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Authors

Schneider, Andrea
Barber, Jason
Temkin, Nancy
et al.

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Associations of Pre-Existing Vascular Risk Factors with Outcomes after Traumatic Brain Injury: A TRACK-TBI Study

Andrea L.C. Schneider, MD PhD[1], **Jason Barber, MS**[2], **Nancy Temkin, PhD**[2,3], **Raquel C. Gardner, MD**[4], **Geoffrey Manley, MD PhD**[5], **Ramon Diaz-Arrastia, MD PhD**[1], **Danielle Sandsmark, MD PhD**[1] **TRACK-TBI Study Investigators***

[1]Department of Neurology, University of Pennsylvania Perelman School of Medicine

[2]Department of Neurological Surgery, University of Washington

[3]Department of Biostatistics, University of Washington

[4]Department of Neurology, University of California San Francisco

[5]Department of Neurosurgery, University of California San Francisco

Abstract

Objective: To evaluate associations of pre-injury vascular risk factors with TBI outcomes.

Setting: The level 1 trauma center based Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) Study.

Participants: 2,361 acute TBI patients aged 18 years or older who presented to the emergency department within 24 hours of head trauma warranting clinical evaluation with a non-contrast head CT between February 26, 2014 and August 8, 2018.

Design: Multicenter prospective cohort study.

Main Measures: Vascular risk factors (hypertension, diabetes, hyperlipidemia, and smoking) were assessed at baseline by self- or proxy-report and chart review. The primary outcome was the 6-month Glasgow Outcome Scale-Extended TBI version (GOSE-TBI). Secondary 6-month outcomes included the Rivermead Post-Concussion Symptoms Questionnaire (RPQ), the Satisfaction with Life Scale (SWLS), and the 18-Item Brief Symptom Inventory Global Severity Index (BSI-18-GSI).

Results: Mean age of participants was 42 years, 31% were women, 16% were Black. Current smoking was the most common vascular risk factor (29%), followed by hypertension (17%), diabetes (8%), and hyperlipidemia (6%). Smoking was the only risk factor associated with worse

Address for Correspondence: Andrea L. C. Schneider MD PhD, 51 North 39th Street, Andrew Mutch Building 416, Philadelphia, Pennsylvania 19104, Phone: 443-827-2352, Fax: 215-662-9858, Andrea.Schneider@pennmedicine.upenn.edu.

*The TRACK-TBI Investigators: V Ramana Feeser, MD, Virginia Commonwealth University; Brandon Foreman, MD, University of Cincinnati; Etienne Gaudette, PhD, University of Toronto; Shankar Gopinath, MD, Baylor College of Medicine; Sonia Jain, PhD, University of California, San Diego; Christopher Madden, MD, UT Southwestern; Michael McCrea, PhD, Medical College of Wisconsin; Randall Merchant, PhD, Virginia Commonwealth University; Pratik Mukherjee, MD PhD, University of California, San Francisco; Laura B. Ngwenya, MD, PhD, University of Cincinnati; David Okonkwo, MD PhD, University of Pittsburgh; Claudia Robertson, MD, Baylor College of Medicine; David Schnyer, PhD, UT Austin; Sabrina Taylor, PhD, University of California, San Francisco; John K. Yue, MD, University of California, San Francisco, Ross Zafonte, DO, Harvard University

scores on all four outcome indices. Hypertension and diabetes were associated with worse RPQ scores, and hypertension was associated with worse BSI-18-GSI scores (all $p<0.05$). Compared to individuals with no vascular risk factors, individuals with 1 but not 2+ vascular risk factors had significantly worse GOSE-TBI and SWLS scores, while a higher burden of vascular risk factors was significantly associated with worse RPQ and BSI-18-GSI scores.

Conclusion: Our study found that pre-injury vascular risk factors, especially smoking, are associated with worse outcomes after TBI. Aggressive post-injury treatment of vascular risk factors may be a promising strategy to improve TBI outcomes.

Keywords

brain injuries; traumatic; cohort studies; prospective studies; hypertension; diabetes mellitus; hyperlipidemias; smoking

INTRODUCTION

Traumatic brain injury (TBI) in the United States is common[1], with approximately 2.8 million TBI-related emergency department visits, hospitalizations, and deaths occurring annually[2]. While it has long been established that moderate and severe TBI are associated with significant disability[3,4], recent data suggests that even mild TBI may be associated with long-lasting functional limitations[5]. In addition to injury-related factors[6], prior studies have identified certain pre-injury characteristics that are associated with worse outcomes after TBI, including older age[7], history of prior TBI[8], and neurologic/psychiatric comorbidities[9], among others. Because the majority of these previously identified factors are non-modifiable; there is a need for the identification of modifiable factors that may impact TBI recovery and outcomes. Vascular risk factors are modifiable through behavioral or pharmacologic interventions. Since TBI itself causes vascular injury and subsequent dysfunction[10,11] and vascular risk factors are modifiable (e.g., with control of hypertension, hyperglycemia, hyperlipidemia, and cessation of smoking), studies investigating associations of vascular risk factors with TBI outcomes are warranted. Indeed, the presence of comorbid vascular risk factors has been shown to be associated with compromised function in other neurologic diseases, such as dementia[12] and Parkinson's disease[13]. However, the impact of the comorbid vascular-related risk factors on post-TBI recovery is not well understood.

Using data from the longitudinal, observational Level 1 trauma center-based Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) Study, the objective of the present study was to evaluate associations of pre-injury vascular risk factors (hypertension, diabetes, hyperlipidemia, and current smoking) with 6-month TBI outcomes. We hypothesized that both individual vascular risk factors and a higher burden of co-morbid vascular risk factors would be associated with worse TBI outcomes.

MATERIALS AND METHODS

Study Population and Study Design

The TRACK-TBI Study[14] is a prospective multicenter study that enrolled TBI patients presenting to 18 level 1 trauma centers in the U.S. between 2/26/2014 and 8/8/2018.

Eligible patients were those aged 16+ years who presented to the emergency department within 24 hours of head trauma warranting clinical evaluation with a non-contrast head CT[15]. Participants took part in a baseline assessment and were followed for outcomes over the first 6-months post-injury (2-week in-person, 3-month telephone, and 6-month in-person assessments). At all assessments, adult proxies provided information for the Glasgow Outcome Scale-Extended (GOSE) for participants who were unable to self-report. All variables were collected in accordance with the TBI common data elements[16,17].

Of the 2,697 participants with TBI enrolled in the TRACK-TBI Study, we restricted our eligible population to the 2,539 adult participants aged ≥18 years. Of these 2,539 eligible participants, 178 were excluded due to missing vascular risk factor data, leaving 2,361 participants included in the present analysis (eFigure 1).

The TRACK-TBI Study was approved by the institutional review board of each site and all participants or legally authorized representatives completed written informed consent.

Vascular Risk Factors

The pre-injury vascular risk factors of hypertension, diabetes, hyperlipidemia, and current smoking were assessed at study baseline using self- or proxy-report questions and medical chart review. Participants were asked if they had ever received a diagnosis of hypertension, diabetes, and/or hyperlipidemia prior to the injury. Participants were also asked if they engaged in cigarette smoking in the 2 weeks prior to the injury. In addition to examining associations of each vascular risk factor individually with TBI outcomes, we also examined associations of the cumulative burden of pre-injury vascular risk factors with TBI outcomes. The cumulative burden of pre-injury vascular risk factors was evaluated by counting the total number of vascular risk factors present for each participant (0, 1, or 2+). In sensitivity analyses, we additionally looked at 0, 1, or 2+ vascular risk factor categories only including diabetes, hypertension, and hyperlipidemia. In supplemental analyses, we additionally looked at associations of smoking cessation patterns post-injury with outcomes.

Information about pre-injury medication use was also assessed at study baseline. Medications were categorized into therapeutic classes using the Multum Lexicon classification system and drug classes used to define hypertension, diabetes, hyperlipidemia, and smoking cessation-related medications are shown in eTable 1. In secondary analyses we examined associations of untreated and treated vascular risk factors with TBI outcomes.

Outcome Measures

Our primary outcome measure was the 6-month GOSE-TBI[18], which is a measure of global functional disability after injury accounting only for disability caused by the head injury, rather than polytrauma, with possible scores ranging from 1 (death) to 8 (upper good recovery). The GOSE-TBI was dichotomized as “more disabled” (not returned to pre-injury baseline function) (score 1-6) versus “less disabled” (near or complete return to pre-injury baseline function) (score 7-8). The GOSE-TBI was also assessed at 2-weeks and 3-months and we looked at trajectories of the GOSE-TBI scores over time. Our secondary outcome measures were assessed at 6-months and included the Rivermead Post-Concussion Symptoms Questionnaire (RPQ, measure of self-reported post-TBI symptoms, higher scores

indicate more severe symptoms)[19], the Satisfaction with Life Scale (SWLS, measure of general life satisfaction, higher scores indicate greater life satisfaction)[20], and the 18-Item Brief Symptom Inventory Global Severity Index (BSI-18-GSI, measure of psychological distress, higher scores indicate more severe psychological symptoms)[21].

Covariates

The following *a priori* selected baseline covariates were included in statistical models: age (continuous), sex (male; female), race (White; Black; other), ethnicity (Hispanic; non-Hispanic), TBI severity [5] (uncomplicated mild [Glasgow Coma Scale (GCS) 13-15 and acute head CT negative for intracranial findings]; complicated mild [GCS 13-15 and acute head CT positive for intracranial findings]; moderate [GCS 9-12]; severe [GCS 3-8]), education (<high school; high school or equivalent; >high school), employment status (full-time; part-time; unemployed; retired/disabled; student), alcohol consumption (0 drinks/day; <3 drinks/day [women] or <4 drinks/day [men]; ≥3 drinks/day [women] or ≥4 drinks/day [men]), illicit drug use (yes; no), history of depression/anxiety (yes; no) and prior TBI (none; yes, received no medical care; yes, treated in emergency room; yes, hospital admission).

Statistical Analyses

Characteristics of the study population are shown overall and stratified by number of pre-injury vascular risk factors (0, 1, 2+) using means and standard deviations (SDs) for continuous variables and using n's and proportions for categorical variables. Characteristics were compared across vascular risk factor groups using Kruskal-Wallis tests for continuous variables and Fisher's exact tests for categorical variables.

As shown in the footnotes of Table 1 and eFigure 1, our data contained varying amounts of missingness in both covariates and outcomes. To address the missing data in our population, we used multiple imputation by chained equations with 5 sets of imputations to account for *missing covariates* and inverse probability of attrition weighting to account for *missing outcomes*[22,23]. Inverse probability of attrition weights were created separately for the main outcome (GOSE-TBI) at 6-months and for each of the secondary outcomes (RPQ, SWLS, BSI-18-GSI) at 6-months from boosted logistic regression models for completion versus non-completion of outcome measures. Separate inverse probability of attrition weights were also created for the GOSE-TBI at 2-weeks and 3-months that were used in the analysis looking at GOSE-TBI score trajectory over time. The weights created were proportional to the inverse of the probability of outcome measure completion and standardized so that the sum of the weights equaled the number of participants with complete outcome data. The following variables were included in both multiple imputation by chained equations and in boosted logistic regression models for the creation of inverse probability of attrition weights: number of vascular risk factors (0; 1; 2+), age, sex, race, ethnicity, TBI severity, education, employment status, alcohol consumption, illicit drug use, history of depression/anxiety, prior TBI, study site, major extracranial injury (injury severity score ≥3), hospital level of care for TBI (emergency room discharge; hospital floor; intensive care unit). Additional variables used only in multiple imputation models included: self-report question response (deceased; proxy; self-report), GOSE-TBI, RPQ, SWLS, and BSI-18-GSI scores.

We used regression models to evaluate associations of pre-injury vascular risk factors with 6-month TBI outcomes (logistic regression for GOSE-TBI score 1-6 versus 7-8, and linear regression for RPQ, SWLS, and BSI-18-GSI scores). We include estimates from the following models to assess the impact of accounting for missing data and of adjustment for *a priori* hypothesized confounders: 1) unadjusted, complete case, 2) unadjusted, inverse probability of attrition weighted for missing outcomes, 3) Model 1 (adjusted for age, sex, race, ethnicity, and TBI severity), inverse probability of attrition weighted for missing outcomes, 4) Model 2 (adjusted for variables included in Model 1 plus education, employment status, alcohol consumption, illicit drug use, history of depression/anxiety, and prior TBI), inverse probability of attrition weighted for missing outcomes. We performed formal testing for interaction by age and by psychiatric comorbidities (depression/anxiety). In sensitivity analyses, we added adjustment for obesity (body mass index [BMI] ≥30 kg/m^2, in the subset n=1,635 participants with BMI data). We also added adjustment for pre-morbid crystallized intelligence (assessed using the Picture Vocabulary Test from the NIH Toolbox, in the subset of n=888 participants with cognitive test data). In the analysis investigating trajectories of GOSE-TBI scores over time by number of pre-injury vascular risk factors (performed using mixed-effect logistic regression with random intercept and variance components correlation structure), we performed formal testing for interaction by time.

All reported p-values were based on 2-sided tests and $p<0.05$ was considered statistically significant. SPSS Statistics (version 26), SAS software (version 9.4), and the TWANG Shiny App (RAND Corporation) were used to perform statistical analyses.

RESULTS

Participant Characteristics

Overall, the mean age of participants was 42 years, 31% were female, 16% were Black, 81% sustained a mild TBI, 54% had no pre-injury vascular risk factors, 35% had 1 pre-injury vascular risk factor, and 11% had 2+ pre-injury vascular risk factors (Table 1). The patterns of vascular risk factors (among the 1,094 participants with at least 1 vascular risk factor) are shown in Figure 1. Current smoking was the most prevalent comorbid vascular risk factor (n=681, of whom 1% were taking smoking cessation medication(s)), followed by hypertension (n=401, of whom 68% were taking hypertension medication(s)), diabetes (n=194, of whom 70% were taking diabetes medication(s)), and hyperlipidemia (n=150, of whom 61% were taking hyperlipidemia medication(s)). Compared to participants with no vascular risk factors, participants with 2+ vascular risk factors were older, more likely to be male, of Black race, non-Hispanic ethnicity, have less than high school education, be retired/disabled, and have a history of depression/anxiety (all $p<0.05$). A greater proportion of individuals with 2+ vascular risk factors suffered a mild TBI with CT evidence of intracranial hemorrhage at presentation compared with individuals with no vascular risk factors (44% versus 27%, $p<0.001$). Compared to individuals with 2+ vascular risk factors, individuals with 1 vascular risk factor were younger ($p<0.001$) and more likely to use alcohol and illicit drugs (both $p<0.001$).

Associations of Pre-Injury Vascular Risk Factors with GOSE Scores

Table 2 shows associations of each individual vascular risk factor with 6-month GOSE scores. In unadjusted complete case and inverse probability of attrition weighted models, both hypertension and smoking were significantly associated with lower GOSE scores (score 1-6 versus 7-8) (both $p<0.05$). However, only smoking remained significantly associated with lower GOSE scores after adjusting for covariates (fully adjusted, inverse probability of attrition weighted OR: 1.49, 95% CI: 1.15, 1.94). Individually, diabetes and hyperlipidemia were not associated with GOSE (both $p>0.05$ for all models). We observed a significant interaction by age the association of hypertension with GOSE (p-interaction=0.002), where associations were stronger among individuals <40 years of age compared to ≥40 years of age (eTable 2). There were no significant interactions by psychiatric comorbidities (p-interaction >0.05). In sensitivity analyses in subsets of the population with BMI data (eTable 3) and with pre-morbid crystallized intelligence data (eTable 4), results were somewhat attenuated, but remained consistent with the main analyses. Supplemental analyses showed no differences in associations with GOSE by treatment status (eTable 5). In analyses looking at smoking cessation patterns post-injury, quitting smoking at 2 weeks post-injury was associated with 2.26 (95% CI:1.36, 3.77) times increased odds of low GOSE compared to no smoking (eTable 6).

Analyses investigating the association of the cumulative burden of vascular risk factors with GOSE scores are shown in Table 3. In fully adjusted models, having 1 vascular risk factor was significantly associated (OR 1.36, 95% CI: 1.07, 1.74) and having 2+ vascular risk factors was not significantly associated (OR 1.23, 95% CI: 0.84, 1.83) with increased odds of GOSE score 1-6 versus 7-8. Sensitivity analyses incorporating only diabetes, hypertension, and hyperlipidemia in the cumulative burden score were similar to main analyses where smoking was also included (eTable 7).

The distributions of 2-week, 3-month, and 6-month GOSE scores by number of vascular risk factors are shown in Figure 2. At 2-weeks, approximately 34% of participants in each vascular risk factor group had GOSE scores of 7-8. Over time, the proportion of "less disabled" participants (GOSE score 7-8) differed by number of vascular risk factors (p-for-interaction-by-time=0.009), with 65% of participants with no vascular risk factors compared to 55% of participants with either 1 or 2+ vascular risk factors having a GOSE score of 7-8 at 6-months post-injury.

Associations of the Pre-Injury Vascular Risk Factors with Secondary TBI Outcomes

In analyses evaluating associations of each vascular risk factor individually with secondary TBI outcomes, hypertension, diabetes, and smoking were significantly associated with more post-TBI symptoms on the RPQ and hypertension and smoking were significantly associated with greater psychological distress on the BSI-18-GSI (all $p<0.05$ in fully adjusted inverse probability of attrition weighted models) (Table 2). Smoking was also associated with lower satisfaction with life on the SWLS (−1.72 points lower, 95% CI: −2.66, −0.77) compared to non-smoking. We observed a significant interaction by age the associations of hypertension with RPQ and BSI-18-GSI (both p-interaction<0.05), where associations were stronger among individuals <40 years of age compared to ≥40 years of age. Associations of smoking

with RPQ were stronger among older compared to younger individuals (p-interaction=0.04) (eTable 2). There was no significant interaction by psychiatric comorbidities (p-interaction >0.05). In sensitivity analyses in subsets of the population with BMI data (eTable 3) and with pre-morbid crystallized intelligence data (eTable 4), results were somewhat attenuated, but remained consistent with our main analyses. Results exploring untreated and treated vascular risk factors showed stronger associations with RPQ and BSI-18-GSI among treated compared to untreated hypertension and diabetes (eTable 5). In analyses looking at smoking cessation patterns post-injury, quitting at 2 weeks post-injury was associated worse SWLS scores, still smoking at 6 months post-injury was associated with worse scores on the RPQ, SWLS, and BSI-18-GSI, and intermittent smoking over 6 months post-injury was associated with worse scores on the RPQ and BSI-18-GSI (eTable 6).

In analyses examining the cumulative burden of vascular risk factors, an increasing number of vascular risk factors was associated with more post-concussive symptoms (fully adjusted, inverse probability of attrition weighted RPQ score 2.04 [95% CI: 0.60, 3.47] and 4.45 [95% CI: 2.14, 6.77] points higher for 1 and 2+ vascular risk factors, respectively, compared to no vascular risk factors) and greater psychological distress (fully adjusted, inverse probability of attrition weighted BSI-18-GSI score 1.82 [95% CI 0.64, 3.00] and 3.44 [95% CI: 1.54, 5.35] points higher for 1 and 2+ vascular risk factors, respectively, compared to 0 vascular risk factors) (Table 3). Having 1 vascular risk factor was associated with less satisfaction with life (fully adjusted, inverse probability of attrition weighted SWLS score 0.89 [95%: CI: 0.02, 1.77] points lower compared to no vascular risk factors) but having 2+ vascular risk factors was not significantly associated with less satisfaction with life after adjustment. Sensitivity analyses incorporating only diabetes, hypertension, and hyperlipidemia (not smoking) in the cumulative burden score showed attenuated associations for RPQ and BSI-18-GSI and were no longer significant for 1 vascular risk factor but remained significant for 2+ vascular risk factors (eTable 7).

DISCUSSION

In this trauma center-based population of acute TBI patients, pre-existing vascular risk factors, especially smoking, were associated with worse TBI outcomes. We did not observe a clear dose-dependent pattern of number of vascular risk factors with TBI outcomes, and our results suggest that the observed associations investigating number of vascular risk factors were driven by the strong association of comorbid smoking with poor outcomes after TBI. Since TBI itself causes vascular injury and subsequent persistent vascular dysfunction[10,11] and many vascular risk factors, including smoking, are modifiable (e.g., with cessation of smoking), future studies investigating if therapies focused on improving overall vascular health may improve TBI outcomes are warranted.

Several prior animal[24,25] and human[9,26–30] studies have investigated associations of individual vascular risk factors with TBI outcomes, but to our knowledge, none have investigated the burden of cumulative vascular risk factors, although one study evaluated associations with a “comorbidity cluster,” which included several vascular risk factors[31]. Results of these prior studies are mixed, with some studies reporting significant associations of hypertension[29,30], diabetes[28–30], and hyperlipidemia[26] with TBI outcomes. Other studies

reported no association of hypertension[9,31], diabetes[31], hyperlipidemia[31], or smoking[27] with TBI outcomes. Interestingly, our study found the most robust associations of smoking with worse TBI-related outcomes. Prior studies have suggested that smoking and TBI lead to blood brain barrier dysfunction[25,32], which is a potential vascular-related mechanism that may underlie the observed observations. In contrast, hyperlipidemia alone was not associated with worse TBI-related outcomes in our study, and in fact, point estimates for hyperlipidemia tended to be in the "better outcomes" direction, although none were significant. This could be consistent with several prior observational studies reporting that statin use (as treatment for hyperlipidemia) is associated with better outcomes after TBI[33–35]. In our analyses investigating pre-injury treatment status, we saw stronger associations for treated versus untreated hypertension and diabetes with worse RPQ and BSI-18-GSI scores, which may indicate that that pre-injury treatment status is a surrogate for disease severity. In the present study, we did not have data on post-injury treatment status or medication compliance, but further work in this area is warranted as medication compliance is a potentially modifiable behavior that may be linked to outcome.

Results from our analyses of individual vascular risk factors were more consistent than our analyses of the cumulative burden of vascular risk factors, suggesting that smoking may be the risk factor driving the observed associations with number of vascular risk factors. Indeed, smoking was highly prevalent in our population and this notion is supported by our cumulative burden sensitivity analysis where results were attenuated when smoking was not included as a vascular risk factor. The high smoking prevalence in our population was related to the overall younger mean age of our population and may contribute to our finding that associations of hypertension with worse TBI outcomes were stronger among younger compared to older individuals. Further research investigating associations of vascular risk factor comorbidities with TBI outcomes in older populations is warranted.

In addition to associations with worse 6-month TBI outcomes, our results also suggested that the trajectory of global functional recovery after TBI differed by the cumulative burden of vascular risk factors; fewer individuals with 1 or 2+ vascular risk factors had achieved a "less disabled" outcome on the GOSE by 6-months post-injury, despite all vascular risk factor groups having the same prevalence of a "less disabled" outcome on the GOSE at 2-weeks post-injury. This, in combination with the evidence that TBI is in itself an injury to the cerebrovasculature[10], suggests that the degree of overall vascular health may be important for TBI recovery. Indeed, this notion is supported by data from several observational studies suggesting that statin use may lead to improved TBI outcomes via their broader neuroprotective and vascular-protective properties, including endothelial protection and increased angiogenesis[33–36].

Certain limitations should be taken into consideration in the interpretation of this study. First, as in many TBI studies[37], our data is limited by study attrition and missing data. However, the TRACK-TBI Study has protocols to maximize data collection, including the use of proxies to provide information on the GOSE-TBI for participants who were unable to answer questions themselves, and we used multiple imputation and inverse probability of attrition weighting to statistically account for missing data in our sample[38,39]. Second, the results of this study are generalizable to populations of TBI patients presenting to

level 1 trauma centers and who are willing and able to complete comprehensive follow-up assessments over time; these results may not generalize to milder populations of TBI patients who either do not present to medical attention or who present as outpatients or to emergency rooms/urgent care centers. Additionally, we did not have information on duration of pre-injury health problems, comorbid end-stage kidney disease/dialysis, or post-injury medication(s)/adherence to medication(s).

In conclusion, our study found that pre-injury vascular risk factors, especially smoking, are associated with worse outcomes after TBI. Further work is needed to investigate the underlying mechanisms by which vascular risk factors and overall vascular health may interact with TBI-related cerebrovascular injury to affect TBI outcomes, but aggressive post-injury treatment of vascular risk factors with the goal of improving overall vascular health has the potential to be a promising strategy to improve TBI outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflicts of Interest and Source of Funding:

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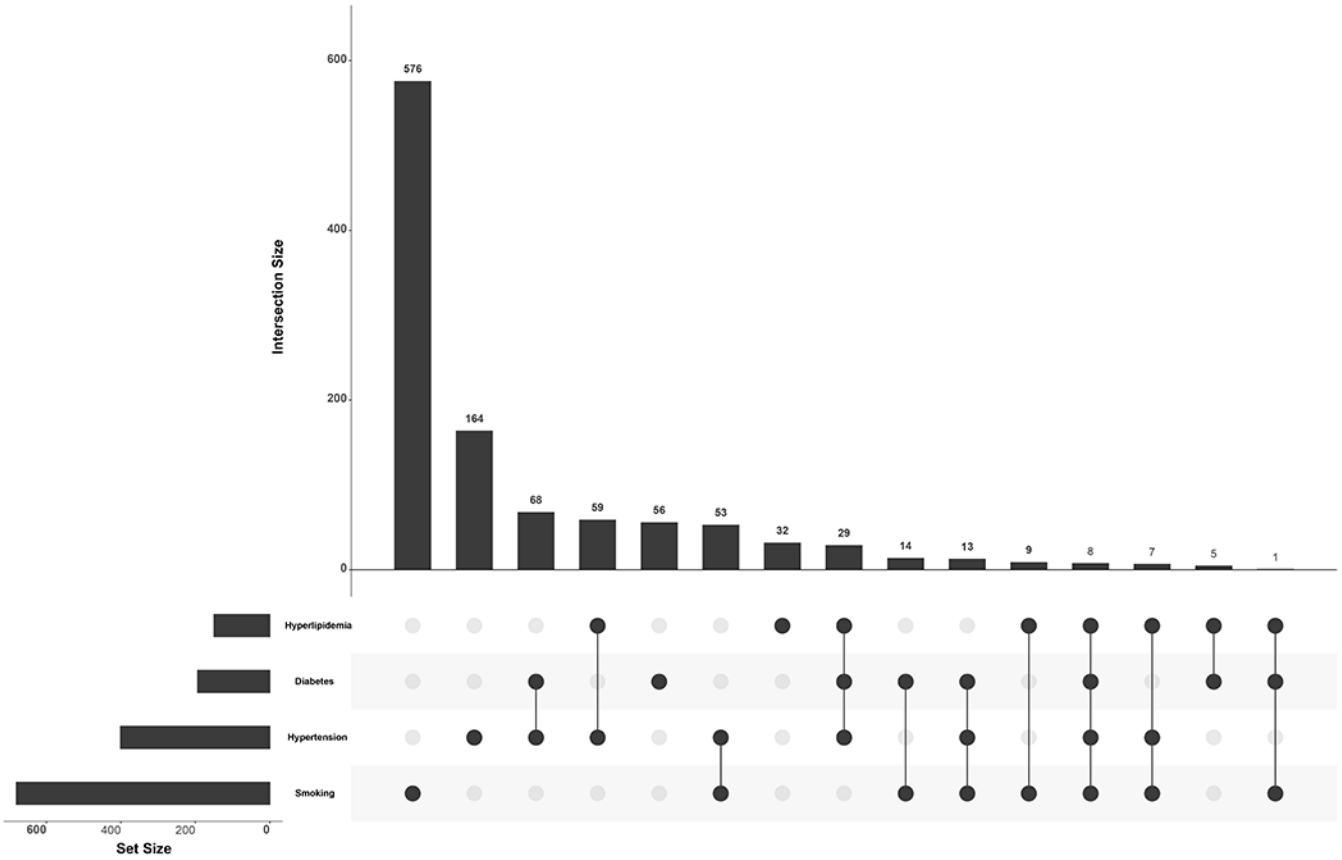

Figure 1.

Patterns of Vascular Risk Factors Among the 1,094 TRACK-TBI Study Participants With at Least 1 Vascular Risk Factor.

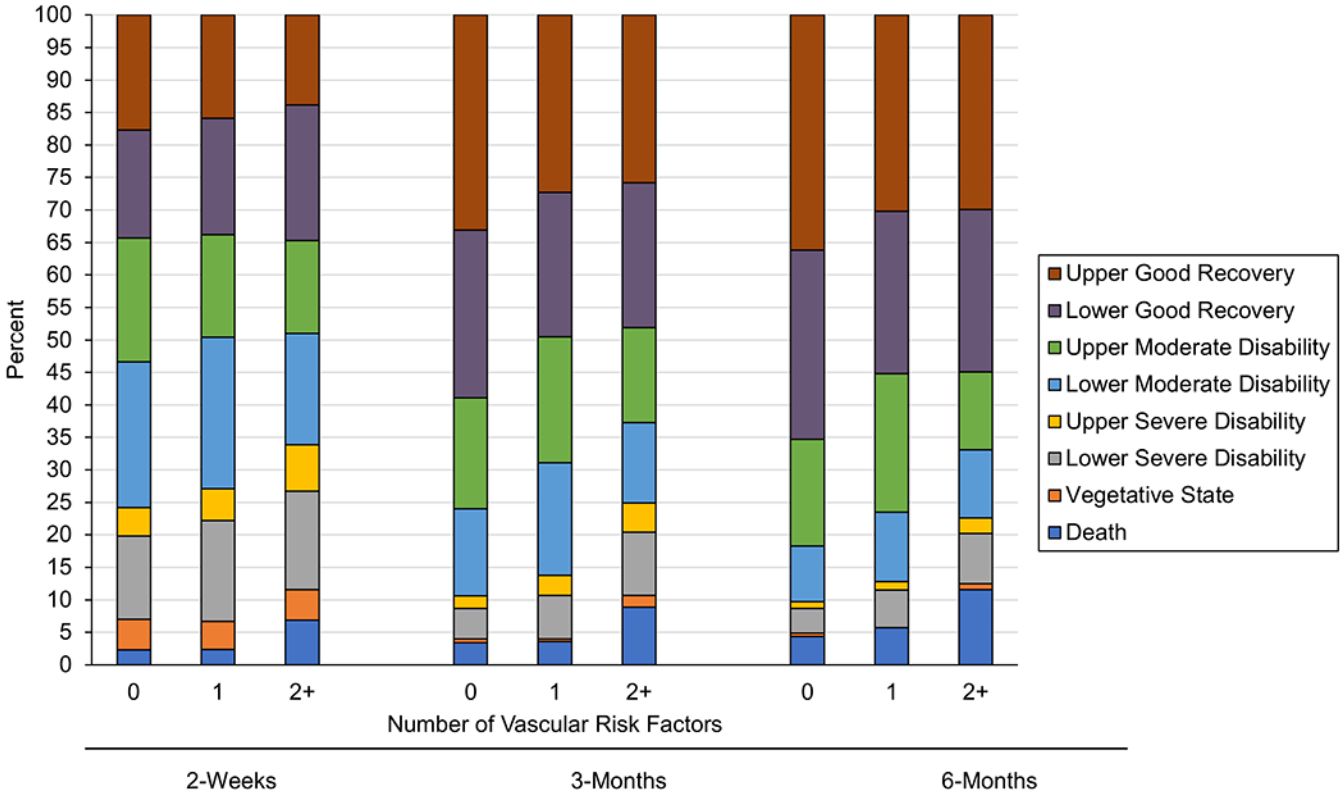

Figure 2.

Inverse Probability of Attrition Weighted Distribution of 2-Week, 3-Month, and 6-Month Glasgow Outcome Scale Extended Scores by Number of Vascular Risk Factors, TRACK-TBI Study. P-value for interaction by time for the association of number of vascular risk factors with GOSE score 1-6 versus 7-8 = 0.009.

Table 1.

Baseline Participant Characteristics Overall and Stratified by Number of Vascular Risk Factors, TRACK-TBI Study.

	Overall (N=2,361)	Number of Vascular Risk Factors			
		0 Vascular Risk Factors (n=1,267)	1 Vascular Risk Factor (n=828)	2+ Vascular Risk Factors (n=266)	P-Value*
Age (years), mean (SD)	41.9 (17.9)	38.6 (16.2)	40.9 (17.1)	60.3 (13.3)	<0.001
Female, n (%)	730 (30.9)	419 (33.1)	230 (27.8)	81 (30.5)	0.038
Race, n (%)					0.001
White	1,818 (77.9)	981 (78.6)	634 (77.2)	203 (76.9)	
Black	379 (16.2)	178 (14.3)	157 (19.1)	44 (16.7)	
Other	136 (5.8)	89 (7.1)	30 (3.7)	17 (6.4)	
Hispanic Ethnicity, n (%)	473 (20.3)	280 (22.4)	149 (18.1)	44 (16.7)	0.021
Education, n (%)					<0.001
<High School	384 (16.9)	153 (12.6)	185 (23.0)	46 (18.2)	
High School or Equivalent	791 (34.8)	409 (33.7)	289 (35.9)	93 (36.8)	
>High School	1,096 (48.3)	652 (53.7)	330 (41.0)	114 (45.1)	
Employment Status, n (%)					<0.001
Full-time	1,324 (57.8)	746 (61.1)	476 (58.5)	102 (39.5)	
Part-time	286 (12.5)	165 (13.5)	101 (12.4)	20 (7.8)	
Unemployed	188 (8.2)	89 (7.3)	86 (10.6)	13 (5.0)	
Retired / Disabled	359 (15.7)	117 (9.6)	122 (15.0)	120 (46.5)	
Student	135 (5.9)	104 (8.5)	28 (3.4)	3 (1.2)	
Alcohol Consumption, n (%)					<0.001
0 drinks/day	495 (21.9)	275 (23.0)	132 (16.3)	88 (34.8)	
1-2 drinks/day (women) or 1-3 drinks/day (men)	821 (36.3)	455 (38.1)	283 (34.9)	83 (32.8)	
≥3 drinks/day (women) or ≥4 drinks/day (men)	943 (41.7)	465 (38.9)	396 (48.8)	82 (32.4)	
Illicit Drug Use, n (%)	617 (27.7)	270 (22.9)	307 (38.3)	40 (16.3)	<0.001
Hypertension, n (%)	401 (17.0)	0 (0.0)	164 (19.8)	237 (89.1)	<0.001
Diabetes, n (%)	194 (8.2)	0 (0.0)	56 (6.8)	138 (51.9)	<0.001
Hyperlipidemia, n (%)	150 (6.4)	0 (0.0)	32 (3.9)	118 (44.4)	<0.001
Current Smoking, n (%)	681 (28.8)	0 (0.0)	576 (69.6)	105 (39.5)	<0.001

	Overall (N=2,361)	Number of Vascular Risk Factors			
		0 Vascular Risk Factors (n=1,267)	1 Vascular Risk Factor (n=828)	2+ Vascular Risk Factors (n=266)	P-Value*
History of Depression/Anxiety, n (%)	461 (19.5)	207 (16.3)	189 (22.8)	65 (24.4)	<0.001
Prior TBI, n (%)					0.004
None	1,518 (69.6)	821 (70.9)	508 (65.1)	189 (78.1)	
No Medical Care Sought	215 (9.9)	120 (10.4)	79 (10.1)	16 (6.6)	
Emergency Room Care	273 (12.5)	134 (11.6)	115 (14.7)	24 (9.9)	
Hospital Admission	174 (8.0)	83 (7.2)	78 (10.0)	13 (5.4)	
Index TBI Severity, n (%)					<0.001
Uncomplicated Mild (GCS 13-15), Head CT negative	1,141 (50.8)	650 (53.3)	405 (51.7)	86 (35.4)	
Complicated Mild (GCS 13-15), Head CT positive	670 (29.8)	334 (27.4)	228 (29.1)	108 (44.4)	
Moderate (GCS 9-12)	113 (5.0)	58 (4.8)	40 (5.1)	15 (6.2)	
Severe (GCS 3-8)	322 (14.3)	178 (14.6)	110 (14.0)	34 (14.0)	
Hospital Level of Care for Index TBI, n (%)					0.003
Emergency Room Discharge	474 (20.1)	289 (22.8)	150 (18.1)	35 (13.2)	
Hospital Floor Admission	830 (35.2)	428 (33.8)	304 (36.7)	98 (36.8)	
Intensive Care Unit Admission	1,057 (44.8)	550 (43.4)	374 (45.2)	133 (50.0)	
Major Extracranial Injury (ISS≥3), n (%)	468 (19.8)	252 (19.9)	164 (19.8)	52 (19.5)	0.997

*P-value reflects comparisons of baseline characteristics across vascular risk factor groups from Kruskal-Wallis tests for continuous variables and Fisher's exact tests for categorical variables.

Note: The following variables contain missing data: race (n=28), Hispanic ethnicity (n=27), education (n=90), employment status (n=69), alcohol consumption (n=102), illicit drug use (n=134), prior TBI (n=181), and TBI severity (n=115).

Abbreviations: CT, computed tomography; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; SD, standard deviation; TBI, traumatic brain injury.

Table 2.

Associations of Individual Vascular Risk Factors with 6-Month TBI Outcomes, TRACK-TBI Study.

	Hypertension	Diabetes	Hyperlipidemia	Current Smoking
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Glasgow Outcome Scale Extended (Score 1-6 versus 7-8)				
Unadjusted, Complete Case	1.31 (1.02, 1.69)	1.32 (0.94, 1.87)	0.97 (0.66, 1.43)	1.56 (1.26, 1.94)
Unadjusted, Inverse Probability of Attrition Weighted for Missing Outcomes	1.33 (1.03, 1.72)	1.22 (0.87, 1.73)	0.95 (0.64, 1.41)	1.58 (1.27, 1.95)
Model 1 *, Inverse Probability of Attrition Weighted for Missing Outcomes	1.21 (0.89, 1.67)	1.10 (0.75, 1.63)	0.84 (0.54, 1.31)	1.75 (1.38, 2.23)
Model 2 **, Inverse Probability of Attrition Weighted for Missing Outcomes	1.16 (0.84, 1.62)	1.02 (0.68, 1.54)	0.89 (0.56, 1.40)	1.49 (1.15, 1.94)
	B (95% CI)	B (95% CI)	B (95% CI)	B (95% CI)
Rivermead Post-Concussion Symptom Questionnaire				
Unadjusted, Complete Case	1.54 (−0.24, 3.32)	3.42 (1.04, 5.81)	−0.05 (−2.80, 2.69)	3.58 (2.09, 5.06)
Unadjusted, Inverse Probability of Attrition Weighted for Missing Outcomes	1.90 (0.11, 3.68)	3.33 (0.95, 5.72)	−0.11 (−2.84, 2.62)	3.73 (2.25, 5.22)
Model 1 *, Inverse Probability of Attrition Weighted for Missing Outcomes	2.82 (0.83, 4.80)	3.36 (0.91, 5.81)	1.20 (−1.58, 3.98)	3.85 (2.37, 5.33)
Model 2 **, Inverse Probability of Attrition Weighted for Missing Outcomes	2.43 (0.46, 4.39)	2.71 (0.29, 5.14)	1.34 (−1.37, 4.05)	3.25 (1.70, 4.80)
Satisfaction with Life Scale				
Unadjusted, Complete Case	−1.86 (−3.04, −0.68)	−1.90 (−3.50, −0.31)	0.66 (−1.18, 2.49)	−2.81 (−3.79, −1.83)
Unadjusted, Inverse Probability of Attrition Weighted for Missing Outcomes	−1.50 (−2.65, −0.35)	−1.37 (−2.93, 0.18)	1.03 (−0.74, 2.79)	−2.68 (−3.63, −1.73)
Model 1 *, Inverse Probability of Attrition Weighted for Missing Outcomes	−1.38 (−2.61, −0.16)	−1.22 (−2.73, 0.29)	1.42 (−0.29, 3.14)	−2.51 (−3.42, −1.61)
Model 2 **, Inverse Probability of Attrition Weighted for Missing Outcomes	−0.87 (−2.08, 0.33)	−0.58 (−2.08, 0.92)	1.31 (−0.35, 2.97)	−1.72 (−2.66, −0.77)
18-Item Brief Symptom Inventory Global Severity Index				
Unadjusted, Complete Case	0.60 (−0.87, 2.07)	1.55 (−0.42, 3.53)	−1.70 (−3.96, 0.56)	3.63 (2.41, 4.85)
Unadjusted, Inverse Probability of Attrition Weighted for Missing Outcomes	0.95 (−0.54, 2.44)	1.57 (−0.42, 3.57)	−1.67 (−3.94, 0.59)	3.70 (2.46, 4.93)
Model 1 *, Inverse Probability of Attrition Weighted for Missing Outcomes	2.65 (0.99, 4.32)	2.35 (0.31, 4.39)	0.01 (−2.31, 2.32)	3.47 (2.24, 4.70)
Model 2 **, Inverse Probability of Attrition Weighted for Missing Outcomes	2.31 (0.69, 3.93)	1.81 (−0.19, 3.80)	0.16 (−2.07, 2.39)	2.36 (1.09, 3.63)

*Model 1: Adjusted for age (continuous), sex (male; female), race (white; black; other), ethnicity (Hispanic; non-Hispanic), and TBI severity (uncomplicated mild [GCS 13-15 and acute head CT negative for intracranial findings]; complicated mild [GCS 13-15 and acute head CT positive for intracranial findings]; moderate [GCS 9-12]; severe [GCS 3-8]).

** Model 2: Adjusted for Model 1 + education (<high school; high school or equivalent; >high school), employment status (full-time; part-time, unemployed; retired/disabled; student), alcohol consumption (0 drinks/day; 1-2 drinks/day [women] or 1-3 drinks/day [men]; ≥3 drinks/day [women] or ≥4 drinks/day [men]), illicit drug use (yes; no), history of depression/anxiety (yes; no), and prior TBI (none; no medical care sought; emergency room care; hospital admission).

Note: Reference groups are no hypertension, no diabetes, no hyperlipidemia, and no current smoking.

Abbreviations: CI, confidence interval; GCS, Glasgow Coma Scale.

Table 3.

Associations of Number of Vascular Risk Factors with 6-Month TBI Outcomes, TRACK-TBI Study.

	Number of Vascular Risk Factors		
	0 Vascular Risk Factors	1 Vascular Risk Factor	2+ Vascular Risk Factors
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Glasgow Outcome Scale Extended (Score 1-6 versus 7-8)			
Unadjusted, Complete Case	1 (Reference)	1.48 (1.20, 1.83)	1.58 (1.15, 2.17)
Unadjusted, Inverse Probability of Attrition Weighted for Missing Outcomes	1 (Reference)	1.53 (1.24, 1.89)	1.55 (1.13, 2.13)
Model 1*, Inverse Probability of Attrition Weighted for Missing Outcomes	1 (Reference)	1.61 (1.27, 2.03)	1.36 (0.94, 1.98)
Model 2**, Inverse Probability of Attrition Weighted for Missing Outcomes	1 (Reference)	1.36 (1.07, 1.74)	1.23 (0.84, 1.83)
	B (95% CI)	**B (95% CI)**	**B (95% CI)**
Rivermead Post-Concussion Symptom Questionnaire			
Unadjusted, Complete Case	0 (Reference)	2.70 (1.25, 4.15)	3.67 (1.47, 5.87)
Unadjusted, Inverse Probability of Attrition Weighted for Missing Outcomes	0 (Reference)	2.86 (1.41, 4.31)	3.95 (1.74, 6.15)
Model 1*, Inverse Probability of Attrition Weighted for Missing Outcomes	0 (Reference)	2.92 (1.51, 4.34)	5.01 (2.69, 7.33)
Model 2**, Inverse Probability of Attrition Weighted for Missing Outcomes	0 (Reference)	2.04 (0.60, 3.47)	4.45 (2.14, 6.77)
Satisfaction with Life Scale			
Unadjusted, Complete Case	0 (Reference)	−2.13 (−3.09, −1.18)	−3.34 (−4.80, −1.87)
Unadjusted, Inverse Probability of Attrition Weighted for Missing Outcomes	0 (Reference)	−1.93 (−2.86, −1.00)	−2.74 (−4.17, −1.32)
Model 1*, Inverse Probability of Attrition Weighted for Missing Outcomes	0 (Reference)	−1.73 (−2.60, −0.86)	−2.31 (−3.75, −0.88)
Model 2**, Inverse Probability of Attrition Weighted for Missing Outcomes	0 (Reference)	−0.89 (−1.77, −0.02)	−1.38 (−2.81, 0.05)
18-Item Brief Symptom Inventory Global Severity Index			
Unadjusted, Complete Case	0 (Reference)	2.72 (1.52, 3.92)	2.25 (0.43, 4.07)
Unadjusted, Inverse Probability of Attrition Weighted for Missing Outcomes	0 (Reference)	2.85 (1.65, 4.06)	2.55 (0.71, 4.38)
Model 1*, Inverse Probability of Attrition Weighted for Missing Outcomes	0 (Reference)	2.94 (1.76, 4.12)	4.29 (2.36, 6.22)
Model 2**, Inverse Probability of Attrition Weighted for Missing Outcomes	0 (Reference)	1.82 (0.64, 3.00)	3.44 (1.54, 5.35)

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[*] Model 1: Adjusted for age (continuous), sex (male; female), race (white; black; other), ethnicity (Hispanic; non-Hispanic), and TBI severity (uncomplicated mild [GCS 13-15 and acute head CT negative for intracranial findings]; complicated mild [GCS 13-15 and acute head CT positive for intracranial findings]; moderate [GCS 9-12]; severe [GCS 3-8]).

[**] Model 2: Adjusted for Model 1 + education (<high school; high school or equivalent; >high school), employment status (full-time; part-time, unemployed; retired/disabled; student), alcohol consumption (0 drinks/day; 1-2 drinks/day [women] or 1-3 drinks/day [men]; ≥3 drinks/day [women] or ≥4 drinks/day [men]), illicit drug use (yes; no), history of depression/anxiety, and prior TBI (none; no medical care sought; emergency room care; hospital admission).

Abbreviations: CI, confidence interval; GCS, Glasgow Coma Scale; TBI, traumatic brain injury.