

Alcohol Consumption Does not Impede Recovery from Mild to Moderate Traumatic Brain Injury

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Abstract

Objectives: To examine the effect of pre-injury alcohol use, acute alcohol intoxication, and post-injury alcohol use on outcome from mild to moderate traumatic brain injury (TBI). **Methods:** Prospective inception cohort of patients who presented to the Emergency Department with mild to moderate TBI and had a blood alcohol level (BAL) taken for clinical purposes. Those who completed the 1-year outcome assessment were eligible for this study ($N = 91$). Outcomes of interest were the count of post-concussion symptoms (British Columbia Post-Concussion Symptom Inventory), low neuropsychological test scores (Neuropsychological Assessment Battery), and abnormal regions of interest on diffusion tensor imaging (low fractional anisotropy). The main predictors were pre-injury alcohol consumption (Cognitive Lifetime Drinking History interview), BAL, and post-injury alcohol use. **Results:** The alcohol use variables were moderately to strongly inter-correlated. None of the alcohol use variables (whether continuous or categorical) were related to 1-year TBI outcomes in generalized linear modeling. Participants in this cohort generally had a good clinical outcome, regardless of their pre-, peri-, and post-injury alcohol use. **Conclusions:** Alcohol may not significantly alter long-term outcome from mild to moderate TBI. (*JINS*, 2016, 22, 816–827)

Keywords: Craniocerebral trauma, Postconcussion symptoms, Neuropsychological tests, Magnetic resonance imaging, Diffusion tensor imaging, Alcohol drinking, Alcohol-related disorders

INTRODUCTION

A disproportionately high number (30–40%) of people who sustain traumatic brain injury (TBI) have a pre-injury history of alcohol use disorder (Bombardier, Rimmele, & Zintel, 2002; Corrigan, 1995; Dikmen, Machamer, Donovan, Winn, & Temkin, 1995; Jorge et al., 2005; Kreutzer, Doherty, Harris, & Zasler, 1990; Ponsford, Whelan-Goodinson, &

Bahar-Fuchs, 2007). Because chronic alcohol use disorders are associated with structural brain abnormalities and neurocognitive impairment (Bühler & Mann, 2011; Grant, 1987; Pfefferbaum et al., 1992; Pfefferbaum, Rosenbloom, Crusan, & Jernigan, 1988), heavy drinkers are theoretically more vulnerable to the effects of TBI. However, the evidence supporting this notion is mixed.

Pre-injury alcohol use predicted TBI outcome in some studies (Barker et al., 1999; Corrigan, Rust, & Lamb-Hart, 1995; Dikmen, Donovan, Lberg, Machamer, & Temkin, 1993; Ponsford, Tweedly, & Taffe, 2013; Wilde et al., 2004) but not all (Allen, Goldstein, Caponigro, & Donohue, 2009; De Guise et al., 2009; Lange et al., 2014; O'Dell et al., 2012;

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Turner, Kivlahan, Rimmele, & Bombardier, 2006; Vickery et al., 2008). It is possible that the duration and recency of pre-injury alcohol use influences its relationship with TBI outcome (Stavro, Pelletier, & Potvin, 2013). Most prior studies classified participants into pre-injury alcohol use categories without consideration of duration or recency (Allen et al., 2009; Barker et al., 1999; O'Dell et al., 2012; Wilde et al., 2004) or measured alcohol use only in the 1–12 months immediately preceding TBI (De Guise et al., 2009; Dikmen et al., 1993; Ponsford et al., 2013; Turner et al., 2006; Vickery et al., 2008). Neither methodology produced consistent findings.

Rodent studies lend support to the importance of distinguishing between recent *versus* chronic pre-injury alcohol use. Heavy alcohol use in the weeks to months before injury, in the absence of a chronic alcohol use disorder, is thought to have neuroprotective effects, such as by inhibiting the responsiveness of NMDA receptors, thereby mitigating excitotoxicity (Baratz, Rubovitch, Frenk, & Pick, 2010). In contrast, chronic alcohol use causes an up-regulation in NMDA receptors, possibly enhancing the excitotoxic effects of TBI (Nagy, 2008).

The effect of pre-injury alcohol use is often confounded with acute alcohol intoxication, as measured by serum blood alcohol level (BAL) (Taylor, Kreutzer, Demm, & Meade, 2003). Approximately 30–55% of patients with TBI have an elevated BAL in the Emergency Department (Corrigan, 1995; Dikmen et al., 1995; Lange, Iverson, & Franzen, 2007; Scheenen et al., 2016; Taylor et al., 2003). This rate is higher in patients with a history of alcohol use disorder (Taylor et al., 2003). Acute alcohol intoxication could theoretically amplify the effects of TBI, such as by reducing respiratory control, cerebral perfusion, or by impairing coagulation, prolonging inflammation, or increasing susceptibility to blood vessel rupture (Altura & Altura, 1999; Teng & Molina, 2014; Zink & Feustel, 1995; Zink, Walsh, & Feustel, 1993).

In rodent models, a low to moderate BAL generally offers neuroprotection, while severe intoxication is associated with worse outcomes (Taylor & Sutton, 2015). Most of the research in humans has focused on the relationship between acute alcohol intoxication and mortality or in-hospital complications (Taylor & Sutton, 2015). Elevated BAL at the time of TBI has also been shown to predict greater trauma-related intracranial pathology on computed tomography (Cunningham, Maio, Hill, & Zink, 2002; Taylor, Mhlanga, & Thomas, 2009). However, the prognostic significance of BAL for post-acute neuropsychological and functional recovery has been mixed (Joseph et al., 2014; Lange et al., 2014, 2007; Lange, Iverson, & Franzen, 2008; O'Dell et al., 2012; Scheenen et al., 2016; Schutte & Hanks, 2010; Tate, Freed, Bombardier, Harter, & Brinkman, 1999).

Alcohol use tends to decrease initially after TBI but then increase (Bombardier, Temkin, Machamer, & Dikmen, 2003; Dikmen et al., 1995; Horner et al., 2005; Ponsford et al., 2007). Patients with a pre-injury alcohol use disorder tend to resume drinking sooner and at higher levels following TBI (Bombardier et al., 2003; Dikmen et al., 1995; Horner et al.,

2005; Ponsford et al., 2007), further obscuring the relationship between pre-injury alcohol use disorder and TBI outcome. Alcohol use following TBI might prolong inflammation (Teng & Molina, 2014) and impair dendritic networking in surviving neurons (Corrigan, 1995).

There is some clinical evidence for detrimental effects of alcohol use after TBI. Post-injury alcohol use was associated with worse executive functioning (but not processing speed or memory) 6 to 12 months after TBI, after controlling for pre-injury consumption (Ponsford et al., 2013). In another study, patients with a pre-injury history of alcohol use disorder who resumed drinking after TBI had reduced frontal gray matter volume and worse performance on certain cognitive tests compared to those who avoided relapse (Jorge et al., 2005).

In summary, the long-term consequences of alcohol use before, at the time of, and after TBI are not well established. This is especially true for milder spectrum TBI. Most research on this topic involved patients with moderate to severe TBI who required admission to hospital. There are several reasons to expect that the influence of alcohol use on recovery differs for milder spectrum TBI. First, any adverse effects of alcohol on long-term outcome might be overwhelmed by the effects of severe TBI, or conversely, be more readily detectable in the context of mild TBI.

In the only study to date with an exclusively uncomplicated mild TBI sample, pre-injury alcohol use disorder had a significant impact on neuropsychological functioning 7 days after injury (Lange et al., 2007). The longer term impact of pre-injury alcohol abuse on neuropsychological or other outcomes in milder spectrum TBI have not been studied. Second, acute alcohol intoxication may exacerbate hypoxia and cerebral edema, and consequently worsen outcome from moderate to severe TBI. These pathological processes are less relevant for milder spectrum TBI. In other words, the primary mechanisms by which acute alcohol intoxication exerts its effect on severe TBI are far less germane in relatively mild TBIs. Consistent with this theory, two emergency department studies examining the relationship between BAL and indices of recovery after *mild* TBI reported null findings (Lange et al., 2014; Scheenen et al., 2016). Third, post-injury alcohol use may be particularly problematic for milder TBI because these patients appear more likely to resume drinking after injury (Beaulieu-Bonneau, Giguere, & Ouellet, 2014).

The present study aims to clarify the influence of alcohol use in patients with mild to moderate TBI. By measuring alcohol use pre-, peri-, and post-injury, and further differentiating lifetime alcohol use from use over the year before injury, we can clarify their relative importance for TBI outcome. The focus on milder spectrum TBI fills a key gap in the literature. Another novel feature of the present study is that we examine long-term (1 year) outcome across multiple dimensions – symptoms, cognition, and white matter integrity. Consistent with the available literature, we hypothesized that alcohol use at all time points would be inter-related and that alcohol use would decrease after TBI in the sample as a whole.

We further hypothesized that lifetime pre-injury alcohol use and post-injury alcohol use would most strongly relate to TBI outcome. In contrast, given its neuroprotective effects in animal models, we expected that alcohol use over the year before injury is less likely to impede recovery. Finally, because the physiological effects of acute alcohol intoxication are less relevant to milder spectrum TBI, we hypothesized that BAL would not significantly predict outcome in the present study.

METHODS

Design

This is a prospective inception cohort study. Consecutive trauma cases who presented to the Emergency Department at Vancouver General Hospital (in British Columbia, Canada) between June 2007 and September 2014, and were 19–55 years old and had a BAL obtained as part of routine clinical care, were screened for eligibility. Participants

completed an in-person assessment at 6 weeks post-injury and again at 1 year post-injury. Each assessment included a structured interview, self-report questionnaires, neuropsychological testing, and a magnetic resonance imaging scan (MRI). Injury characteristics and BAL values were obtained through Emergency Department chart review. This study was conducted with approval from the University of British Columbia research ethics board. Note that 6-week outcomes from an overlapping sample were reported in a prior publication (Lange et al., 2014).

Participants

Participants in the TBI group ($N = 144$) had at least one indication of brain injury: (i) witnessed LOC ≥ 1 min, (ii) post-traumatic amnesia ≥ 15 min, (iii) Glasgow Coma Scale (GCS) < 15 , or (iv) trauma-related abnormal day-of-injury computed tomography scan. Figure 1 depicts the flow of participants through the study and how after applying exclusion criteria, we arrived at the final sample of 81 patients

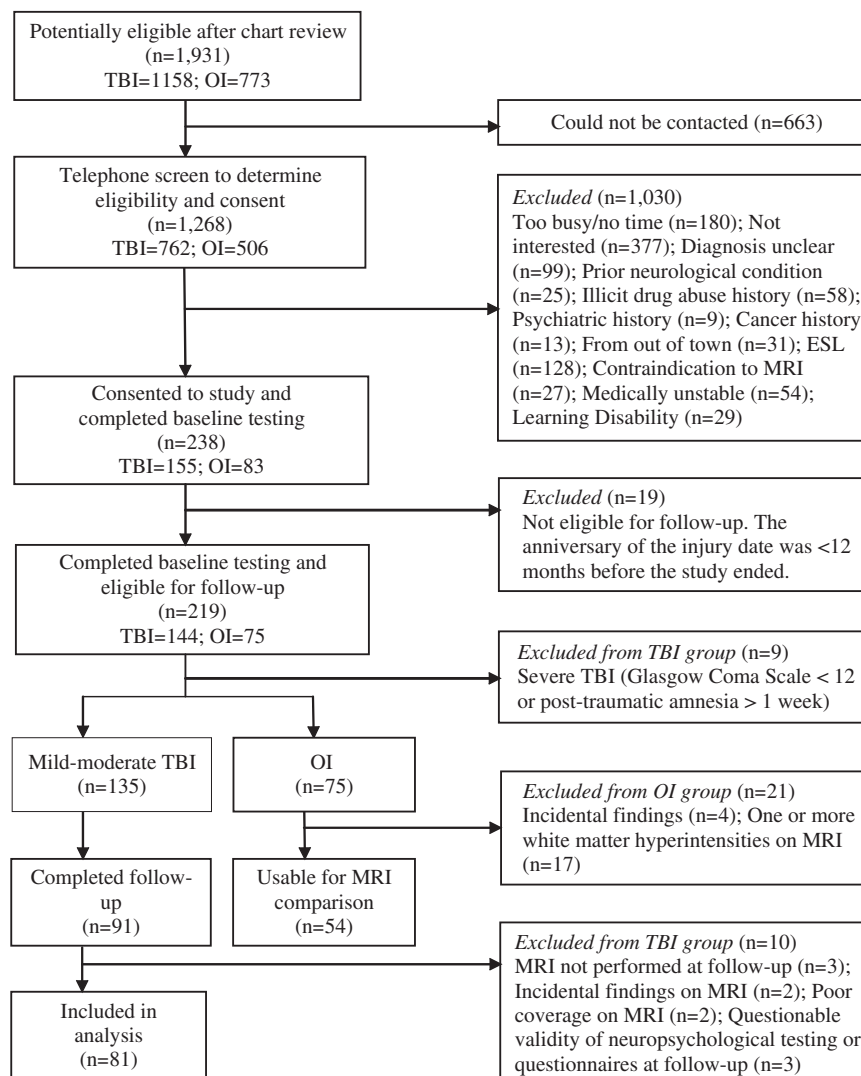


Fig. 1. Flow diagram. ESL = English as a second language; OI = orthopedic injury; MRI = magnetic resonance imaging; TBI = traumatic brain injury.

Table 1. Characteristics of the sample

Age	Mean = 32.3 years, <i>SD</i> = 10.4
Sex	Males = 62 (76.5%) Females = 19 (23.5%)
Ethnicity	Caucasian = 66 (81.5%) Asian-Canadian = 8 (9.9%) Other = 7 (8.7%)
Education	Mean = 14.9 years, <i>SD</i> = 2.4
Mechanism of injury	Cyclist accident = 27 (33.3%) Motor vehicle accident = 14 (17.3%) Assault = 12 (14.8%) Fall = 11 (13.6%) Pedestrian struck by car = 10 (12.4%) Sports injury = 5 (6.2%) Other = 2 (2.5%)
Glasgow Coma Scale	15 = 42 (51.9%) 14 = 33 (40.7%) 13 = 2 (2.5%) 9–12 = 4 (5%)
Loss of consciousness duration	None = 3 (3.7%) Transient = 15 (18.5%) <5 minutes = 25 (30.9%) 5–30 minutes = 14 (17.3%) >30 minutes = 5 (6.2%) Unknown/could not be determined = 19 (23.6%)
Post-traumatic amnesia duration	<15 minutes = 5 (6.2%) 15–60 minutes = 21 (25.9%) 1–12 hours = 34 (42%) 12–24 hours = 6 (7.4%) >24 hours = 10 (12.3%) Unknown/could not be determined = 5 (6.2%)
Admitted to hospital	No = 40 (49.4%) Yes = 41 (50.6%)
Computed tomography	Not ordered = 2 (2.5%) Normal = 52 (64.2%) Abnormal = 27 (33.3%)
Magnetic resonance imaging (at 6 weeks post-injury)	Normal = 38 (46.9%) Abnormal = 41 (53.1%)
Seeking financial compensation for injury	Unknown = 3 (3.7%) No = 25 (30.9%) Yes = 53 (65.4%)

who sustained a mild to moderate TBI. Their demographic and injury characteristics are presented in Table 1.

Trauma patients without TBI were also enrolled ($N = 75$). These participants sustained a soft tissue or orthopedic injury below the neck and had none of the following evidence of brain injury: GCS score < 15, loss of consciousness (LOC), post-traumatic amnesia, facial or head lacerations or contusions, traumatic impact involving the head, whiplash mechanism or cervical strain, or complaint of neck or head pain. In the present study, MRI data from the trauma controls was used as the normative reference for diffusion tensor

imaging values. Trauma controls with incidental findings on MRI (i.e., abnormalities unrelated to recent trauma) or one or more white matter hyperintensities were excluded (see Figure 1), leaving $N = 54$.

Measures

Acute alcohol intoxication

BALs were obtained in the Emergency Department of Vancouver General Hospital as part of standard clinical care. BALs at the hospital are measured using a high volume analyzer (Beckman CX7, Model 7566, Beckman Instruments, Inc. Fullerton, CA) and are reported as millimoles per liter.

Lifetime preinjury alcohol consumption

The Cognitive Lifetime Drinking History interview⁴² is a structured interview that probes for the type of alcohol, typical drink size, number of drinks, and frequency of consumption over “drinking intervals.” The drinking intervals represent a participant’s regular pattern of drinking within a certain life period and are identified with the aid of a life events calendar (e.g., marriage, job change, etc.) to cue remote autobiographical memory. The present study analyzed the total number of ounces consumed over the participant’s lifetime, which takes into account the quantity, frequency, and duration of drinking. This composite metric has been shown to correlate with macro- and microstructural neuroimaging changes (Le Berre et al., 2015; Pfefferbaum et al., 1988; Pfefferbaum & Sullivan, 2002). The interview was conducted in an in-person visit 6 weeks after TBI.

Alcohol Consumption over the Year before Injury

Participants were asked to recall how many days per week (or month) they drank as well as the number of drinks and typical drink size (facilitated by flashcards displaying common drink sizes) over the 1-year period immediately preceding TBI. The total number of alcoholic drinks consumed over this period was converted to ounces by multiplying the number of (assumed standard) drinks by 0.6 (National Institute on Alcohol Abuse and Alcoholism, 2015). The purpose of including this measure was to decouple relatively recent from remote/lifetime alcohol use, motivated by the finding that mice who were fed alcohol over the 4 weeks preceding closed-head weight drop injury had *improved* neurobehavioral outcomes (Baratz et al., 2010). Although this timeframe is difficult to translate into humans, we wanted to capture the likely detrimental consequences of high lifetime alcohol use (Bühler & Mann, 2011; Grant, 1987; Pfefferbaum et al., 1992) separately from the possibly neuroprotective effects of “recent” pre-injury alcohol use.

Postinjury alcohol consumption

Alcohol consumption after TBI is dynamic, with most patients abstaining initially and then resuming at variable

rates (Bombardier et al., 2003; Dikmen et al., 1995; Horner et al., 2005; Ponsford et al., 2007). For the purposes of this study, we, therefore, created a structured interview to estimate alcohol consumption over the 1-year period immediately following TBI, modeled after the Cognitive Lifetime Drinking History interview⁴². Participants were prompted to identify distinct patterns of alcohol consumption (“drinking intervals”) lasting from 1 to 12 months.

We summed the number of drinks consumed across all drinking intervals, and converted this total to ounces by multiplying the number of (assumed standard) drinks by 0.6 (National Institute on Alcohol Abuse and Alcoholism, 2015). The post-injury drinking intervals should sum to 12 months, but only summed to 11 months for 20% of the sample and less than 11 months for another 18% of the sample. For participants who provided less than 12 months of post-injury alcohol consumption data, their total consumption for the year following TBI was prorated based on the monthly average for which data was available.

Symptoms

The British Columbia Post-Concussion Symptom Inventory (BC-PSI; Iverson, Zasler, & Lange, 2007) prompts participants to rate the frequency (0 = “not at all” to 5 = “constantly”) and intensity (0 = “not at all” to 5 = “very severe problem”) of 13 common post-concussion symptoms, such as headache, fatigue, irritability, and poor concentration. Frequency and intensity ratings are multiplied for each item, and a product of 1 or higher indicates that an item was endorsed (with at least “mild” severity; Iverson et al., 2007).

Neurocognition

The Neuropsychological Assessment Battery (Stern & White, 2003) is a comprehensive co-normed battery of standardized cognitive tests that has been validated in TBI (Donders & Levitt, 2012; Zgaljardic & Temple, 2010). To reduce administration time, 16 of the 24 subtests most likely to be sensitive to TBI were included in the study protocol. These 16 subtests yield 23 scores of interest, covering the domains of attention and processing speed (Digits Forward, Digits Backward, Dots, Numbers & Letters, Driving Scenes), language (Oral Production, Naming), visuospatial functioning (Visual Discrimination, Design Construction), memory (List Learning, Shape Learning, Story Learning, Daily Living Memory), and executive functioning (Categories, Mazes, Word Generation).

Diffusion tensor imaging (DTI)

DTI is an MRI-based technology for quantifying white matter integrity. DTI can yield several metrics, but fractional anisotropy (FA) is the most widely studied in TBI and has a relatively well-understood pathophysiological mechanism (Hulkower, Poliak, Rosenbaum, Zimmerman, & Lipton, 2013; Shenton et al., 2012). Whereas some DTI metrics tend to normalize with time since injury, FA may be the most

persistently altered DTI metric in milder spectrum TBI (Mac Donald et al., 2011; Yuh et al., 2014). The majority of DTI studies have reported reduced FA in post-acute mild to moderate TBI (Aoki, Inokuchi, Gunshin, Yahagi, & Suwa, 2012; Eierud et al., 2014; Hulkower et al., 2013; Mac Donald et al., 2011; Silverberg et al., 2015; Yuh et al., 2014).

Reduced FA has also been reported in chronic alcohol use disorder samples (Pfefferbaum et al., 2000; Pfefferbaum, Rosenbloom, Rohlfing, & Sullivan, 2009; Yeh, Simpson, Durazzo, Gazdzinski, & Meyerhoff, 2009), and so may be sensitive to possible synergistic effects of alcohol and TBI. FA differences are not restricted to a small number of brain regions; rather, there is considerable regional heterogeneity in TBI (Ling et al., 2012; Lipton et al., 2012; Yuh et al., 2014). As in prior studies (e.g., Yuh et al., 2014), we examined the rate of low FA across the whole brain.

MRI data were acquired on a Philips Achieva 3 Tesla scanner with Dual Nova Gradients (maximum gradient strength 80 mT/m, maximum slew rate 200 mT/m/s) and an eight-channel phased array head coil in parallel imaging mode. Diffusion tensor imaging (DTI) data were acquired using an eddy current compensated, single-shot, spin-echo, echo planar imaging sequence with unipolar diffusion weighting along 16 noncollinear directions and a maximum b value of 1000 s/mm². Further DTI parameters were as follows: acquisition matrix 96*96, 50 contiguous slices, 2.5*2.5*2.5mm isotropic acquisition resolution, time to echo 75 ms, time to repetition 5600 ms, parallel imaging SENSE-factor = 2.4.

DTI sequences with poor field-of-view resulting in significant deficits in whole brain coverage or artifacts were not considered in the analysis. Motion and artifacts in the diffusion data were corrected using affine registration of all gradient volumes with the b = 0 volume (FLIRT; FMRIB Software Library, Oxford, UK), and gradient directions were compensated for rotations (Landman et al., 2007). This was followed by creation of a manual brain mask based on the b = 0 image using FSL FreeView from the FSL Version 4.1.9 suite (Smith et al., 2004). Individual FA maps were then non-linearly registered *via* FSL-FNIRT to the JHU-ICBM FA template provided by FSL (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). To calculate mean FA values within each individual region of interest (ROI), in each individual patient, we used FSL statistics using the JHU transformed FA map. ROIs were defined by overlay of the JHU-ICBM-DTI-81 atlas (Hua et al., 2008; Mori, Wakana, Nagae-Poetscher, & Van Zijl, 2005; Wakana et al., 2007).

Statistical Analyses

For ease of interpretation and model comparison, all dependent variables were converted to a common metric, count data. The number of items endorsed as mild or worse on BC-PSI was summed to create a post-concussion symptom count. The number of NAB subtest scores falling below the 16th percentile (relative to the standardization sample of

healthy subjects) was summed to create a count of low neuropsychological scores. FA values for 25 regions of interest as defined by the JHU-ICBM-DTI atlas were included in further analyses. These 25 areas were chosen as per the Transforming Research and Clinical Knowledge in TBI protocol (TRACK-TBI; Yuh et al., 2014) to represent (i) the tracts most commonly affected by TBI and (ii) areas that are less prone to artefact.

In detail, the regions included were the anterior corona radiata, superior corona radiata, posterior corona radiata, anterior limb of internal capsule, posterior limb of internal capsule, external capsule, superior longitudinal fasciculus, ventral cingulum (parahippocampal gyrus), dorsal cingulum (cingulate gyrus), sagittal striatum (including inferior fronto-occipital fasciculus and inferior fronto-occipital fasciculus), and superior fronto-occipital fasciculus, each on the left and right; and also the body, genu, and splenium of the corpus callosum.

The ROIs in participants with TBI were compared to a trauma control sample with no TBI (described in another publication by our group; Lange et al., 2014), yielding Z scores for each region of interest. An ROI was considered abnormal if the Z score for FA fell more than two standard deviations below the control group mean. The number of abnormal ROIs was summed to create a summary DTI score for each participant.

Participants who completed the follow-up assessment *versus* dropped out of the study after the initial assessment were compared on a panel of demographic, injury severity, and alcohol consumption variables with *t* tests (for continuous measures) and χ^2 (for proportions). Spearman rho correlations were computed to examine the associations between the alcohol use variables. The Wilcoxon Signed Rank Test, a non-parametric alternative to the paired *t* test, was used to compare pre-injury *versus* post-injury alcohol consumption.

Because our dependent measures were count data at a single time point (1 year post-injury), we first fit generalized linear models with a Poisson distribution and log link function. There was evidence of over-dispersion in all models (residual deviance/degrees of freedom >1). We, therefore, refit each with a negative binomial distribution and log link. This resulted in improved deviance measures and model fit (lower Akaike Information Criterion). Age and sex were included as covariates in all models because these variables are associated with both alcohol consumption and TBI outcome (Corrigan, 1995; Dikmen et al., 1993; Horner et al., 2005; Ponsford et al., 2007). An absence of problematic multicollinearity was confirmed by Variance Inflation Factors < 10 and Conditional Indices < 30.

It is theoretically plausible for alcohol use to have a non-linear relationship with TBI outcome. For example, TBI outcome might be the same for patients with alcohol consumption in the low to moderate range, but worse for the heaviest drinkers. We, therefore, categorized the alcohol use variables based on their distribution properties and re-ran the generalized linear models with categorical predictors. BAL had a bimodal distribution, with a high 0 count ($N = 47$;

58.0%) and a Gaussian-like curve peaking around 40 mmol/L. BAL was, therefore, dichotomized into 0 *versus* detectable. Of note, all but two participants with a detectable BAL exceeded the threshold for impaired driving according to federal law (≥ 17.3 mmol/L).

The distribution of pre- and post-injury alcohol consumption variables were both highly positively skewed. The majority of participants ($N = 66$; 81.5%) consumed less than 10,000 oz lifetime (~16,700 drinks), with the remainder consuming between 10,000 and 60,000 oz. This subgroup with high pre-injury lifetime use consumed an average of 22,139 oz (~36,900 drinks), or 1,292 oz (~2,150 drinks) per year since the age of 15. One quarter of the sample ($N = 20$; 26.3%) reported drinking no alcohol in the year following TBI, more than half ($N = 46$; 60.5%) reporting drinking between 1 and 500 oz (~2 to 830 drinks), and a minority ($N = 10$; 13.1%) consumed more than 500 oz (up to 2400) in the year following TBI. So, we categorized pre-injury alcohol consumption into low (0) and high (1) groups, and post-injury alcohol consumption into none (0), some (1), and high (2) groups. Alcohol use over the year before injury was left continuous, because no natural breaks or valleys in the distribution were observed.

RESULTS

Study completers and drop-outs did not differ on demographic variables (age, education, gender), injury severity (GCS score, CT results, admission to hospital), or any of the alcohol use variables collected in the first assessment (all $p > .05$). The following analyses involve only participants who completed both assessments. Post-injury alcohol consumption was strongly related to both alcohol use over the year before injury ($r = 0.79$; $p < .001$) and over the participants' lifetime ($r = 0.68$; $p < .001$). BAL was related to alcohol consumption at all time points ($r = 0.43$ for lifetime, $r = .61$ for year before injury, $r = .45$ for year after injury; all $p < .001$).

Descriptive statistics for the alcohol use variables are reported in Table 2. Lifetime average annual alcohol consumption (lifetime pre-injury consumption divided by adult years; median = 171 oz; ~285 drinks) was similar to alcohol consumption during the year before TBI. In comparison, alcohol consumption during the year following TBI was approximately 50% lower, which was statistically significant (Wilcoxon Signed Rank Test = -2.98; $p = .003$ for lifetime pre-injury and Wilcoxon Signed Rank Test = -4.44; $p < .001$ for year before injury).

The results of generalized linear modeling are presented in Table 3. No alcohol use variable, whether continuous or categorical (data not shown), predicted any TBI outcome, including post-concussion symptoms, neuropsychological functioning, or white matter integrity at 1-year post-injury. The 95% confidence interval for all exponentiated parameter estimates included 1.0, except for older age and female sex predicting worse white matter integrity (more abnormal

Table 2. Descriptive statistics for predictor variables and outcome measures

		Mean (SD)	Median (IQR)	Range
Predictors	Total pre-injury alcohol consumption	6,219 (9,768)	2,760 (697–6841)	0–57,607
	Consumption in year prior to TBI	378 (475)	187 (62–468)	0–2,184
	BAL in Emergency Department	20.3 (26.1)	0 (0–43)	0–80
	Consumption in year after TBI	260 (477)	83 (0–288)	0–2321
Outcomes	Symptoms ^a	2 (2.6)	1 (0–3)	0–12
	Cognition ^b	1.6 (2.0)	1 (0–2)	0–9
	White matter ^c	1.9 (3.2)	0 (0–2)	0–15

BAL = blood alcohol level; IQR = interquartile range; TBI = traumatic brain injury

^aNumber of symptoms (out of 13) endorsed on the British Columbia Post-Concussion Symptom Inventory, mild or greater severity.

^bNumber of scores (out of 23) on the Neuropsychological Assessment Battery that fell below the 16th percentile based on the normative standardization sample.

^cNumber of regions of interest (out of 25) with low fractional anisotropy (more than two standard deviations below the mean of a trauma control group with no brain injury).

ROIs). One possible explanation for the lack of relationship between post-injury alcohol use and TBI outcome is that patients who are more affected by TBI tend to restrict their alcohol consumption after TBI.

Exploratory comparisons revealed that post-injury alcohol consumption was not related to GCS score ($M = 302$, $SD = 529$ oz for 15; $M = 215$, $SD = 417$ oz for <15; $p = .971$), CT results ($M = 245$, $SD = 478$ oz for normal/not ordered; $M = 284$, $SD = 500$ oz for abnormal; $p = .837$), or admission to hospital ($M = 245$; $SD = 451$ oz for admitted; $M = 273$; $SD = 506$ oz for evaluated and discharged; $p = .800$). Post-concussion symptoms, neuropsychological functioning, and white matter integrity at 6 weeks post-injury were also minimally correlated with alcohol consumption over the year following TBI (Spearman rho correlations all $p > .05$).

DISCUSSION

Alcohol use is presumed to worsen long-term outcome from TBI, but evidence supporting this relationship is far from clear, especially for milder spectrum TBI. The present study examined the relationship between alcohol use (pre-, peri-, and post-injury) on multidimensional outcome from mild to moderate TBI. None of the alcohol use variables were related to 1-year TBI outcomes, including post-concussion symptoms, neuropsychological functioning, and white matter integrity. Regardless of their pre-, peri-, post-injury alcohol consumption, patients with mild to moderate TBI generally had a good clinical outcome, defined by few symptoms and few low neuropsychological test scores. This is consistent with systematic reviews demonstrating that mild TBI

Table 3. Parameter estimates for models with continuous predictor variables

Outcome	Alcohol use predictors	Exponentiated coefficient	95% confidence interval	Overall model (χ^2 , p)
Symptoms ^a	Age	0.98	0.95–1.01	6.83, .337
	Sex	0.68	0.32–1.46	
	Lifetime pre-injury	1.00	1.00–1.00	
	Recent pre-injury	0.99	0.97–1.01	
	BAL	1.01	0.99–1.03	
	Post-injury consumption	1.00	0.99–1.01	
Cognition ^b	Age	1.03	0.99–1.06	5.52, .480
	Sex	1.18	0.55–2.55	
	Lifetime pre-injury	1.00	1.00–1.00	
	Recent pre-injury	1.01	0.99–1.01	
	BAL	1.01	0.98–1.02	
	Post-injury consumption	0.99	0.99–1.01	
White matter ^c	Age	1.07	1.03–1.11	26.56, <.001
	Sex	2.68	1.21–5.91	
	Lifetime pre-injury	1.00	1.00–1.00	
	Recent pre-injury	1.00	1.00–1.00	
	BAL	1.01	0.99–1.02	
	Post-injury consumption	1.00	0.99–1.00	

BAL = Blood alcohol level

^aNumber of symptoms (out of 13) endorsed on the British Columbia Post-Concussion Symptom Inventory, mild or greater severity.

^bNumber of scores (out of 23) on the Neuropsychological Assessment Battery that fell below the 16th percentile based on the normative standardization sample.

^cNumber of regions of interest (out of 25) with low fractional anisotropy (more than two standard deviations below the mean of a trauma control group with no brain injury).

generally has a favorable prognosis (Cassidy et al., 2014; Karr, Areshenkoff, & Garcia-Barrera, 2014). Categorizing alcohol consumption to explore non-linear relationships with TBI outcome also yielded null findings. In short, alcohol consumption was unrelated to 1-year outcome from mild to moderate TBI.

The present study adds to the sparse literature on alcohol and milder spectrum TBI. Prior studies (Lange et al., 2007; Scheenen et al., 2016), including one by our group reporting on an overlapping sample (Lange et al., 2014), provided little evidence that high pre-injury alcohol use and/or acute alcohol intoxication affected short-term outcome (2–6 weeks) from mild to moderate TBI. These data left open the possibility that the effects of alcohol use on recovery may only emerge after this subacute period, as recovery plateaus for some patients and continues for others (i.e., alcohol does not slow recovery but limits the extent of recovery). The present study found no effects of alcohol use on 1-year outcome after mild to moderate TBI, suggesting that this hypothesis is unlikely. The present study further showed that lifetime alcohol use had no association with TBI outcome even after adjusting for prior year alcohol consumption. That is, disentangling remote *versus* more recent pre-injury alcohol consumption did not uncover an effect for either of these variables. Another novel finding in the present study was that post-injury alcohol use also appeared unrelated to outcome from mild to moderate TBI.

The few prior studies reporting a significant relationship between pre-injury alcohol use and outcome all involved samples with more severe TBIs (Barker et al., 1999; Dikmen et al., 1993; Ponsford et al., 2013; Wilde et al., 2004) in comparison to the present sample. Although this suggests TBI severity as a potential moderator variable, it is noteworthy that the study by Dikmen et al. (1993) found a similar magnitude alcohol effect across their TBI subgroups with the least severe (time to follow commands less than 6 hours) and most severe injuries. Between-study differences in pre-injury alcohol exposure might also help explain its inconsistent relationship with TBI outcome. It is difficult to compare the extent of pre-injury alcohol use across studies because of diverse constructs being measured (quantity of alcohol consumption *versus* patterns of alcohol consumption *versus* problematic consequences of alcohol use *versus* indicators of alcohol dependence) and the methodology for obtaining these data (structured interviewing *vs.* chart reviews *vs.* screening questionnaires).

In the present study, patients with mild to moderate TBI who consumed higher amounts of alcohol in the year before their injury were more likely to present to the Emergency Department with acute alcohol intoxication at time of injury. A similar relationship has been demonstrated compellingly for traumatic injuries other than TBI (Cherpitel et al., 2012). Our participants reduced their alcohol consumption by approximately half during the year following TBI. Post-injury alcohol use was predicted by pre-injury alcohol use and BAL. These findings are largely consistent with prior research examining the relationship between alcohol use before, at the time of, and after TBI (Bombardier et al., 2003;

Dikmen et al., 1995; Horner et al., 2005; Ponsford et al., 2007; Taylor et al., 2003).

TBI severity and early outcome did not predict post-injury alcohol use in the present study. This is at odds with at least one prior report, which found that patients with less severe TBI consume more alcohol after their injuries (Beaulieu-Bonneau et al., 2014). Our pattern of findings supports early intervention efforts for problematic drinking after TBI (Tweedly, Ponsford, & Lee, 2012) that target patients who acknowledge drinking heavily before their TBI and/or present to the Emergency Department with acute alcohol intoxication, regardless of their TBI severity.

The present study has important limitations. BALs were obtained as part of a routine trauma panel for patients who presented to the ED with decreased consciousness, and by clinical indication for less severely injured patients. This may have resulted in an over-representation of patients with significant alcohol use histories in our sample (i.e., selection bias). Of note, the rate of acute alcohol intoxication in our TBI sample (39.5% based on a cut-off of ≥ 17.3 mmol/l) was squarely within the range of prior studies (Corrigan, 1995; Dikmen et al., 1995; Lange et al., 2007; Scheenen et al., 2016; Taylor et al., 2003).

The drop-out rate in our cohort was substantial, although comparable to other longitudinal TBI studies (Corrigan et al., 2003). Although participants who returned for the 1-year outcome assessment *versus* those who dropped out of the study did not differ on baseline measures, we cannot assume that drop-out was completely random and that our findings are free of attrition bias. Given our modest sample size, it is possible that the present study was insufficiently powered to detect a true effect of alcohol consumption. If present, these effects must be relatively subtle. We used total consumption by volume as the primary measure of alcohol use to maximize statistical efficiency.

Our study was not sufficiently powered to examine whether particular patterns of alcohol use, such as infrequent but episodic heavy drinking (binging) *versus* regular moderate use, might be associated with different TBI outcomes. Regular moderate use may be associated with a lower risk of re-injury and be less detrimental to brain health and other organ systems compared to episodic heavy use (Cherpitel et al., 2012; Hayes, Deeny, Shaner, & Nixon, 2013; Mukamal et al., 2003).

The present study cannot rule out that alcohol is more detrimental if consumed during a critical time period after TBI, such as in the first weeks post injury. We did not have large enough sample sizes to compare subgroups of patients who resumed drinking earlier *versus* later following TBI. Given the minimal but consistent prior evidence that alcohol use after moderate-to-severe TBI may hinder recovery (Jorge et al., 2005; Ponsford et al., 2013), further research is needed to clarify how the timing, pattern, and quantity of alcohol use after TBI relate to long-term outcome. Self-reported alcohol use history is vulnerable to recall bias and impression management, although it has been shown to have strong test-retest reliability (Russell et al., 1997) and correspond closely to estimates from relatives of patients with TBI (Sander, Witol, & Kreutzer, 1997).

Our study design does not allow us to conclude whether alcohol use was associated with poor white matter integrity, independent of TBI. That is because a proportion of the trauma control sample we used as a reference group for DTI analyses would be expected to have a history of high pre-injury alcohol consumption, like our TBI sample. Areas of poor white matter integrity 1 year after TBI could theoretically reflect TBI pathology or the interaction of alcohol use and TBI, but could not be attributed to pre-injury alcohol use.

The present study can also not rule out adverse effects of pre-injury alcohol consumption on mild to moderate TBI outcome in the heaviest and most chronic alcohol users. We did not conduct diagnostic assessments to determine whether participants in the current study met criteria for alcohol use disorder. Participants categorized as high pre-injury alcohol consumption in our study represented the top quartile of patients who arrived at the Emergency Department with a TBI. Their average annual consumption was more than triple that of the average Canadian (or American; World Health Organization, 2014). Their total lifetime alcohol consumption had an overlapping range but lower group mean in comparisons to prior studies of patients with alcohol use disorders recruited from substance abuse treatment programs (Le Berre et al., 2015; Pfefferbaum et al., 1988).

A final noteworthy limitation is that resolution of post-traumatic amnesia in our sample was determined by retrospective medical chart review, supplemented by a structured interview each participant. Post-traumatic amnesia duration can be more accurately estimated by prospective serial assessment (Roberts, Spitz, & Ponsford, 2016).

In conclusion, pre-injury alcohol use, acute alcohol intoxication, and post-injury alcohol use were related to each other. The present study found no relationship between alcohol use at any time point and multidimensional outcome from mild to moderate TBI at 1 year following injury. Patients in our cohort recovered well regardless of their alcohol use. Even if alcohol has little impact on TBI outcomes, interventions to prevent problematic alcohol use after TBI are important to reduce recurrent injury, interactions with prescription medications, other alcohol-related health problems.

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