of pediatric traumatic brain injury (TBI). Int J Dev Neurosci 2013; 31:811–819 [PubMed: 24140241]
21. Hessen E, Nestvold K, Anderson V: Neuropsychological function 23 years after mild traumatic brain injury: a comparison of outcome after paediatric and adult head injuries. Brain Inj 2007; 21: 963–979 [PubMed: 17729049]
22. Cattelani R, Lombardi F, Brianti R, et al. : Traumatic brain injury in childhood: intellectual, behavioural and social outcome into adulthood. Brain Inj 1998; 12:283–296 [PubMed: 9562911]
23. Jonsson CA, Horneman G, Emanuelson I: Neuropsychological progress during 14 years after severe traumatic brain injury in childhood and adolescence. Brain Inj 2004; 18:921–934 [PubMed: 15223744]
24. Nybo T, Koskiniemi M: Cognitive indicators of vocational outcome after severe traumatic brain injury (TBI) in childhood. Brain Inj 1999; 13:759–766 [PubMed: 10576460]
25. Koskiniemi M, Kyykkä T, Nybo T, et al. : Long-term outcome after severe brain injury in preschoolers is worse than expected. Arch Pediatr Adolesc Med 1995; 149:249–254 [PubMed: 7532073]
26. Boden JM, Fergusson DM, Horwood LJ: Associations between exposure to stressful life events and alcohol use disorder in a longitudinal birth cohort studied to age 30. Drug Alcohol Depend 2014; 142:154–160 [PubMed: 25001278]
27. Levy S, Katusic SK, Colligan RC, et al. : Childhood ADHD and risk for substance dependence in adulthood: a longitudinal, population-based study. PLoS One 2014; 9:e105640 [PubMed: 25162629]
28. Moffitt TE, Caspi A, Taylor A, et al. : How common are common mental disorders? Evidence that lifetime prevalence rates are doubled by prospective versus retrospective ascertainment. Psychol Med 2010; 40:899–909 [PubMed: 19719899]
29. Moffitt TE, Harrington H, Caspi A, et al. : Depression and generalized anxiety disorder: cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. Arch Gen Psychiatry 2007; 64:651–660 [PubMed: 17548747]
30. Teasdale G, Jennett B: Assessment of coma and impaired consciousness. A practical scale. Lancet 1974; 2:81–84 [PubMed: 4136544]
31. Marshall LF, Marshall SB, Klauber MR, et al. : The diagnosis of head injury requires a classification based on computed axial tomography. J Neurotrauma 1992; 9(Suppl 1):S287–S292 [PubMed: 1588618]
32. Chambers WJ, Puig-Antich J, Hirsch M, et al. : The assessment of affective disorders in children and adolescents by semistructured interview: test-retest reliability of the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present Episode Version. Arch Gen Psychiatry 1985; 42:696–702 [PubMed: 4015311]

33. Orvaschel H, Puig-Antich J, Chambers W, et al. : Retrospective assessment of prepubertal major depression with the Kiddie-SADS-e. J Am Acad Child Psychiatry 1982; 21:392–397 [PubMed: 7119313]
34. Max JE, Castillo CS, Lindgren SD, et al. : The Neuropsychiatric Rating Schedule: reliability and validity. J Am Acad Child Adolesc Psychiatry 1998; 37:297–304 [PubMed: 9519635]
35. Sparrow S, Balla D, Cicchetti D: The Vineland Adaptive Behavior Scales. Circle Pines, Minn., American Guidance Services, 1984
36. Lindgren SD, Koeppl GK: Assessing child behavior problems in a medical setting: Development of the pediatric behavior scale; in Advances in Behavioral Assessment of Children and Families. Edited by Prinz RJ. Greenwich, Conn., JAI Press, 1987; 3:57–90
37. Andreasen NC, Endicott J, Spitzer RL, et al. : The family history method using diagnostic criteria. Reliability and validity. Arch Gen Psychiatry 1977; 34:1229–1235 [PubMed: 911222]
38. Andreasen NC, Rice J, Endicott J, et al.: The family history approach to diagnosis, in Psychatric Epidemiology Assessment Concepts and Methods. Edited by Mezzich JE, Jorge MR, Salloum IM. Baltimore, The John Hopkins University Press, 1994, pp 349–367
39. Max JE, Arndt S, Castillo CS, et al. : Attention-deficit hyperactivity symptomatology after traumatic brain injury: a prospective study. J Am Acad Child Adolesc Psychiatry 1998; 37:841–847 [PubMed: 9695446]
40. Miller IW, Kabacoff RI, Epstein NB, et al. : The development of a clinical rating scale for the McMaster model of family functioning. Fam Process 1994; 33:53–69 [PubMed: 8039568]
41. Hollingshead A: Four Factor Index of Social Status. New Haven, Conn., Department of Sociology, Yale University,, 1975
42. Hieronymus AN, Hoover HD: Manual for School Administrators: Iowa Tests of Basic Skills, Forms G/H. Chicago, Riverside Publishing Company, 1986
43. Sheehan DV, Lecrubier Y, Sheehan KH, et al. : The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998; 59(Suppl 20):22–33
44. Leckman JF, Sholomskas D, Thompson WD, et al. : Best estimate of lifetime psychiatric diagnosis: a methodological study. Arch Gen Psychiatry 1982; 39:879–883 [PubMed: 7103676]
45. Arif H, Troyer EA, Paulsen JS, et al. : Long-term psychiatric outcomes in adults with history of pediatric traumatic brain injury. J Neurotrauma 2021; 38:1515–1525 [PubMed: 33765846]
46. Kent JT: Information gain and a general measure of correlation. Biometrika 1983; 70:163–173
47. Vittinghoff E, Glidden DV, Shiboski SC, et al.: Predictor Selection: Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models, 2nd ed. New York, Springer, 2012, pp. 395–429
48. Team RCR: A Language and Environment for Statistical Computing. Vienna, Austria, R Foundation for Statistical Computing, 2020
49. Max JE, Bigler ED, Hesselink JR, et al.: Phineas Re-enGage: long-term psychiatric follow-up of pediatric traumatic brain injury, in Pediatric Neuropsychiatry: A Clinical Casebook. Edited by Hauptman A, Salpekar JA. Cham, Switzerland, Springer International Publishing, 2019, pp. 13–23
50. Donders J, Kim E: Effect of cognitive reserve on children with traumatic brain injury. J Int Neuropsychol Soc 2019; 25:355–361 [PubMed: 31050332]
51. Black P, Jeffries JJ, Blumer D, et al.: The posttraumatic syndrome in children: characteristics and incidence; in Walker AE, Caveness WF, Critchley M. The Late Effects of Head Injury. Springfield, Ill, C. C. Thomas, 1969, pp. 142–149
52. Max JE, Wilde EA, Bigler ED, et al. : Psychiatric disorders after pediatric traumatic brain injury: a prospective, longitudinal, controlled study. J Neuropsychiatry Clin Neurosci 2012; 24:427–436 [PubMed: 23224448]
53. Matte B, Anselmi L, Salum GA, et al. : ADHD in DSM-5: a field trial in a large, representative sample of 18- to 19-year-old adults. Psychol Med 2015; 45:361–373 [PubMed: 25066615]
54. Ruscio AM, Hallion LS, Lim CCW, et al. : Cross-sectional comparison of the epidemiology of DSM-5 generalized anxiety disorder across the globe. JAMA Psychiatry 2017; 74:465–475 [PubMed: 28297020]

55. Prigatano G: Psychiatric aspects of head injury: problem areas and suggested guidelines for research, in Neurobehavioral Recovery From Head Injury. Edited by Grafman J, Levin HS, Eisenberg HM. New York, Oxford University Press, 1987, 215–231

56. Stein MB, McAllister TW: Exploring the convergence of posttraumatic stress disorder and mild traumatic brain injury. Am J Psychiatry 2009; 166:768–776 [PubMed: 19448186]

TABLE 1.

Characteristics of participants versus nonparticipants at 24 years after traumatic brain injury (TBI)

Characteristic	TBI group (N=45)		Lost to follow-up group (N=4)	
	Mean	**SD**	**Mean**	**SD**
Age (years)	34.29	2.72	36.14	1.55[a]
	N	**%**	**N**	**%**
Male	29	64.4	2	50
White	44	97.8	4	100
	Mean	**SD**	**Mean**	**SD**
Socioeconomic status[b]	2.18	0.98	4.0[b]	1.0
	N	**%**	**N**	**%**
Injury severity				
Uncomplicated mild TBI	24	53	2	50
Complicated mild TBI	5	11	0	0
Moderate TBI	4	9	0	0
Severe TBI	12	27	2	50

[a]Age for individuals lost to follow-up was calculated by designating the calendar midpoint of the long-term assessment study phase as their date of would-be participation.

[b]In the lost-to-follow-up group, socioeconomic class data were available for three participants.

TABLE 2.

Novel psychiatric disorders following traumatic brain injury (TBI) at the 24-year follow-up assessment

	Current novel psychiatric disorders	
Disorder	**N**[a]	**%**
Organic mental disorders		
Personality change due to TBI	2/44	4.5
Labile type	2/44	4.5
Aggressive type	1/44	2.3
Disinhibited type	1/44	2.3
Neurodevelopmental disorders		
ADHD	12/40	30.0
Predominantly inattentive presentation	5/40	12.5
Combined presentation	0/40	0
Other specified or unspecified ADHD	7/40	17.5
Persistent motor tic disorder	1/45	2.2
Depressive disorders		
Major depressive disorder	5/40	12.5
Other specified depressive disorder	2/40	5.0
Anxiety disorders		
Social anxiety disorder	3/42	7.1
Panic disorder	2/45	4.4
Agoraphobia	1/43	2.3
Generalized anxiety disorder	7/43	16.3
Obsessive-compulsive and related disorders		
Obsessive-compulsive disorder	2/44	4.6
Trauma- and stressor-related disorders		
Posttraumatic stress disorder	5/44	11.4
Disruptive, impulse-control, and conduct disorders		
Conduct disorder	1/44	2.3
Substance-related and addictive disorders		
Alcohol use disorder	5/45	11.1
Substance use disorder	6/45	13.3
Other		
Other specified mental disorder[b]	1/45	2.2

[a]The denominators vary from 45 to 40, reflecting the fact that participants with a specific preinjury disorder were not able to develop that specific novel psychiatric disorder (e.g., five participants had preinjury attention deficit hyperactivity disorder [ADHD], and therefore only 40 of the 45 participants were able to develop novel ADHD). Substance use disorder in an individual was not counted as resolved when the participant discontinued using one substance but still abused at least one other substance (N=3). The index injury was not the source of the trauma in any of the participants with novel posttraumatic stress disorder.

[b]One individual was assigned a diagnosis of other specified mental disorder. The individual reported chronic and impairing irritability and anger but did not meet full criteria for a depressive or bipolar spectrum disorder.

TABLE 3.

Prediction domains of current novel psychiatric disorders at 24 years following pediatric traumatic brain injury (TBI)[a]

Prediction domain	Factor loadings	PVE_1	R^2	p
Severity of injury (lowGCS, CT, DAI)[b]	0.54, −0.61, 0.57	0.80	0.071	0.072
Lifetime psychiatric disorder	1	1.00	0.107	0.024
Behavior/adaptive function (ABCSS, PBStot)[c]	0.71, −0.71	0.80	0.065	0.100
Family psychiatric history (famstat1, famstat2)[d]	0.71, −0.71	0.76	0.000	0.99
Family function (CRS, FAD)[e]	−0.71, 0.71	0.68	0.026	0.31
SES and preinjury intellectual function (SES, ability, achievement, NPRVocab)[f]	−0.29, 0.59, 0.58, 0.49	0.57	0.074	0.106

[a]Current novel psychiatric disorder (NPD-C) refers to a psychiatric disorder present at the 24-year follow-up assessment that was not evident at any point before the injury; factor loading refers to the relative weight of each standardized test in the first principal component (PC1) for that domain; PVE_1=proportion of variance of domain tests explained by PC1. R^2=proportion of variance in NPD-C outcome explained by PC1 predictor. The p value is derived from the likelihood ratio test of association in single-predictor logistic regression.

[b]Severity of injury domain variables consist of the lowest postresuscitation Glasgow Coma Scale score (lowGCS), day-of-injury computerized tomography (CT) scan, and diffuse axonal injury (DAI) score on the Traumatic Coma Data Bank categorization.

[c]Behavior/adaptive function domain variables consist of the adaptive behavior composite standardized score (ABCSS) on the Vineland Adaptive Behavior Scales and the Total Score on the Pediatric Behavior Scale (PBStot).

[d]Family psychiatric history domain variables consist of the family psychiatric history score in first-degree relatives (famstat1) and in first- and second-degree relatives (famstat2).

[e]Family function domain variables consist of the family function score on the McMaster Clinical Rating Scale (CRS) from the McMaster Structured Interview of Family Function and the global functioning score on the Family Assessment Device (FAD).

[f]Socioeconomic class and preinjury intellectual function domain variables consist of socioeconomic status (SES), teacher-report of preinjury intellectual ability (ability) and of academic achievement (achievement) on the Pediatric Behavior Scale, and the preinjury national percentile rank for vocabulary (NPRVocab) on the Iowa Tests of Basic Skills.

TABLE 4.

Novel psychiatric disorder present at the 24-year follow-up among participants with traumatic brain injury (TBI), stratified by injury severity and preinjury psychiatric disorder status[a]

	Severe TBI (N=12)		Moderate TBI (N=4)		Complicated mild TBI (N=5)		Uncomplicated mild TBI (N=24)	
Disorder	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
No lifetime psychiatric disorder preinjury	5/6	83.3	0/3	0	1/2	50.0	2/11	18.2
Lifetime psychiatric disorder preinjury	5/6	83.3	1/1	100	3/3	100	7/13	53.9

[a]Lifetime psychiatric disorders are those detected at baseline assessment (i.e., with onset prior to TBI and regardless of whether the disorder had remitted prior to the injury or persisted up to the time of injury).