

## Traumatic brain injury and suicide risk

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### Summary

*Among the various consequences of traumatic brain injury (TBI), evidence supports the notion that individuals exposed to such events may be at higher risk of suicide. We therefore aim at reviewing the literature by focusing on possible association between TBI and features of the suicidal spectrum, such as suicidal ideation, suicide attempts and completed suicides. We carried out a computerized search for reports of studies involving TBI and suicide risk. A total of 35 reports provide data with preliminary support of this association. Seven articles showed a direct correlation between TBI and completed suicides. Thirteen articles have shown a direct relationship between TBI and suicide attempts; five articles demonstrated a positive correlation with suicidal ideation and suicidality. We also found negative results failing to show a correlation between TBI and completed suicides (one article), suicide attempts (one article) and suicidality (one article). In addition, one article showed that patients who received psychological treatment (CBT therapy) after suffering a head injury showed a significant reduction in suicidal ideation.*

*These preliminary findings encourage further testing of the association between TBI and suicide risk regardless of the psychiatric history. Furthermore, those who have a history of psychiatric illness before the TBI present a greater risk of suicide than those who do not have psychiatric precedents.*

### Key words

Traumatic brain injury • Suicide risk • Psychiatric history • Prevention

### Introduction

Traumatic brain injury (TBI) <sup>1-5</sup> is defined as a change in neural functioning as a result of an external force which acts on the brain, either directly or indirectly <sup>5</sup>. In Europe, the incidence of TBI is around 235 cases per 100,000 inhabitants per year <sup>6</sup>. Head injuries, in terms of frequency and the use of medical resources, are one of the major health problems and the leading cause of death in people aged 15-44. In Italy, the hospitalization rate is about 250-300 cases per 100,000 inhabitants each year<sup>7</sup>, which is in line with other European countries <sup>8-12</sup>. The most frequent causes of head injuries in Europe are road accidents (10-56%), accidental falls (31-62%), interpersonal aggression (6-34%), suicide (12%), and other causes (9-15%) <sup>13-19</sup>.

After a TBI, most patients have a complete resolution within a few weeks or months, while about 10-25% will have persistent symptoms accompanied by social and occupational consequences based on the severity of the initial neurological trauma <sup>19-32</sup>. These symptoms, defined as post-concussive syndrome (PCS), include somatic, cognitive and emotional disorders (such as headaches, increased fatigue, sleep disturbances, balance disorders, mood and behavioral changes) <sup>33</sup>. People with a history of head injury have a suicide risk ranging from 1.55 to 4.05 times higher than the general population <sup>34-38</sup>.

The association between TBI and suicide has been evaluated in several studies. In particular, a higher rate of suicide among people with brain injuries has been found <sup>39-40</sup>, although the sample sizes are small. TBI and

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suicide share some risk factors, namely being male, with young age, living in unfavorable social conditions and having and abuse of alcohol and drugs<sup>41-43</sup>. Therefore, it is of interest to understand the extent to which *TBI itself* is a risk factor for suicide.

The above-mentioned background encouraged the present overview of research pertaining to suicidal risk in relation to TBI. Given the relatively early state of this area of inquiry, we viewed our task as gathering and critically appraising the available research relevant to the topic, with the aim of formulating a hypothesis to be tested with further research.

By reviewing selected articles we identified some specific fields of interest. We also consulted a number of international experts in the field to determine whether the studies selected were relevant for discussing preventive measures for suicide risk in TBI. The authors and experts consulted performed a careful analysis of the literature data and agreed on a number of key subjects relevant to the aim of this paper.

We will therefore review studies dealing with the impact of TBI on completed suicide, attempted suicide, suicidal ideation and suicide risk as a whole. The aim of this paper is to evaluate the role of TBI as a risk factor for suicide and stimulate further discussion on the field of prevention of suicidal behaviour in TBI.

### Studies evaluating the impact of TBI on completed suicide

The relationship between TBI and suicide has been confirmed in several studies. In a retrospective cohort study<sup>44</sup>, it has been found that people with TBI had a 3-times higher risk of dying by suicide than people without a history of TBI (SMR: 2.95; CI 95%; 1.42-5.43).

In particular, Brenner et al.<sup>45</sup> studied 7,850,472 veterans. Veterans with a previous TBI were 1.55 times more likely to die by suicide than those without TBI ( $p < 0.0001$ ): those with concussion or cranial fracture were 1.98 times more likely to die by suicide ( $p = 0.0002$ ) and those with cerebral contusion or traumatic intracranial hemorrhage were 1.34 times more likely to die by suicide ( $p = 0.006$ ) as compared to those without a TBI.

Richard et al.<sup>46</sup> found that the association between TBI and death by suicide was higher if the trauma occurred in adulthood [(HR) = 2.53, 95% CI: 1.79-3.59] compared to adolescence [(HR) = 1.57, 95% CI: 1.09-2.26] or infancy [(HR) = 1.49, 95% CI: 1.04-2.14]. The death by suicide was higher in subjects with male gender (HR: 4.69 vs 1.00), with the more serious injuries [HR = 2.77, 95% CI: 2.01-3.83], and with a mental disorder prior to the trauma. In a study conducted in Finland<sup>47</sup>, it was found that the interval between the TBI and suicide was shorter if the individual had a prior psychiatric disorder. Patients with TBI had a higher risk of premature death in general and by suicide in the 6 months after a TBI

compared to the general population. Death by suicide occurred significantly more often in TBI patients than in general population (OR = 3.3; CI 95%: 2.9-3.7)<sup>47</sup>.

In a 20-year follow-up study carried out in Canada<sup>48</sup>, the authors found 667 suicide deaths after a median of 9.3 years since the TBI (a rate of 31 suicides per 100,000 patients annually).

In Denmark, Teasdale and Enberg<sup>49</sup> found standardized mortality ratios for suicide that were higher in patients with concussion (3.02, 95% CI: 2.82-3.25), cranial fracture (2.7, 95% CI: 2.01-3.59) and brain lesions (4.1, 95% CI: 3.33-4.93) compared to the general population. Standardized mortality ratios for suicide were greater among females than male subjects in all groups. The suicide rate was higher in those aged 21-60, with substance abuse and with prolonged hospitalization [ $< 1$  week (HR): 3.51, 95% CI: 2.08-5.92;  $> 3$  months (HR): 4.85, 95% CI: 2.97-7.92).

Only one study by Shavelle et al.<sup>50</sup>, including 2,320 subjects with intellectual disability, found that TBI increased the overall mortality risk (SMR = 3.1; CI 95% 2.5-3.7), but not by suicide compared to the general population.

### Studies evaluating the impact of TBI on attempted suicide

The association between having a TBI and suicide attempts have been evaluated in several longitudinal and cohort studies. In particular, Fonda et al.<sup>51</sup> found, in a cohort study including 273,591 veterans (42,392 [16%] with TBI and 231,199 [84%] without TBI), a 4-times higher risk of attempted suicide for those with TBI (hazard ratio = 3.76, 95% CI: 3.15-4.49). Moreover, veterans with TBI more frequently had a psychiatric disorder than those without TBI. Comorbidity with psychiatric disorders explained 83% of the association between TBI and attempted suicide, with PTSD having the largest impact. Brenner et al.<sup>52</sup> studied 133 veterans and they found that veterans with a previous suicide attempt and TBI did not show any learning over the course of the Iowa Gambling Test (IGT) unlike all the other groups. No differences were found on other aspects of executive function.

Several studies<sup>53-57</sup> have found a positive association between having a TBI and suicidal attempts after adjusting for any comorbid psychiatric disorder, demographic variables and quality of life.

In several longitudinal studies, it has been confirmed that rates of suicide attempts, suicidal ideation and of depressive symptoms were higher in patients with a TBI than in the general population<sup>58 59</sup>.

Homafair et al.<sup>60</sup> explored the relationship between TBI, executive dysfunction and suicide attempts, and found that patients attempting suicide had a higher level of perseveration than subjects without a previous suicide attempts ( $p = 0.04$ ).

Illie et al.<sup>61</sup> found a statistically significant difference in psychological distress, suicidal ideation and suicide attempts in TBI patients compared to patients without TBI. However, in a study on the impact of PTSD and TBI on suicidal attempts, after adjusting for age and gender, the odds of a suicide attempt for subjects with PTSD were 2.8 (95% CI: 1.5, 5.1), while it was 1.03 if TBI was considered alone. When the impact of PTSD and TBI were evaluated together, only PTSD was significant<sup>62</sup>.

### Studies evaluating the impact of TBI on suicidal ideation

Several factors have been investigated as possible predictors of suicidal ideation in patients suffering from TBI. In particular, it was found that the trauma mode<sup>63</sup> and sleep quality<sup>64</sup> are significant factors.

In a study by Gunter et al.<sup>65</sup>, having a TBI was found to be a risk factor for suicidal ideation or behaviour ( $p \leq 0.007$ , OR = 2.63, 95% CI: 1.30-5.35), together with other factors such as Caucasian ethnicity ( $p \leq 0.001$ , OR = 5.98, 95% CI: 2.38-14.97), depressive symptoms ( $p \leq 0.003$ , OR = 1.13, 95% CI: 1.04-1.23), childhood trauma ( $p \leq 0.008$ , OR = 2.70, 95% CI: 1.30-5.61) and avoidant personality ( $p \leq 0.028$ , OR = 2.97, 95% CI: 1.12-7.87).

Wisco et al.<sup>66</sup> examined the association between TBI history and suicidal ideation and found that TBI was significantly associated with suicidal ideation only in male veterans (RR = 1.55). Moreover, multiple TBIs and TBI with loss of consciousness, depressive symptoms and PTSD were more strongly associated with suicidal ideation.

In a longitudinal study, it was reported that people with TBI are at higher risk to report suicidal ideation, even one year after the trauma<sup>67</sup>.

Moreover, the mediating role of anger and depressive symptoms has been explored as an explanation for suicidal ideation in patients with TBI. It was found that TBI significantly predicted anger ( $B = 11.845$ ,  $SE = 5.281$ ,  $p = 0.026$ ); anger significantly predicted depression ( $B = 0.020$ ,  $SE = 0.002$ ,  $p < 0.001$ ) and depression significantly predicted suicide risk ( $B = 0.788$ ,  $SE = 0.178$ ,  $p < 0.001$ )<sup>68</sup>.

An association between disinhibition and suicidal behavior was found 6 and 12 months after the TBI ( $p = 0.045$ ,  $p = 0.033$ , respectively)<sup>69</sup>. Bryan et al.<sup>70</sup> found that TBIs were significantly associated with increases in depression and PTSD symptom intensity. TBIs were also associated with a greater incidence of lifetime suicidal thoughts or behaviors. Greater suicide risk was related to the number of TBIs ( $\beta$  [SE] = 0.214 [0.098];  $p = 0.03$ ) after correcting for the influence of depression, PTSD, and TBI symptom intensity. Cumulative TBIs were also associated with a higher severity of depressive symptoms ( $\beta = 0.580$  [0.283];  $p = 0.04$ ).

### Studies evaluating the impact of TBI on suicide risk

The association between suicide risk and presence of TBI has been confirmed in several studies with veterans. In particular, Brenner et al.<sup>71</sup> found that veterans with TBI were 3.6 times more likely to report suicide risk, even after correcting for the number of psychiatric diagnoses (95% CI: 1.4, 9.0;  $p = 0.007$ ). This finding has been confirmed in another study<sup>72</sup>, showing that depressive and PTSD symptoms were significantly associated with increased suicide risk among patients with a diagnosis of TBI ( $p < 0.001$ ). Moreover, veterans at greater risk of suicide exhibited post-TBI symptoms more frequently than those with no or low risk, including blurred vision, seizures, memory difficulties or problem-solving difficulties and difficulty in managing stress<sup>73</sup>.

The association between suicide risk and TBI has been confirmed also in samples with college students<sup>74</sup>, even after controlling for other well-known risk factors such as depression, perceived burdensomeness, thwarted belongingness, and acquired capability.

Only one study did not confirm the association between TBI and suicide risk<sup>75</sup>. Simpson and Tate<sup>76</sup> found no relationship between injury severity and suicide risk.

## Discussion

The present review aimed to investigate the relationship between TBI and suicide and, in particular, the relationship between head injuries and suicidal ideation, suicide behaviors, suicide attempts and completed suicides. According to our findings, TBI is a risk factor for suicidal ideation, suicide attempts and deaths by suicide. In particular, the consequences of TBI can include psychological distress, depression and suicidal behavior. Furthermore, suicide and TBI share several common risk factors such as younger age, male sex, substance use and aggression. The present findings are consistent with previous reviews<sup>79-81</sup>.

It is important to understand how TBI can indirectly increase the risk of suicidal ideation and behaviors, suicide attempts and complete suicide. Head injuries, especially mild ones, cause an indirect increase in suicide risk mediated by the worsening of depressive symptoms and aggressiveness<sup>68</sup>.

Other factors can explain the increased risk of suicidal behaviours in patients with TBI, such as the increase in levels of TNF- $\alpha$  and the alteration of sleep quality.

Moreover, the suicidal risk is even higher in patients with TBI and a history of mental and substance abuse disorders.

Therefore, in order to avoid the onset of suicidal ideation and suicide attempts, it is extremely important to detect and appropriately treat TBI and its consequences. In particular, in patients with TBI, it is the frequent development of post-traumatic amnesia and hopelessness,

which represent *per se* a relevant risk factor for suicide<sup>79</sup>. It is necessary to promote screening programs for an early identification of patients at higher suicide risk, using the TBI-4 scale<sup>73</sup>.

Several studies were conducted on war veterans. Veterans with a history of TBI and PTSD<sup>51</sup> are at greater risk of suicide than those without a history of TBI<sup>34 45 57 71</sup>. According to Barnes et al.<sup>75</sup>, if PTSD and TBI are associated with a higher risk of suicide than PTSD alone, the added risk is attributable to the severity of the PTSD symptoms. A greater risk of dying by suicide has been shown in children, adolescents and adults with a history of TBI compared with those with no TBI<sup>46 61</sup>. The risk of death by suicide is greater in subjects who suffered from TBI in adulthood compared to those experiencing TBI in childhood or adolescence<sup>46</sup>.

### Psychopathological implications

Traumatic brain injury is an alteration in brain function, or other evidence of brain pathology, caused by an external force<sup>79</sup>. Neurotrauma can cause brain alterations that result in neuropsychiatric sequelae and functional deficits in those who experience such injuries. The brain regions most frequently affected by TBI damage are the frontal cortex and the subfrontal white matter, the basal ganglia and the diencephalon, the rostral cerebral trunk and temporal lobes including the hippocampus. In relation to the post-TBI brain damage, there is a consequent profile of neurobehavioural sequelae characterized by cognitive deficits (memory, attention, executive function, speed of information processing), personality changes (better characterized as dysexecutive syndromes involving social behavior, cognition and motivated behavior) and increased rates of psychiatric disorders, including mood disorders, sleep disorders, sub-

stance abuse, psychotic syndromes and post-traumatic stress disorder<sup>80</sup>.

### Limitations

This review has several limitations, which must be acknowledged. Firstly, it was not possible to carry on a meta-analysis due to the variety of methodologies adopted in the included studies. Second, only studies published in English and in peer-reviewed journals were considered. Furthermore, although our approach was comprehensive, we did not attempt a systematic analysis which may have left out of this review possible papers of interest. We chose to report those studies available in the literature that could support a broad analysis of the topic so as to offer a tutorial paper. After a careful and systematic search, we extrapolated from those studies with the aim of formulating a hypothesis to be tested with further research.

### Conclusions

Although TBI represents a risk factor for suicidal ideation and suicide attempts, patients with a history of psychiatric illness prior to the TBI present a higher risk than those who do not have psychiatric precedents, and they die by suicide sooner after the initial evaluation than those who do not have psychiatric precedents<sup>46</sup>. Indeed, it is important to note how subjects with a TBI, not only have an increased risk of developing suicidal behaviors, but they also die by suicide earlier than others regardless of the presence or absence of a psychiatric history.

### Conflict of Interest

The authors have no conflict of interests.

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## POSITIVE FINDINGS

| Completed suicide           |                                   |   |   |
|-----------------------------|-----------------------------------|---|---|
| Author, year                | Study                             | Sample  | Aims  |
| Teasdale & Engberg, 2001    | Population study                  | 145,440 patients admitted for TBI between the years 1979 and 1993: patients with concussion (n = 126, 114), with a cranial fracture (n = 7,560), with a cerebral contusion or traumatic intracranial haemorrhage (n = 11,766) | To evaluate the suicide rate in a group of Danish patients with a history of TBI  |
| Mainio et al., 2007         |                                   | 1,877 suicide victims   | To study the prevalence of TBI among suicides and to evaluate the association of suicide, TBI and psychiatric disorders |
| Harrison-felix et al., 2009 | Retrospective cohort study        | 1,678 TBI patients admitted to Craig Hospital within 1 year of injury (between 1961 to 2002)  | To investigate mortality in patients with TBI   |
| Brenner et al, 2011         | Observational retrospective study | 81 veterans with a history of suicide attempts between October 2004 and February 2006   | To examine the association between suicide attempt history among veterans with PTSD and/or TBI                          |
| Fazel et al.; 2014          |                                   | 218,300 patients with a previous TBI studied between 1969-2009 compared to 2,163,190 controls; and 150,513 TBI patients with siblings without TBI compared with 237,535 sibling controls without TBI                          | To evaluate premature mortality in TBI patients vs general population   |
| Richard et al., 2015        |                                   | 134,629 children aged 0-17 years  | To evaluate the association between TBI and the subsequent risk of suicide deaths in a population of children           |
| Fralick et al., 2016        | Longitudinal cohort study         | 235,110 patients who received a diagnosis of concussion from 1 <sup>st</sup> April 1992 to 31 <sup>st</sup> March 2012 (weekend concussion n = 39,940; week-day concussion n = 195,170)                                       | To evaluate if concussion could influence long-term risk of suicide   |

| Material and methods   | Follow-up | Results   |
|--|-----------|---|
| Subjects identified in a computerized National Bureau of Health register of hospitalizations which documents all admissions to hospital in Denmark since 1979  | 14 years  | 0.62% (895) of TBI patients died from suicide. The standardized mortality ratios for suicide showed that the incidence was increased relative to the general population and was lower for patients injured before the age of 21 or after 60. There was a significantly higher risk of suicide among patients with cerebral contusions or traumatic intracranial haemorrhages than those with concussion or cranial fractures. In all diagnosis groups the ratios were higher for females than for males   |
| This study examines all the suicides during the years 1988-2004 in a province of Finland   | 16 years  | Among all suicides, 103 (5.5%) had sustained a TBI. Patients with TBI died by suicide within 3 years after TBI (this time interval was shorter if the subject had a psychiatric disorder before TBI)  |
| Social Security Death Index was used to determine features of patients. Death certificates were used to identify causes of death   | 40 years  | 130 deaths occurred after 1-year post injury (mortality rate: 7.7%) Standardized mortality ratio was 1.51 (95% C.I.:1.25-1.78). 10 deaths caused by suicide. TBI patients are 3 times more like to commit suicide than general population   |
| 81 cases and 160 matched controls randomly selected from a Veterans Affairs Medical Center clinical database. Inclusion criteria: Veterans Affairs health care services received and an electronic medical record note reporting a suicide attempt   |           | PTSD history was associated with an increased risk for a suicide attempt (OR = 2.8). No differences between those with and without a history of TBI emerged   |
| Evaluation of mortality rate in TBI compared to general population and to unaffected siblings of TBI patients  |           | 11,053 premature deaths occurred in TBI population. Compared with controls and with unaffected siblings, the OR was respectively 3.2 (CI 95%, 3.0-3.4) and 2.6 (CI 95%, 2.3-2.8).<br>There were 522 deaths by suicide. Compared with controls, OR was 3.3 (CI 95%; 2.9-3.7). Compared with unaffected siblings, OR was 2.3 (CI 95%; 1.9-2.9)  |
| The cohort was assembled using information from 4 provincial administrative databases. Those 4 databases were the physician billing claims database from the Quebec Health Insurance Board, the hospital admission and discharge database (MEDECHO), the Quebec Institute of Statistics database and the Quebec Coroner Database | 21 years  | The study found a higher risk of suicide for people who sustained a TBI during adulthood [(HR): 2.53] rather than during adolescence [(HR) = 1.57] and childhood [(HR) = 1.49]. Males who sustained a TBI were at a much higher risk for suicide than females [(HR): 4.69 vs 1.00]. More severe injuries were associated with a higher risk of suicide than low severity injuries [(HR): 2.77 vs 2.18]. Sustaining repeated injuries increased the risk of suicide for children [(HR) = 1.23], adolescents [(HR) = 1.41] and adults [(HR) = 1.61] |
| Data were extracted from the Office of the Registrar General database. Cause of death was assessed by death certificates   | 20 years  | 667 patients committed suicide, with a median follow-up of 9.3 years (31 suicides/100,000 subjects annually). 519 suicides occurred after weekday concussion (29 suicides/100,000 subjects annually; $\geq 3$ -times the general population) and 148 after weekend concussion (39 suicides/100 000 subjects annually; $\geq 4$ times the general population). Weekend concussion was associated with a greater risk of suicide than weekday concussion (RR = 1.36; CI 95% 1.14-1.64)  |



| Attempted suicide             |                     |  |   |
|-------------------------------|---------------------|--|---|
| Author, year                  | Study               | Sample   | Aims  |
| Jonathan et al., 2001         |                     | 5,034 participants in the Epidemiologic Catchment Area Study   | To explore the relationship between a history of TBI and suicide attempts   |
| Oquendo et al., 2004          |                     | 325 patients with a diagnosis of major depressive episode. 44% of them had an history of TBI   | To evaluate the relationship between suicidal behavior, depression and mild traumatic brain injury  |
| Simpson and Tate et al., 2005 |                     | 172 outpatients with TBI from the Liverpool Hospital Brain Injury Rehabilitation Unit (BIRU) in Sydney aged between 16 and 61  | To study demographic, temporal and clinical parameters for the suicide attempts after TBI   |
| Gutierrez et al., 2008        |                     | 22 veterans who suffered head injury and hospitalized in psychiatric department between 1968 and 2005 (4 subjects had pre-existing brain injury between 1971 and 2003) | To evaluate suicidal behavior in patients psychiatrically hospitalized with history of TBI  |
| Homaifar et al., 2012         | Pilot study         | Veterans with TBI with previous suicide attempts (n=18) and with no history of suicide attempts (n 29)   | To evaluate if there was an association between executive dysfunction, TBI and suicide  |
| Bryan et Clemans, 2013        | Observational study | 161 military personnel evaluated or treated for suspected head injury at a TBI's military clinic in Iraq   | To identify if there is an increase in suicide risk among military personnel with a single or no TBIs and those with multiple lifetime TBIs |
| Gunter et al., 2013           |                     | 418 community-supervised offenders served by office Iowa's Sixth Judicial District   | To determine which factors differentiate suicidal ideation and actions group from control group in community corrections sample             |

| Material and methods   | Follow-up | Results  |
|--|-----------|--|
| Hamilton Depression Rating Scale (HAM-D) was used for depression; Beck Hopelessness Scale (BHS) was used for hopelessness. Suicidal ideation was assessed with the Beck Scale for Suicide Ideation (BSS). Suicide attempts were assessed with the Suicide Intent Scale and Lethality Rating Scale                                  |           | 361 (7.2%) of the participants had a history of TBI. Suicide attempts were more frequent in patients with a history of TBI compared with subjects without TBI (8.1% vs 1.9%, $p = 0.0001$ ).<br><br>Subjects with TBI presented a higher rate of suicide attempts compared with subjects without TBI (60% vs 47%).<br>80% of the TBI suicide attempters made the first attempt after TBI   |
| Beck Hopelessness Scale (BHS) and Beck Scale for Suicide Ideation (BSS) were used to assess levels of hopelessness and suicide ideation  | 24 months | 43 patients (25%) attempted suicide: 14 patients made a pre-injury attempt, 29 patients made a post-injury attempt. The authors found a high frequency of post-TBI attempts compared to the period before the trauma (30% pre-injury vs 70% post-injury). The main mode of attempting suicide was overdose (62.5%), followed by cutting (17.5%). Patients with a post-TBI history of psychiatric disorders and substance abuse were 21 times more likely to have an attempt post-TBI (OR: 20.62, CI 5.10-83.40) compared with people without the same post-TBI history                                     |
| Suicide ideation and suicide attempts were evaluated. The Lethality of Suicide Attempts Rating Scale (LSARS) was used to characterize suicidal behaviors   |           | 72.7% of patients presented suicide ideation during at least one hospitalization. 27.3% of subjects made at least one suicide attempt after TBI. The number of attempts per person was between 1 and 5 (median: 2)   |
| Executive function was evaluated with different scales: making decision with Iowa Gambling Task (IGT); impulsivity with Immediate and Delayed Memory Test (IMT/DMT); abstract reasoning with Wisconsin Card Sorting Test (WCST). Previous suicide attempts and suicidal ideation were evaluated with Columbia Suicide History Form |           | 66% of patients without a history of suicide attempts reported suicidal ideation.<br>Abstract reasoning, especially perseveration, was the only measure which differed significantly between the two groups ( $p$ value = 0.04). Patients with suicide attempts had higher level of perseveration than patients with no prior suicide attempts   |
| 4-item Suicidal Behaviors Questionnaire–Revised, 5-item depression subscale of the Behavioral Health Questionnaire–20, PTSD Checklist–Military Version, history clinical interview (Military Acute Concussion Evaluation), physical examination  |           | The number of TBIs was significantly associated with an increase in depression, PTSD, and TBI symptom severity. The number of TBIs was also correlated with an increased incidence of lifetime suicidal thoughts or behaviors (no TBIs, 0%; single TBI, 6.9%; and multiple TBIs, 21.7%; $p = .009$ ). Greater suicide risk was associated with the number of TBIs ( $\beta$ [SE] = .214 [.098]; $p = .03$ ) after checking of the effects of depression, PTSD, and TBI symptom severity. Depression was also correlated with cumulative TBIs ( $\beta = .580$ [.283]; $p = 0.04$ )                         |
| Alcoholism Revised (SSAGA-II) to assess substance use and co-occurring disorders, Hare Psychopathy Checklist Screening Version (PCL:SV) to assess psychopathy and Achenbach Adult Self Report (ASR) to evaluate the subject's attention to the six-month period before the interview   |           | Three groups obtained: the control group with no suicide ideation or actions ( $n = 235$ , 56%), the ideator group with suicidal ideation without suicidal actions ( $n = 70$ , 17%) and the actor group with suicide-related actions regardless of suicidal ideation ( $n = 113$ , 17%). Caucasian race, depressive symptoms, TBI, childhood trauma and avoidant personality characterized the actor and ideator group more than the control group; moreover, the same five items associated with antisocial lifestyle and lifetime anxiety disorder distinguished the actor group from the control group |

| <b>Attempted suicide</b> |                     |   |   |
|--------------------------|---------------------|---|---|
| <b>Author, year</b>      | <b>Study</b>        | <b>Sample</b>   | <b>Aims</b>   |
| Ilie et al., 2014        |                     | 4,685 students (aged 11-20) with and without a life time TBI (respectively n = 882; n = 3,803)  | To explore whether there is a relationship between TBI and psychiatric disease in adolescent population   |
| Brenner et al., 2015     | Observational study | 133 veterans: 48 without suicide attempt (SA) or TBI; 51 with TBI, but without SA; 12 with SA, but without TBI; 22 with SA and TBI  | To explore the relationship between executive dysfunction and suicide attempt history in a high-risk sample of veterans with moderate to severe TBI |
| Fonda et al., 2016       | Cohort study        | 273,591 veterans deployed in support of three military operation (OEF/OIF/OND), who received health care from the Veterans Affairs (VA) between April 2007 and Sept. 2012; 42,392 (16%) with TBI and 231,199 without TBI. | To evaluate the possible mediating role of common comorbid psychiatric conditions in the association between TBI and suicide attempt                |
| Schneider et al., 2016   |                     | 1,097 veterans  | To determine whether a positive screen on the TBI-4 is associated with increased risk for suicide attempt within 1-year post-screening              |
| Fisher et al., 2016      | Longitudinal study  | Patients presenting at Traumatic Brain Injury Model System hospital within 72 h of brain injury (n = 8,547 for suicide attempts; n = 3,192 for suicidal ideation; n = 3,182 for depression)                               | To evaluate the prevalence of depression and suicidal behaviour in TBI patients   |
| Kesinger et al., 2016    |                     | 3,575 patients with TBI enrolled in Traumatic Brain Injury Model System (TBIMS) National Database   | To explore if there is a relationship between severity of TBI/ extracranial injuries and suicide ideation/suicide attempts                          |
| <b>Suicidal ideation</b> |                     |   |   |
| Simpson et al., 2002     |                     | 172 out-patients with TBI from the Liverpool Hospital Brain Injury Rehabilitation Unit (BIRU) in Sydney (Australia)   | To evaluate the suicidal ideation, suicide attempts, hopelessness and other clinical correlates after TBI   |

| Material and methods  | Follow-up                         | Results  |
|---|-----------------------------------|--|
| Measures were: assessment of TBI; Mental/emotional Health with General Health Questionnaire (GHQ12); suicide ideation and suicide attempts; asking help through a crisis help-line/website; need to receive pharmacological treatment for anxiety, depression or both; evaluation of conduct behaviours   |                                   | There was a significantly difference in suicide ideation and attempts between adolescents with and without TBI (suicide ideation: AOR = 1.93, CI = 95% 1.42-2.63, p value $\leq$ 0.001; suicide attempts: AOR = 3.39, CI 95% 2.15-5.35, p value $\leq$ 0.001)  |
| Iowa Gambling Test (IGT), Immediate and Delayed Memory Test, State-Trait Anger Expression Inventory-2, Wisconsin Card Sorting Test  |                                   | Veterans with a history of both SA and TBI demonstrated a lack of learning over the course of the IGT, unlike all the other groups. No significant differences were identified on other measures of executive functioning among the groups   |
| TBI exposure: VA primary TBI screen and comprehensive TBI evaluation; Suicide attempt and outcome: ICD-9 injury E codes (E950–E959); Covariates: sex, race (white, black, other, unknown/missing), age, marital status (single, married, or divorced/separated/other), and psychiatric conditions (using ICD-9 diagnosis code)                  | From April 2007 to September 2012 | 545 attempted suicides, more frequently among veterans with TBI (n = 227, 0.54%) than those without TBI (n = 318, 0.14%). Veterans with TBI had higher proportion of each psychiatric condition than those without TBI (from 16% vs 5% for substance-use disorder to 63% vs 10% for PTSD). Co-occurring psychiatric conditions mediated 83% of the association between TBI and attempted suicide: PTSD had the largest impact (73% of the association) |
| The TBI-4 was administered to 1,097 veterans at the time of mental health intake. Follow-up data regarding suicide attempts for one year post-mental health intake were obtained from suicide behavior reports (SBRs) in Veteran electronic medical records (EMRs)  | 1 year                            | 468 participants screened positive on Question 2 (Have you ever been knocked out or unconscious following an accident or injury?) of TBI-4. 7 (1,5%) of them made a suicide attempt 1-year post-assessment (vs 0% in those who did not endorse this item)  |
| Patient Health Questionnaire (PHQ-9) was used to assess depression and suicidal ideation. Previous suicide attempts were self-reported by patients. Patients were evaluated at 1,2, 3, 10, 15 and 20 years after brain injury   |                                   | Suicidal ideation and depression rates were, respectively, 7-10% and 24.8-28.1% 20 years after brain injury. The prevalence of suicide attempts was 0.8-1.7% at the end of follow-up. The highest rates of suicidal ideation and depression were registered after 5 years form TBI. Patients with head injury presented a greater risk of suicide attempts, suicidal ideation and depression than general population                                   |
| PHQ-9 was used to evaluate suicidal ideation. Suicide attempts were assessed with an interview. Severity of TBI and extracranial injuries were evaluated respectively with Abbreviated Injury Scale head score and with Injury Scale (non-head). Measures were assessed at 1 <sup>st</sup> , 2 <sup>nd</sup> and 5 <sup>th</sup> year after TBI |                                   | 8.2% of subjects presented with suicide ideation without suicide attempts.<br>3.0% committed at least one suicide attempt during 5 years after TBI.<br>There was a relationship between severe extracranial injury and suicide ideation (OR = 2.73 CI 95%, 1.55-4.82; p value = 0.001), and between use of alcohol and drugs and suicide ideation (OR = 1.69 CI 95%, 1.11-2.86; p value = 0.015)   |
| Hopelessness and suicide ideation were assessed using the Beck Hopelessness Scale (BHS) and the Beck Scale for Suicidal Ideation (BSS)  |                                   | 35% patients had moderate-severe levels of hopelessness, 23% had suicidal ideation and 17.4% attempted suicide after TBI. No relationship was found between injury severity and suicidality  |

| <b>Suicidal ideation</b>               |                                       |  |   |
|--|---------------------------------------|--|---|
| <b>Author, year</b>                    | <b>Study</b>                          | <b>Sample</b>  | <b>Aims</b>   |
| Wisco et al., 2014                     |                                       | 824 male and 825 female U.S. veterans  | To evaluate the relationship between TBI history and suicidal ideation in a group of U.S. veterans  |
| Mackelprang et al., 2014               | Recruitment phase of a clinical trial | 559 patients admitted to Harborview medical Center (Seattle) for TBI between June 2001 and March 2005  | To assess the rate of suicidal ideation in patient with TBI   |
| Bethune et al., 2016                   |                                       | 871 patients in an urban tertiary care ED enrolled at 3 months post injury, between 1998 and 2012  | To clarify psychosocial and injury features contributing to suicidal ideation (SI) after concussion or mTBI and the time it takes to develop  |
| DeBeer et al., 2017                    | Observational study                   | 145 Iraq/Afghanistan veterans within the Central Texas Veterans Health Care System   | To evaluate whether sleep quality influence the association between TBI history and current suicidal ideation   |
| <b>Suicidality</b>                     |                                       |  |   |
| Brenner, Ignacio et al., 2011          | Observational retrospective study     | 7,850,472 veterans who received care between fiscal years 2001 to 2006: 49,626 with a history of TBI (12,159 with concussion or cranial fracture and 39,545 with cerebral contusion/traumatic intracranial hemorrhage), and 389,053 patients without TBI | To evaluate any association between death by suicide and history of traumatic brain injury (TBI) diagnosis among individuals receiving care within the Veterans Health Administration                     |
| Bryan, Clemans, Hernandez et al., 2013 | Observational study                   | 158 military personnel as outpatients TBI clinic in Iraq: 135 (85.4%) with diagnosis of mTBI and 23 (14.6%) without  | To determine which clinical outcomes were associated with suicidality in military personnel with mTBI   |
| Juengst et al., 2014                   |                                       | 74 patients with TBI (acute cerebrospinal fluid (CSF) levels of TNF- $\alpha$ : n = 37 vs n = 15 controls; acute serum levels of TNF- $\alpha$ : n = 48 vs n = 15 controls; chronic serum levels of TNF- $\alpha$ : n = 48 vs n = 15 controls)           | To measure the association between high level of Tumor Necrosis Factor- $\alpha$ (TNF- $\alpha$ ), disinhibition and suicidal behaviour   |
| <b>Suicidality</b>                     |                                       |  |   |
| Bryson et al., 2017                    | Observational study                   | 42 college students self-reported a history of TBI (42 controls matched)   | To investigate the association between TBI and suicide, assessing the weight of TBI in the risk of suicide TBI and whether the Interpersonal-Psychological Theory of Suicide can be applied to TBI status |

| Material and methods  | Follow-up                     | Results   |
|---|-------------------------------|---|
| TBI history was assessed using a structured interview. The prime-MD Patient Health Questionnaire was used to evaluate depressive symptoms. The Mini-International Neuropsychiatric Interview, English version 5.0 (M.I.N.I.) was used to evaluate suicidality             |                               | TBI was significantly associated with suicidal ideation among male (RR = 1.55), but not female, veterans. In addition, multiple TBI and TBI with loss of consciousness were more strongly associated with suicidal ideation. Depressive symptoms and PTSD were associated with greater risk of ideation in both groups (male and female)  |
| PHQ-9 was used to evaluate suicidal ideation. A structured telephone interview was conducted at month 1-6-8-10 and 12 after brain injury  |                               | 25% of patients reported suicidal ideation during the first year after brain injury. Rate of ideation was highest (10%) during months 2 and 8. Patients with history of previous suicide attempts presented a risk 5 times more to have suicidal ideation after injury than patients without a history of a suicide attempt (OR: 4.81; 95% CI: 2.83-8.17)   |
| Psychiatric (DSM-IV, MMSE, General Health Questionnaire) and social-demographic (clinical interview) assessments at 3 and 6 months after injury. The Rivermead Post-Concussion Disorder Questionnaire (RPDQ) to record the post concussion syndrome symptoms              | At 3 and 6 months post injury | SI emerged in 6.3% of patients at 3 months and in 8.2% at 6 months. It was independently associated with speaking English as a second language and injury mechanism (motor vehicle crashes/passenger) at 3 and 6 months, and with history of depression and marital status at 3 months only   |
| Defense and Veterans Brain Injury Center Brief Traumatic Brain Injury Screening Tool, Pittsburgh Sleep Quality Index, Beck Scale for Suicide Ideation   |                               | Sleep quality influenced the effect of TBI history on current suicidal ideation (indirect effect = 0.0082): individuals with history of TBI suffered worse sleep quality, which was also associated with increased suicidal ideation  |
| ICD-9 (Diagnosis of TBI), National Death Index (vital status or dates/causes of death)  |                               | Veterans with a history of TBI were 1.55 times more likely to die by suicide than those without a history of TBI. Those with concussion/cranial fracture were 1.98 times more likely to die by suicide and cerebral contusion/traumatic intracranial hemorrhage were 1.34 times more likely to die by suicide, compared to those without an injury history. The presence of psychiatric disorders or demographic factors didn't explain this increased risk |
| 4-item Suicidal Behaviors Questionnaire-Revised, 5-item Depression subscale of the Behavioral Health Measure-20, PTSD Checklist-Military Version, Insomnia Severity Index, 2008 TBI Task Force's criteria of the Department of Defense and Department of Veterans Affairs |                               | Depression and its interaction with PTSD symptoms were significantly associated with increased suicidality among patients with diagnosis of mTBI. Decreased probability for any suicidality was correlated with a longer duration of loss of consciousness  |
| TNF- $\alpha$ levels were collected for 12 months after TBI. Frontal System Behaviour Scale (FrSBe) Disinhibition Subscale and PHQ-9 were used to assess respectively disinhibition and suicidal behavior   |                               | Acute CSF level of TNF- $\alpha$ was associated with suicidal behaviour at 12 months from TBI ( $p = 0.014$ ). Acute and chronic serum TNF $\alpha$ level was not related with suicidal behaviour but was significantly associated with disinhibition at 6 months post-injury (respectively $p = 0.009$ ; $p = 0.029$ ). Disinhibition was associated with suicidal behaviour at 6 and 12 months (respectively $p = 0.045$ ; $p = 0.033$ )                  |
| Depression Anxiety Stress Scale – 21, Interpersonal Needs Questionnaire, Acquired Capability for Suicide Scale, Suicidal Behaviors Questionnaire-Revised  |                               | Higher suicide risk emerged in individuals with a TBI than those without, even accounting for the relative influence of 2 strong suicide risk factors (i.e., depression, perceived burdensomeness, thwarted belongingness, and acquired capability). The interaction of perceived burdensomeness, acquired capability and thwarted belongingness (IPTs) was significantly associated with suicide risks   |

| <b>Suicidality</b>       |                             |  |   |
|--------------------------|-----------------------------|--|---|
| <b>Author, year</b>      | <b>Study</b>                | <b>Sample</b>  | <b>Aims</b>   |
| Palladino et al., 2017   |                             | 103 homeless veterans with TBI   | To evaluate the associations between suicide risk and physical, psychological, social and military characteristics among homeless veterans with TBI             |
| <b>NEGATIVE FINDINGS</b> |                             |  |   |
| <b>Completed suicide</b> |                             |  |   |
| Shavelle et al., 2001    |                             | 2,320 subjects who had TBI at the age of 10 or more and with a mental disability after TBI followed-up between 1988 and 1997   | To assess causes of death in patients with previous TBI vs in general population  |
| <b>Attempted suicide</b> |                             |  |   |
| Brenner et al., 2017     | Observational study         | 309 veterans seeking homeless services: 282 with a history of TBI and 27 without a history of TBI  | To find out any difference in negative psychiatric results among veterans seeking homeless services, with and without a history of traumatic brain injury (TBI) |
| <b>Suicidal ideation</b> |                             |  |   |
| Stanley et al., 2016     |                             | 149 military service members referred to a TBI clinic within a military hospital in Iraq during a 6-month span in 2009   | To determine if the relationship between mild TBI and suicide risk is statistically accounted for by anger and depression symptoms                              |
| <b>Suicidality</b>       |                             |  |   |
| Barnes et al., 2012      |                             | 92 male veterans in treatment for PTSD between 2006 and 2010 at a Midwestern Veterans Affairs Medical Center; 46 of these patients had sustained an mTBI                         | To investigate whether mTBI increases suicide risk beyond the risk associated with PTSD alone   |
| <b>Treatment</b>         |                             |  |   |
| Simpson & Tate, 2011     | Randomized controlled trial | 17 patients with severe TBI (aged 18 or older at injury and current < 65 years) and moderate/severe levels of hopelessness and/or suicide ideation (BHS-Beck Hopelessness Scale) | To evaluate the efficacy of a psychological treatment (CBT therapy) to reduce the hopelessness after severe TBI   |

TBI: Traumatic Brain Injury; PHQ-9: Patient Health Questionnaire

| Material and methods  | Follow-up                                | Results  |
|---|--|--|
| TBI-4 Questionnaire and Ohio State University TBI Identification Method (OSU TBI-ID) were used to find positive subjects for TBI. MINI International Neuropsychiatric Interview (MINI) was used to investigate the presence of psychiatric disorders including suicidal ideation  | 1 year<br>(December 2010-September 2011) | Veterans with high risk of suicide reported significantly more frequently the following TBI related symptoms than those with no or low risk: blurred vision (81.8 vs 45.7%), seizures (36.4 vs 4.3%) and difficulty with memory/problem-solving (81.8 vs 37%) and managing stress (63.6 vs 27.2%). Veterans with PTSD had 8 times the odds of being at high risk for suicide |
| Subjects were identified from a database with people who received assistance from the California Department of Developmental Services. Death information were extracted from annual computer register   | 9 years                                  | TBI subjects presented higher risk of death than general population (SMR = 3.1; CI 95% 2.5-3.7). 3% of patients had attempted suicide before TBI. 2 suicides occurred during the follow-up period  |
| The Ohio State University TBI-Identification Method (structured interview); the MINI international neuropsychiatric interview (short, structured diagnostic interview)  |  | Veterans with a history of TBI received significantly more psychiatric diagnoses ( $p = 0.0003$ ), and showed higher risk for suicide ( $p = 0.007$ ) than those without a history of TBI  |
| Mild TBI diagnosis was confirmed by a licensed clinical psychologist or physician during a clinical interview.<br>Suicide risk was assessed utilizing the Suicidal Behaviors Questionnaire (SBQ-R).<br>Anger was assessed utilizing the mood scale module of the Automated Neuropsychological Assessment Metrics (ANAM).<br>Depression symptoms were assessed utilizing the Behavioral Health Measure-20 (BHM-20) | 6 months                                 | The relationship between mild TBI and suicide risk is fully mediated by anger and depression symptoms: mild TBI significantly predicted anger; anger significantly predicted depression symptoms and depression symptoms significantly predicted suicide risk  |
| PTSD Scale assesses <i>DSM-IV-TR</i> PTSD diagnostic criteria; SCID-I to detect current and/or lifetime presence of Axis I psychiatric disorders.<br><i>Self-report measures:</i> BDI-II for assessing depressive symptoms; the PCL-S (PTSD Checklist Stressor Specific Version) instructs patients to rate the severity of their PTSD symptoms in relation to a specific traumatic stressor                      |  | No significant differences emerged in the assessed risk factors suggesting that, if PTSD and mTBI are associated with greater suicide risk relative to PTSD alone, the added risk is attributable to PTSD symptom severity   |
| Participants were aged between 18 and 65 years, experienced post traumatic amnesia more than 1 day and moderate/severe hopelessness (evaluated with the Beck Hopelessness Scale) and/or suicide ideation (evaluated with the Beck Scale for Suicide Ideation)   | 3 months                                 | The treatment group improved with a reduction of 6 BHS points, whereas the wait-list group increased scores by 1 BHS point. Was also observed a significant reduction in suicide ideation scores in the treatment group  |