The Impact of Traumatic Brain injury and Aggregate Comorbidities on Cognitive Functioning in a Marginally Housed Sample

by

Tiffany A. O'Connor

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Name: **Tiffany A. O'Connor**

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Examining Committee: **Chair:** Dr. Shannon Zaitsoff
Assistant Professor

Dr. Allen E. Thornton
Senior Supervisor
Associate Professor _____

Dr. Wendy Thornton
Supervisor
Associate Professor _____

Dr. Donna Lang
Supervisor
Assistant Professor
Department of Radiology
University of British Columbia _____

Dr. Naznin Vurji-Babul
External Examiner
Assistant Professor
Department of Physical Therapy
University of British Columbia _____

Date Defended/Approved: June 28, 2016

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Abstract

Individuals living in marginal urban housing face numerous health risks that impair cognition and produce burden in these individuals that may differentially attenuate capacity to tolerate further brain insult. We investigated the effect of self-reported traumatic brain injury (TBI) on cognition in persons with differential levels of neurocognitive burden. Two hundred and twenty participants (age: 23-68; 170 M, 50 F), recruited from single-room occupancy hotels underwent neurocognitive testing. A statistically weighted neurocognitive burden index was created reflecting the aggregate extent to which non-TBI comorbidities (vascular health, mental health, substance use, viral infection, neurological illness) and demographics (age, education, premorbid IQ) were associated with overall cognition. This index was investigated for its moderating influence on the relationship between self-reported TBI history (loss of consciousness of 30 minutes or more) and neurocognition. Hierarchical linear regression revealed that the burden index accounted for 31.4% of the total variance in cognition ($F(1, 212) = 97.052$, $p < .001$). TBI itself did not account for additional variance in cognition; nor did burden moderate the effect of TBI. Self-reported TBI history, as defined in the present study, has minimal value in signifying cognitive dysfunction in multimorbid marginally housed individuals.

Keywords: multimorbidity; marginalization; traumatic brain injury

To my family for supporting me in every way possible.

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Chapter 1. Introduction

Residents of single-room occupancy hotels (i.e. government-owned low-income housing; SROs) in Vancouver make up one of the most marginalized groups in Canadian society (Linden, Mar, Werker, Jang, & Krausz, 2013), living in substandard housing that is often the only alternative to homelessness for low-income tenants (Vila-Rodriguez et al., 2013). Individuals living in marginal urban housing face numerous mental and physical health risks, including substance dependence, mental illness, infectious disease, neurological illness or insult, and increased mortality rate (Ludwig et al., 2012; Patel & Burke, 2009; Shannon, Ishida, Lai, & Tyndall, 2006; Vila-Rodriguez et al., 2013).

Neurologically, marginalized populations experience high rates of traumatic brain injury (i.e. an alteration in brain function, or other evidence of brain pathology, caused by an external force [TBI]; Menon, Schwab, Wright, & Maas, 2010). We recently characterized the physical and mental health of a large cohort of individuals living in SRO hotels in the Downtown Eastside of Vancouver, British Columbia (The Hotel Study; Vila-Rodriquez et al., 2013), and found approximately 64 percent of participants reported a history of head or face injury, with approximately 11 percent having definite TBI. This rate is consistent with that found in marginalized populations (Hwang et al., 2008), yet almost double the incidence proportion of individuals with TBI worldwide (i.e. approximately 600 per 100,000 individuals of the population; Cassidy et al., 2004).

In marginalized populations, TBI has many cognitive, physical, and emotional consequences that may persist and place individuals at risk for social failure (Topolovec-Vranic et al., 2012), with subsequent low employment rates increasing the risk of homelessness (van Velzen, van Bennekom, Edelaar, Sluiter, & Frings-Dresen, 2009) and the chronicity of remaining homeless (Backer & Howard, 2007). According to BC Housing, in 2001 the change in cost of health care, social services, and criminal justice

systems to the province of British Columbia was estimated to be approximately $30,000 to $40,000 on average per person annually if a resident left a SRO and returned to homelessness (British Columbia Ministry of Social Development and Economic Security [BCMSDES], 2001). In a 2006 study, this number rose to an estimated $55,000 per person annually (Patterson, Somers, McIntosh, Shiell, & Frankish, 2008). Understanding the effects of TBI in marginally housed persons has the potential to reduce the number of individuals that will face negative outcomes, including homelessness. This will provide significant financial, societal, and individual implications (Topolovec-Vranic et al., 2012).

Although acute deficits in cognition can be found at all severities of TBI (i.e. mild, moderate, severe), there is a dose-response relationship between the length of unconsciousness following a TBI and the level of performance on neuropsychological measures at one year post-injury (Dikmen, Machamer, Winn, & Temkin, 1995). A systematic review of meta-analyses on the cognitive sequelae of mild TBI by Karr, Areshenkoff, and Garcia-Barrera (2014) showed that overall cognitive functioning recovery following mild TBIs (i.e. head injuries that result in a loss of consciousness for 30 minutes or less; Kay et al., 1993) occurred within 90 days post-injury for most individuals. Those with mild TBI have been found to be comparable to controls on measures of cognition at three months (Frencham, Fox, & Mayberry, 2005) and one year (Dikmen et al., 1995) post-injury. Single-incident mild TBI has been found to have little clinical significance to long-term cognitive and symptom outcome (Ettenhofer & Abeles, 2009). Following moderate to severe TBI (i.e. head injury that result in a loss of consciousness for more than 30 minutes; Kay et al. 1993), cognition improves during the first two years, but remains impaired even among patients assessed more than two years post-injury. Averaged across all follow-up periods, the effect of moderate and severe TBI in individuals with low levels of multimorbidity was more than three times the effect of mild TBI on overall cognitive functioning (Schretlen & Shapiro, 2003).

In otherwise high functioning individuals, moderate to severe TBIs cause cognitive deficits predominantly in the areas of attention, processing speed, and verbal learning and memory (Fleminger, 2008; Griffen, & Hanks, 2014; Hopkins, Tate, & Bigler, 2005; Mathias & Wheaton, 2007; Miotto et al., 2010). A single moderate to severe TBI has been found to have negative implications for the brain and cognition with advanced

age, suggesting interplay between early head trauma and the aging process (Ozen, Fernandes, Clark, & Roy, 2015). Those with a history of moderate to severe TBI also have an increased risk of developing Alzheimer's disease (Plassman et al., 2000).

Although much is known about the effects of TBI on cognition in the general population, more research is needed to understand its impact in marginalized persons (Hwang et al., 2008). Interpreting and predicting cognitive deficits after traumatic brain injury in persons living in SROs may be difficult due to the many potential interacting factors that can influence it. The multitude of risk factors that marginalized populations face across the lifespan (e.g. developmental, substance use, viral infection, psychiatric illness, and brain injury) is apt to impose a substantial neurocognitive burden (Gicas et al., 2014), making individuals less able to deal with further brain insult. One risk factor for neurocognitive burden is captured in the comprehensive theories of brain (Satz, 1993) and cognitive (Stern, 2002) reserve. Reserve theories attempt to explain individual differences in functional outcome following brain insult (Kesler, Adams, Blasey, & Bigler, 2003), based on the repeated observation that there does not appear to be a direct relationship between the degree of brain damage and the clinical manifestation of that damage (Stern, 2002).

Although models of reserve have been supported in research on brain injury outcomes, low cognitive reserve may be only one possible risk factor for neurocognitive burden. Nunnari, Bramanti, and Marino (2014) note that the current literature has focused on only a targeted subset of risk factors for neurocognitive burden in individuals with TBI (i.e. education, premorbid IQ). TBI is thought to have a synergistic deleterious impact on cognition by interacting with many other risk factors for neurocognitive burden to produce poor brain health and functional outcomes (Monti et al., 2013; Moretti et al., 2012). For instance, compared to those with TBI alone, additional neurocognitive deficits have been found in persons with TBI and substance abuse (Corrigan, 1995). In a study by Kelly, Johnson, Knoller, Drubach, and Winslow (1997), neuropsychological outcome was examined in severe traumatic brain injury patients who were drug users, alcohol users, or neither. Following acute recovery, non-alcohol or drug using patients with TBI performed significantly better than both alcohol and drug users on composite and verbal intelligence, as well as measures of general and verbal memory, attention and

concentration. Similarly, a study by Dikmen, Donovan, Løberg, Machamer, and Temkin (1993) found that neuropsychological impairment following mild to severe head injury was related both to the severity of injury and preinjury alcohol abuse. In individuals with mild to moderate TBI, additional neurocognitive deficits have also been found in persons with comorbid depression (Chamelian & Feinstein, 2006). Midlife cardiovascular health has been associated with cognitive decline at six (Knopman et al., 2001) and 20 years later (Virta et al., 2013), as well as late life dementia (Whitmer, Sidney, Selby, Claiborne Johnston, & Yaffe, 2005). Cognitive impairment has been associated with psychotic disorders (Heinrichs & Zakzanis, 1998), viral infection (Dieperink, Willenbring, & Ho, 2000; Reger, Welsh, Razani, Martin, & Boone, 2002), and neurological illness or insult (Vermeer et al., 2003).

Given the ubiquity of multiple comorbid risk factors among marginally housed persons with a history of head injury, greater clarity of the relative impact of these risk factors, both individually and in aggregate, on cognition is of value. Rather than a simple linear relationship between TBI and cognition in marginalized populations, there is likely to be a complex process influenced by both acquired and inherited neuroprotective factors, and factors that increase the neurocognitive burden on the brain, causing or predisposing persons to negative outcomes (Mesulam, 2000; Fotuhi, Hachinski, & Whitehouse, 2009).

To explore the complex interactions of multiple co-morbid factors on cognitive dysfunction in marginalized persons with TBI, this study will examine the effect of self-reported moderate to severe traumatic brain injury on cognition in persons with differential levels of neurocognitive burden, since those with history of mild TBI are not expected to have lasting impairments. Better understanding of the various processes that can add to one's level of neurocognitive burden, impacting brain and cognitive health, is crucial in understanding individual differences in functioning following TBI. Furthermore, understanding the impact of specific risk factors for neurocognitive burden on cognition will identify the most influential treatment foci (e.g. vascular health versus mental illness) in multimorbid marginalized populations. The main objective of this study is to create a neurocognitive burden index to determine:

1. If certain risk factors for neurocognitive burden differentially predict cognition.

2. The potential aggregate impact of multimorbid risk factors for neurocognitive burden on cognition.

3. The potential association between TBI and cognition after controlling for level of neurocognitive burden.

4. If the level of neurocognitive burden moderates the effect of TBI on cognition.

Chapter 2. Methods

2.1. Participants

Three hundred seventy four participants were recruited from the downtown eastside of Vancouver. Participants were recruited by approaching all tenants within four single room occupancy hotels in the area. Participation was voluntary, with honorarium given. All participants had adequate English language fluency for the purpose of valid psychometric testing. Of the individuals approached (N=406), 92% (N=374) provided informed consent to communicate clinically significant findings to the participants' physicians. The final sample was reduced to 220, after excluding those with missing/invalid cognitive or injury data or magnetic resonance image (MRI) scans (used to objectively verify self-report from non-TBI controls; see Appendix A for participant flow chart). The participants (170 M, 50 female) had an age range of 23 to 68 years (mean age = 43 yrs). The sample was 59% Caucasian, 28% Aboriginal, 3% Asian, 2% African American, and 8% mixed/other ethnicities. Sixty percent of participants did not complete high school, 37% completed high school, and 3% completed a college or university program. The average monthly income was $887 CDN, with 8% of participants earning an income with benefits. There was ubiquitous substance dependence (95%), with 61% engaged in injection drug use. Viral infection was present in 70% of participants, and 22% of participants have a history of self-reported acquired TBI (moderate to severe). These characteristics make this sample appropriate for the study of individuals with multiple comorbidities. Table 1 presents frequencies of demographic and clinical characteristics of the final sample and pre-sampling population.

Table 1. Final Sample Characteristics Compared to Pre-Sampling Population (i.e. all those entered into the study, including those excluded in the analyses)

	Study Sample			Pre-sampling Population		
Clinical Characteristic	**Total N**	**N**	**%**	**Total N**	**N**	**%**

Clinical Characteristic	Study Sample			Pre-sampling Population		
	Total N	N	%	Total N	N	%
Drug Dependence						
Alcohol	220	35	15.9	371	67	18.1
Cocaine	220	157	71.4	371	253	68.2
Methamphetamine	220	56	25.5	371	93	25.1
Heroin	220	83	37.7	371	137	36.9
Other Opiate	220	45	20.5	371	72	19.4
Methadone	220	92	41.8	371	146	39.4
Cannabis	220	68	30.9	371	115	31.0
Mental Illness						
Psychotic illness, any	220	104	47.3	371	175	47.2
Depression	220	34	15.5	371	54	14.6
Viral Infection						
HIV	220	33	15.0	356	61	17.1
HepB	220	82	37.3	354	143	40.4
HCV (cleared/active)	208	138	66.3	338	226	66.9
Cytomegalovirus	220	146	66.4	353	236	66.9
Herpes Simplex Virus	219	194	88.6	253	314	89.0
Vascular Health						
History of stroke	219	11	5.0	348	16	4.6
High Cholesterol	218	41	18.8	339	62	18.3
Heart Attack/Disease	219	21	9.6	348	34	9.8
Diabetes	219	9	4.1	348	14	4.0
BMI Obese	217	13	6.0	361	26	7.2
Neurological Illness/Insult						
Movement disorder	215	35	16.3	337	63	18.7
Infarct	220	11	5.0	290	15	5.2
Lacune	219	10	4.6	289	15	5.2
Stroke	220	22	10.0	290	30	10.3
Stroke with Hemorrhage	219	3	1.4	371	3	0.8
Traumatic Brain Injury						
Moderate to Severe TBI	220	49	22.3	287	49	17.1
TBI as defined by MRI	220	8	3.6	287	21	7.3
Penetrating TBI	220	0	0	372	2	0.5
Clinical cognitive impairment	220	11	5.0	371	32	8.6

Note. HIV = human immunodeficiency virus; HepB = hepatitis B virus; HCV = hepatitis C virus; BMI = body mass index; MRI = magnetic resonance imagine.

2.2. Procedures

Cognitive testing was conducted by trained research assistants. To ensure standardization, reports were made of the subjective validity of each assessment and the occurrence of any outstanding events. Demographic information, premorbid intelligence (IQ), viral infection, mental health, substance dependence (i.e. substances used, amount, frequency of use), and self-reported histories of TBI were collected. Cognition was assessed using a comprehensive neuropsychological battery. High-field magnetic resonance images were collected to ascertain multi-modal *in-vivo* structural brain data. Each full data assessment lasted approximately 5 hours.

2.3. Measures Used

2.3.1. Traumatic brain injury measures.

Participants completed an interviewer administered medical review form (MRQ; see Appendix B question 8 for more details regarding relevant questions), a 17-item questionnaire assessing previous medical history and current medical conditions. Participants were asked about the occurrence of any previous head or face injuries. Those with a history of injury in this area were further asked to describe their age at the time of the injury, the event that caused the injury, the injury itself, the length of any memory loss and loss of consciousness, and any hospitalizations for the injury. Participants were asked if they experienced a variety of common neuropsychological complaints after acquired TBI, and for how long these occurred.

2.3.2. Risk factors for neurocognitive burden measures.

Cognitive reserve. Demographic information was obtained using a standardized form that asked participants to report their age, gender, ethnicity, number of years of education completed, and average monthly income. Premorbid IQ was assessed by the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001). The WTAR is an estimate of an individual's level of IQ before the onset of illness or injury (i.e. TBI). Participants were presented with 50 atypical words and asked to read each aloud. Total

scores range from 0 to 50, measuring the number of correctly read words. This measure has been found to have high stability during recovery from TBI (r = .97) and convergent validity with demographic estimates of premorbid IQ at both two (r = .54) and five (r = .58) months post injury (Green et al., 2008). As reported in recent studies, cognitive reserve was calculated as a standardized composite of years of education attained and premorbid IQ (i.e. reading ability (Brickman et al., 2011; Patel et al., 2013; Rentz et al., 2010).

Vascular Health. Participants were assessed for a range of risk factors for poor vascular health, including history of heart attack or heart disease, history of stroke, diabetes, high cholesterol, high blood pressure, and obesity.

History of heart attack/disease, history of stroke, and diabetes. Participants self-reported if they had ever experienced a stroke, heart attack or heart disease, or diabetes via an interviewer-administered medical review questionnaire. Of those with self-reported history of stoke, 18% showed evidence of stroke on MRI or were currently on related doctor prescribed medication. Of those with a history of heart attack or disease, 9% are currently on related doctor prescribed medication. Of those with self-reported diabetes, 67% are currently on doctor prescribed medication to manage diabetes or showed average blood sugar levels in the diabetic range according to blood work (i.e. 6.5 % or higher of glycated hemoglobin).

Cholesterol. Blood testing of all participants was done at the BC Centre for Disease Control. Participants were coded at having optimum levels (i.e. less than or equal to 5 mmol) or mild to very high level (i.e. greater than 5 mmol) of cholesterol.

Pulse pressure. A calculation (i.e. systolic [minus] diastolic blood pressure) was done for all participants based off an average of three blood pressure measurements. All individuals with abnormal levels of pulse pressure (i.e. 60 or higher) were on doctor prescribed medication for hypertension.

Obesity. Body mass index was calculated based off of measurements of participant height and weight (i.e. BMI = kg/m^2, where kg as weight in kilograms and m^2 as height in metres squared).

Substance dependence. Drug (i.e. alcohol, cocaine, methamphetamine, heroin, methadone, cannabis) dependence was diagnosed through psychiatric interview according to the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text revision; DSM-IV-TR; American Psychiatric Association, 2000) in consensus with the Best Estimate Clinical Evaluation and Diagnosis 2 (BECED-II; Endicott, 1988). The best estimate procedure has been found to be optimal in studies investigating a broad range of disorders, where the use of drugs is not an exclusion criterion (Fennig, Craig, Lavelle, Kovasznay, & Bromet, 1994).

Mental illness. Mental disorders were diagnosed through psychiatric interview according to the DSM-IV-TR criteria in consensus with the BECED-II.

Viral infection. Blood samples underwent serology testing at the BC Centre for Disease Control for antibodies to the human immunodeficiency virus (HIV), hepatitis B, hepatitis C, herpes simplex, and cytomegalovirus. This method has been found to have strong sensitivity in detecting recent infections (89%), specificity in detecting established infections within the first year of transmission (86.8%), and specificity in detecting infections of durations longer than one year (98%; Guy et al., 2009).

Neurological insult or illness. Diagnoses were made with anatomic MRI, with scans reviewed by a neuroradiologist. Relevant diagnoses included cerebral infarcts, lacunes, non-TBI encephalomalacia, stroke with hemorrhage, hemorrhage not due to stoke, possible multiple sclerosis, and non-TBI lesions/trauma (e.g. due to infection).

2.3.3. Dependent Measures.

Cognition. Verbal learning and memory, working memory, and selective and sustained attention were assessed. These domains of cognition have been found to be

sensitive to the effects of traumatic brain injury on cognition (Dikmen et al., 1995). All three cognitive measures were significantly correlated with each other (i.e. $r > .3$, $p < .001$), and were subsequently combined into a standardized cognitive composite score.

Verbal learning and memory. Participants completed the Hopkins Verbal Learning Test – Revised (HVLT-R; Brandt, 1991), where trials of 12 words are orally presented and participants are assessed for immediate and delayed recall, and delayed recognition. This measure has been shown to have adequate construct, concurrent, and divergent validity (Shapiro, Benedict, Schretlen, & Brandt, 1999).

Selective attention. Participants completed the Stroop Color and Word Test (Golden, 1978), where a list of colour words printed in a conflicting colour (e.g. “green” printed in blue ink) are presented and participants are asked to identify the ink colour as quickly as possible within a time limit. This measure has been found to have high reliability and a valid test of attention and executive functioning in both normal humans and those with neuropsychological impairments (MacLeod, 1991).

Sustained attention and working memory. Participants completed the Rapid Visual Information Processing (RVP) subtest of the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition, 2002). The RVP is a computer-administered nonverbal task designed to assess sustained attention where participants are presented with a series of pseudo-random ordered numbers and tested on their ability to detect target sequences of digits (e.g. 2-4-6) by responding using a press pad. The CANTAB has been found to be sensitive to frontal lobe dysfunction and differences in executive functioning in adults (Robbins et al., 1994; Robbins et al., 1998), and modestly associated with traditional neuropsychological measures (Smith, Need, Cirulli, Chiba-Falek, & Attix, 2013).

Chapter 3. Analysis

3.1. Design

Operational definitions of TBI and comparator group. Two groups were included in the design: multimorbid, poly-substance abusing individuals who have 1) self-reported a previously acquired moderate to severe TBI (i.e. head injury that resulted in unconsciousness for more than 30 minutes or post-traumatic amnesia for more than 24 hours) with or without MRI verified TBI, since mild TBI has been found to have little clinical significance to long-term cognitive and symptom outcome (Ettenhofer & Abeles, 2009), and 2) non-TBI controls with no MRI verified history of traumatic brain injury, and either no reported head/face trauma or head/face trauma with no hospitalization, loss of consciousness, confusion or loss of memory, dizziness, headache, blurred vision, or other problems relating to the injury. Those who were unsure as to whether they had acquired a head/face injury were included in the nTBI group as they did not differ from the controls on cognition, demographics, clinical characteristics or MRI verification status. To ensure that we had a clean sample of non-TBI controls, those with a reported head/face injury with an unknown amount of unconsciousness or post-traumatic amnesia, a mild TBI (i.e. a head injury with a loss of consciousness of 30 minutes or less or post-traumatic amnesia of 24 hours or less), or no reported head/face injury but a TBI as verified by MRI, were excluded. These definitions of TBI severity are consistent with standardized consensus criteria (Kay et al., 1993). A validity check was done to test the convergence between TBI classification based on the MRQ and that done on a subset of individuals using the Brain Injury Screening Questionnaire. To examine the validity of self-reported traumatic brain injury in this sample, the effect of objective TBI (i.e. TBI as determined by MRI alone) on cognition was examined.

Statistical Approach. To create a neurocognitive burden index, an approach derived by Patel et al.'s (2013) study examining the aggregate effect of multiple comorbid risk factors in cognition among HIV-infected individuals was used. First, TBI and all risk factors for neurocognitive burden were screened for their individual impact on composite cognition. To include all variables associated with deficits in cognition, variables with a small effect size (d = .2; Cohen, 1992) or higher in the appropriate direction (i.e. negatively associated with cognition) were included in the index, while all other variables were dropped (see Appendix C for list of all independent measures, descriptions, effect sizes, and coding for inclusion in neurocognitive burden index). Included risk factors were then weighted based on their unstandardized beta coefficients, and then combined to create the neurocognitive burden index. This was done by saving the unstandardized predicted value from the regression.

Subsequently, hierarchical regression using the neurocognitive burden index assessed the aggregate impact of multimorbid risk factors on cognition, the association between TBI and cognition (controlling for level of burden), and the extent to which burden moderates the effect of TBI in its impact on cognition. Finally, hierarchical regression analyses were conducted to determine 1) the effects of neurocognitive burden and TBI on individual cognitive domains (i.e. verbal learning and memory, selective attention, and sustained attention and working memory); and 2) the extent to which aspects of neurocognitive burden (e.g. age, mental illness) and TBI predict cognition.

3.2. Data Diagnostics

Descriptive statistics were examined for all variables on measures central tendency (i.e. mean, median, and mode), as well as the distribution of scores (i.e. minimum, maximum, range, standard deviation, skewness, and kurtosis). An initial inspection of the minimum and maximum values, along with a histogram of each variable data, was done to check for floor effects and possible outliers. Table 2 presents descriptive statistics for each individual cognitive measure, indicating that there were no

floor effects observed in any area of cognition. See Figure 1 for frequency tables of each individual cognitive measure.

Table 2 Descriptive Statistics of Each Individual Cognitive Measure (N = 220)

	Cognitive Measure		
Statistic	**HVLT imm**	**Stroop CW**	**RVP**
M	19.168	35.429	.863
SD	5.638	9.827	.059
Skewness	-.177	.259	-.325
Kurtosis	-.464	.091	.462
Range	27	52	.34
Minimum	4	13	.66
Maximum	31	65	1

Note. HVLT imm = Hopkins Verbal Learning Test immediate recall; Stroop CW = Stroop Color and Word Test interference; RVP = Rapid Visual Information Processing; NBI = neurocognitive burden index; TBI = traumatic brain injury.
*p < .05. **p < .01. *** p < .001.

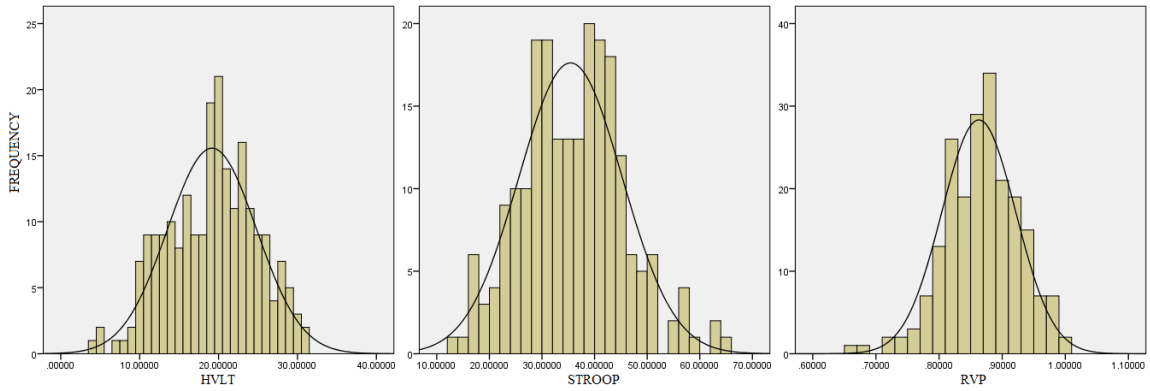

Figure 1 Frequency tables of each cognitive measure indicating no floor or ceiling effects.

Data points with absolute-value z-scores greater than 3.29 were considered outliers. Valid scores were adjusted to one unit above of the highest non-outlying value (Tabachnick, 2001). Multicollinearity was assessed by examining the variance inflation factor, with a cut-off of 5 or higher indicating possible multicollinearity. Table 3 presents correlation coefficient values between all possible predictor variables. The assumption that the model correctly specified all relevant predictors and the form of the relationship between predictors and the criterion was checked by inspecting the scatterplot of

residuals to predicted values. Homoscedasticity of errors was assessed by examining the variance in residuals at each estimated value of cognition. Normality of errors was assessed with Normal Q-Q Plots of residuals. Fixed factors were checked with Cronbach's alpha ≥7 (Taylor, 1990). The independence of errors were checked with a Durbin-Watson test of lag 1 autocorrelation.

Table 3 Correlation Coefficient Values (Spearman's Rho) Between Predictor Variables (N = 220)

Predictor	1	2	3	4	5	6	7	8	9	10	11
TBI (1)											
Cognitive reserve (2)	.077										
Schizophrenia (3)	-.093	-.033									
Age (4)	.110	-.054	-.192**								
Psychosis NOS (5)	.086	.161*	-.103	-.012							
Heart attack/ disease (6)	.015	-.011	-.103	.055	-.103						
Stroke with hemorrhage (7)	.033	-.109	-.037	.073	-.038	-.039					
Non-TBI brain lesion/trauma (8)	.127	-.043	-.037	.043	.095	-.039	-.014				
HIV (9)	.020	.040	-.044	.085	.080	.123	.062	-.049			
Diabetes (10)	-.054	.030	.014	.206**	-.066	.245***	-.025	-.025	.041		
Hepatitis B (11)	.062	.222**	-.178**	.277***	.102	-.060	.072	-.009	.176**	-.018	
Brain Lacunes (12)	.040	.331	-.067	.171*	.152*	.003	-.026	-.026	-.031	.065	.057

Note. TBI = traumatic brain injury; NOS = not otherwise specified; HIV = human immunodeficiency virus.
*p < .05. **p < .01. *** p < .001.

3.3. Power

A power profile calculation was conducted using G*Power 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009), which indicated a strong power profile. For 11 predictors (i.e. all risk factors for neurocognitive burden), a sample size of 220, alpha of 0.05, and a low observed R^2 of 0.1, the observed statistical power is 0.93.

Chapter 4. Results

As anticipated, a simultaneous linear regression revealed that risk factors for neurocognitive burden differentially predicted composite cognition. Table 4 displays the unstandardized regression coefficients (*B*), the standard error of *B* (*SE B*), and the standardized regression coefficients (*β*) after entry of all 11 predictors. The R^2 value of .312 indicates that more than a third of the variance in cognition was accounted for by cognitive reserve, schizophrenia, age, and psychosis not otherwise specified. History of heart attack or disease, diabetes, HIV, hepatitis B, non-TBI brain lesions or trauma, stroke with hemorrhage, or brain lacunes did not significantly predict composite cognition.

Table 4 Summary of Simultaneous Regression Analyses for Risk Factors for Neurocognitive Burden Predicting Composite Cognition (N = 220)

	Composite Cognition		
Predictor	***B***	***SE B***	***β***
Cognitive reserve	-.401	.061	-.402***
Schizophrenia	-1.007	.210	-.290***
Age	-.245	.064	-.245***
Psychosis NOS	-.465	.207	-.137*
Heart attack/disease	-.400	.208	-.118
Stroke with hemorrhage	-.610	.506	-.071
Non-TBI brain lesion/trauma	-.429	.504	-.050
HIV	-.128	.168	-.046
Diabetes	-.156	.310	-.031
Hepatitis B	-.052	.133	-.025
Brain Lacunes	.049	.287	.010
R^2		.312	
F		8.416***	

Note. NOS = not otherwise specified; HIV = human immunodeficiency virus.
*p < .05. **p < .01. *** p < .001.

Next, a hierarchical regression was employed using the neurocognitive burden index created in the initial regression (Block 1), history of TBI (Block 2), and their interaction (Block 3), as predictors of composite cognition. Table 5 displays the unstandardized regression coefficients (*B*), the standard error of *B* (*SE B*), and the standardized regression coefficients (*β*) for each predictor. The neurocognitive burden index accounted for 31.4% of the variance in composite cognition, indicating a significant aggregate impact of multiple comorbid risk factors on cognition. Traumatic brain injury did not account for a significant amount of additional variance in composite cognition, after controlling for level of neurocognitive burden. Similarly, level of neurocognitive burden was not found to moderate the relationship between TBI and cognition as the interaction was not significant (see below). Thus, contrary to the prediction, TBI was not a significant predictor of cognition regardless of level of neurocognitive burden.

Table 5 Summary of Hierarchical Regression Analyses for Neurocognitive Burden Index and Traumatic Brain Injury Predicting Composite Cognition (N = 220)

	Composite Cognition		
Predictor	***B***	***SE B***	***β***
Block 1			
Neurocognitive burden index	-1.002	.102	-.560***
R^2		.314	
F Change		97.052***	
Block 2			
Neurocognitive burden index	-1.013	.102	-.566***
Traumatic brain injury	.149	.137	.062
R^2		.318	
F Change		1.190	
Block 3			
Neurocognitive burden index	-.988	.115	-.553***
Traumatic brain injury	.158	.138	.066
NBI × TBI interaction	-.115	.252	-.030
R^2		.319	
F Change		.210	

Note. NBI = neurocognitive burden index; TBI = traumatic brain injury.
*p < .05. **p < .01. *** p < .001.

Exploratory 1. Separate exploratory hierarchical regression analyses were conducted to determine whether level of neurocognitive burden (Block 1), traumatic brain injury (Block 2), and their interaction (Block 3) predicted the individual cognitive domains of verbal learning and memory (i.e. HVLT), selective attention (i.e. Stroop CW), and sustained attention and working memory (i.e. RVP). Table 6 displays the unstandardized regression coefficients (*B*), the standard error of *B* (*SE B*), and the standardized regression coefficients (*β*), squared Pearson correlation coefficient (R^2), *F* statistics for the change in R^2 (*F*) and for each predictor.

Similar to the composite results, level of neurocognitive burden was a significant predictor of performance in all three cognitive domains, accounting for 19.2, 20.8, and 16.9% of the variance in verbal learning in memory, selective attention, and sustained attention and working memory, respectively. Consistent with performance on composite cognition, traumatic brain injury and the neurocognitive burden by TBI interaction did not accounted for a significant amount of variance in any cognitive domain. Thus, traumatic brain injury was not a significant predictor of any individual cognitive domain regardless of level of neurocognitive burden.

Table 6 Summary of Hierarchical Regression Analyses for Neurocognitive Burden Index and Traumatic Brain Injury Predicting Each Cognitive Measure (N = 220)

	Cognitive Measure		
Predictor	**HVLT imm**	**Stroop CW**	**RVP**
Neurocognitive burden index			
B	-7.852	-7.612	-.042
SE B	1.282	1.204	.007
β	-.436***	-.439***	-.417***
R^2	.192	.208	.169
F Change	49.052***	54.465***	39.419***
Traumatic brain injury			
B	.962	.923	.009
SE B	1.539	1.459	.009
β	.040	.040	.066
R^2	.194	.209	.173
F Change	.369	.307	.993

	Cognitive Measure		
Predictor	**HVLT imm**	**Stroop CW**	**RVP**
NBI × TBI interaction			
B	-.520	-1.866	.000
SE B	2.803	2.758	.016
β	-.013	-.048	-.001
R^2	.194	.211	.173
F Change	.034	.468	.000

Note. HVLT imm = Hopkins Verbal Learning Test immediate recall; Stroop CW = Stroop Color and Word Test interference; RVP = Rapid Visual Information Processing; NBI = neurocognitive burden index; TBI = traumatic brain injury.
*p < .05. **p < .01. *** p < .001.

Exploratory 2. A simultaneous linear regression was conducted to compare the extent to which aspects of neurocognitive burden (i.e. age, cognitive reserve, mental illness, viral infection, vascular health, neurological illness) and TBI predict cognition. Table 7 displays the unstandardized regression coefficients (*B*), the standard error of *B* (*SE B*), and the standardized regression coefficients (*β*) after entry of all seven predictors. In order of highest to lowest predictive power, cognitive reserve (i.e. composite of education and premorbid intelligence), mental illness (i.e. composite of schizophrenia and psychosis not otherwise specified), age, and vascular health (i.e. composite of history of diabetes, and heart attack/disease) were significant predictors of composite cognition. The R^2 value of .296 indicates that close to one third of the variance in cognition (26.9% shared, 2.7% unique) was accounted for by these four aspects of neurocognitive burden. Viral infection (i.e. composite of HIV and hepatitis B), neurological illness (i.e. composite of presence of brain lacunes, non-TBI lesion/trauma, and stroke with hemorrhage), and traumatic brain injury were not significant predictors of cognition.

Table 7 Summary of Simultaneous Regression Analyses for Domains of Risk Factors for Neurocognitive Burden Predicting Composite Cognition (N = 220)

	Composite Cognition			
Predictor	***B***	***SE B***	***β***	***sr²***
Cognitive reserve	-.379	.060	-.379***	-.135
Mental illness	-.714	.153	-.279***	.074

	Composite Cognition			
Predictor	***B***	***SE B***	***β***	***sr²***
Age	-.229	.063	-.229***	.045
Vascular health	-.318	.151	-.126*	.015
Viral infection	-.070	.095	-.046	.002
Neurological illness	-.124	.229	-.032	.001
Traumatic brain injury	.156	.142	.065	.004
R^2		.296		
F		12.431***		

Note. sr^2 = the squared semipartial correlation which indicates the unique variance predicted by the independent variable.
*p < .05. **p < .01. *** p < .001.

Validity of self-reported TBI. TBI classification based on the Medical Review Questionnaire was found to have fair agreement with that done on a subset of individuals (N=54) using the Brain Injury Screening Questionnaire (BISQ), K = .281 (96% hits, 65% misses; Landis & Koch, 1977). A hierarchical regression analysis was rerun (i.e. neurocognitive burden in Block 1, history of TBI in Block 2, interaction term Block 3) using the BISQ to classify those with TBI from controls. Table 8 displays the unstandardized regression coefficients (*B*), the standard error of *B* (*SE B*), and the standardized regression coefficients (β) for predictors of composite cognition when TBI is defined both according to the MRQ (as reported in Table 5) and the BISQ. Results were consistent whether traumatic brain injury was defined according to the MRQ or the BISQ. Regardless, while the neurocognitive burden index was a significant predictor of cognition, traumatic brain injury did not account for a significant amount of variance in composite cognition, after controlling for level of neurocognitive burden. Level of neurocognitive burden was again did not moderate the relationship between TBI and cognition. Thus, traumatic brain injury was not a significant predictor of cognition, regardless of level of neurocognitive burden or whether TBI was defined according to the MRQ or BISQ.

Table 8 **Summary Comparison of Hierarchical Regression Analyses for Neurocognitive Burden Index and Traumatic Brain Injury as Defined by MRQ (N = 220) and BISQ (N = 54) Predicting Composite Cognition**

	Composite Cognition		
Predictor	***B***	***SE B***	***β***
MRQ defined TBI			
Neurocognitive burden index	-.988	.115	-.553***
Traumatic brain injury	.158	.138	.066
NBI × TBI interaction	-.115	.252	-.030
R^2		.319	
F Change		.210	
BISQ defined TBI			
Neurocognitive burden index	-.849	.394	-.475*
Traumatic brain injury	-.019	.219	-.009
NBI × TBI interaction	-.204	.469	-.095
R^2		.316	
F Change		.190	

Note. MRQ = Medical Review Questionnaire; BISQ = Brain Injury Screening Questionnaire; NBI = neurocognitive burden index; TBI = traumatic brain injury.
*p < .05. **p < .01. *** p < .001.

To further examine the validity of self-reported traumatic brain injury in this sample, the effect of objective TBI (i.e. TBI as determined by MRI alone) on cognition was examined. Hierarchical linear regression was rerun (i.e. neurocognitive burden index in Block 1, history of TBI in Block 2, interaction term in Block 3), using MRI defined TBI as predictors of composite cognition. Table 9 displays the unstandardized regression coefficients (*B*), the standard error of *B* (*SE B*), and the standardized regression coefficients (β) for predictors of composite cognition when TBI is objectively defined by MRI. Again, results were consistent with that found with self-reported TBI. The neurocognitive burden index was a significant predictor of cognition, accounting for 31.4% of the variance. MRI defined traumatic brain injury did not accounted for a significant amount of variance in composite cognition, after controlling for level of neurocognitive burden. Again, the neurocognitive burden index did not moderate the relationship between TBI and cognition. Thus, similar to that found with multiple

measures of self-reported TBI, objectively defined traumatic brain injury was not a significant predictor of cognition regardless of level of neurocognitive burden.

Table 9 Summary of Hierarchical Regression Analyses for Neurocognitive Burden Index and Objective Traumatic Brain Injury Predicting Composite Cognition (N = 220)

	Composite Cognition		
Predictor	***B***	***SE B***	***β***
Block 1			
Neurocognitive burden index	-1.002	.102	-.560***
R^2		.314	
F Change		97.052***	
Block 2			
Neurocognitive burden index	-.990	.103	-.554***
Traumatic brain injury	.215	.307	-.040
R^2		.316	
F Change		.489	
Block 2			
Neurocognitive burden index	-1.017	.106	-.569***
Traumatic brain injury	-.457	.317	-.086
NBI × TBI interaction	-.569	.490	.083
R^2		.320	
F Change		1.349	

Note. NBI = neurocognitive burden index; TBI = traumatic brain injury.
*p < .05. **p < .01. *** p < .001.

Chapter 5. DISCUSSION

The main objectives of this study were to create an index to examine the independent and aggregate impact of various multimorbid risk factors for neurocognitive burden on cognitive functioning, as well as the impact of traumatic brain injury on neurocognition in individuals with varying levels of neurocognitive burden. Although much is known about the effects of TBI on cognition in the general population, more research is needed to understand its impact in marginalized persons (Hwang et al., 2008). Rather than a simple linear relationship between TBI and cognition in marginalized populations, there is likely to be a complex process influenced by both acquired and inherited neuroprotective factors, and factors that increase the neurocognitive burden on the brain, causing or predisposing persons to negative outcomes (Mesulam, 2000; Fotuhi, Hachinski, & Whitehouse, 2009). Given the ubiquity of multiple comorbid risk factors among marginally housed persons with a history of head injury, greater clarity of the relative impact of these risk factors, both individually and in aggregate, on cognition is necessary.

5.1. Pattern of Findings

As expected, initial analyses revealed that many multimorbid risk factors for neurocognitive burden predicted neurocognitive functioning in this marginally housed sample. Cognitive reserve, defined by education and premorbid intelligence, appeared to be the strongest predictor of composite cognitive functioning. Other significant predictors of cognition, in order of influence, were schizophrenia, older age, and psychosis not otherwise specified. Individual indices of vascular health, including diabetes and history of heart attack or heart disease, were not significant predictors of neurocognition. Viral infections, including HIV and hepatitis B, were also not found to be associated with cognition. Lastly, MRI defined brain lesions or trauma due to infection, stroke with hemorrhage, or brain lacunes did not predict cognitive functioning.

Due to the manner in which the neurocognitive burden index was created, it is unsurprising that there was a main effect of burden on cognition. Level of neurocognitive burden predicted differential composite neurocognitive functioning, such that individuals with higher levels of neurocognitive burden (due to multiple factors including older age, lower cognitive reserve, poor vascular health, and the presence of mental and neurological illness) demonstrated greater cognitive impairment than those with lower levels of burden. Level of neurocognitive burden was also a significant predictor of performance in all individual domains of cognition examined, including verbal learning and memory, selective attention, and sustained attention and working memory. These findings are consistent with previous literature examining the aggregate effects of multimorbid risk factors on cognitive functioning (Patel et al., 2013).

Although we would expect those with a history of moderate to severe TBI to demonstrate greater cognitive dysfunction, while controlling for the level of neurocognitive burden, this was not shown to be the case. TBI was not found to be a significant predictor of composite cognition, regardless of the level of neurocognitive burden. Furthermore, it was expected that the impact of history of TBI on cognition would be greater in persons with higher levels of neurocognitive burden (i.e. those with a history of TBI and high burden would show larger cognitive deficits than those with a history of TBI and low neurocognitive burden), however the TBI by neurocognitive burden interaction term did not account for a significant amount of the variance in composite cognition. These findings were consistent across the individual cognitive domains of verbal learning and memory, selective attention, and sustained attention and working memory. These findings indicate that self-reported TBI history may have minimal value in signifying cognitive dysfunction in multimorbid marginally housed individuals.

Although counter to our hypotheses, the lack of interaction between neurocognitive burden and TBI falls in line with some previous research by Dikmen and colleagues (1993) examining whether preinjury history of alcohol abuse exacerbates the neuropsychological deficits associated with mild to severe head trauma. Researchers found no evidence of a greater effect of head injury in those with greater alcohol problems, despite neuropsychological outcome being significantly related to both head

injury severity and prior alcohol use. Similarly, a study by Wilde and colleagues (2004) examining the effects of alcohol abuse and TBI on brain atrophy and neuropsychological outcome found patients with a history of moderate to heavy alcohol use to have increased general brain atrophy, but no significant difference in cognition, compared to non-alcohol abusing TBI patients.

Supplemental analyses compared the predictive power of different domains of risk factors for neurocognitive burden (i.e. demographics, cognitive reserve, mental illness, viral infection, vascular health, neurological illness) and TBI on composite cognition. Again, cognitive reserve was found to be the strongest predictor of neurocognition. In order of greatest to weakest influence, mental illness, older age, and poor vascular health were found to be associated with cognitive dysfunction. Viral infection, neurological illness, and history of TBI did not predict neurocognition. These findings suggest that in multimorbid marginally housed individuals, non-TBI risk factors including cognitive reserve, mental illness, age, and vascular health, are better predictors of cognitive dysfunction and may be the most influential treatment foci in this complex population.

5.2. Limitations and Future Research

First, this study relied on a self-report measure for information on the presence and severity of past traumatic brain injury. In a subset of individuals, the measure used (i.e. MRQ) was found to have fair convergence with another interviewer administered self-report measure (i.e. BISQ) given to a subset of individuals (Landis & Koch, 1977). Although the MRQ was able to correctly identify almost all of those with reported TBIs, some participants were classified as having no TBI on the MRQ when they reported an injury on the BISQ. Although this calls into question the validity of the control group in this study, the analysis was re-run using the BISQ classification and there was no change in results. Similarly, when the control group included those with no reported TBI on both the MRQ and the BISQ there was no change in results.

As both the MRQ and BISQ were interviewer-administered self-report measures of traumatic brain injury, these methods may have been susceptible to response styles,

lack of insight, and recall errors due to cognitive deficits. In a study by Sherer et al. (2015), researchers found that individuals with medically verified history of TBI reported longer periods of loss of consciousness and posttraumatic amnesia than indicated on medical records. This was especially true for individuals with lower cognitive functioning and longer time since injury. To examine the validity of self-reported traumatic brain injury in this sample, the effect of objective TBI as determined by MRI on cognition was examined. Findings were congruent whether traumatic brain injury was defined from self-report or magnetic resonance imaging. Thus, findings do not appear to be a function of the method that information was obtained. However, it is possible that some individuals may have been unaware of their own history of brain injury, or failed to report it, yet showed no signs of past traumatic brain injury on brain imaging measures. This would have allowed them to be included in the control group of the study. Inadvertently classifying participants incorrectly could have resulted in a smaller sample size of individuals in the traumatic brain injury group, resulting in lower power to detect the effect of TBI on cognition, which would also be wrongly skewed. Given the logistical difficulties inherent in using self-reported history of brain injury in a marginalized population, future studies may benefit from using self-report measures of TBI proximal to the incident, and follow individuals longitudinally to determine the acute effects and recovery from TBI in this complex multimorbid sample.

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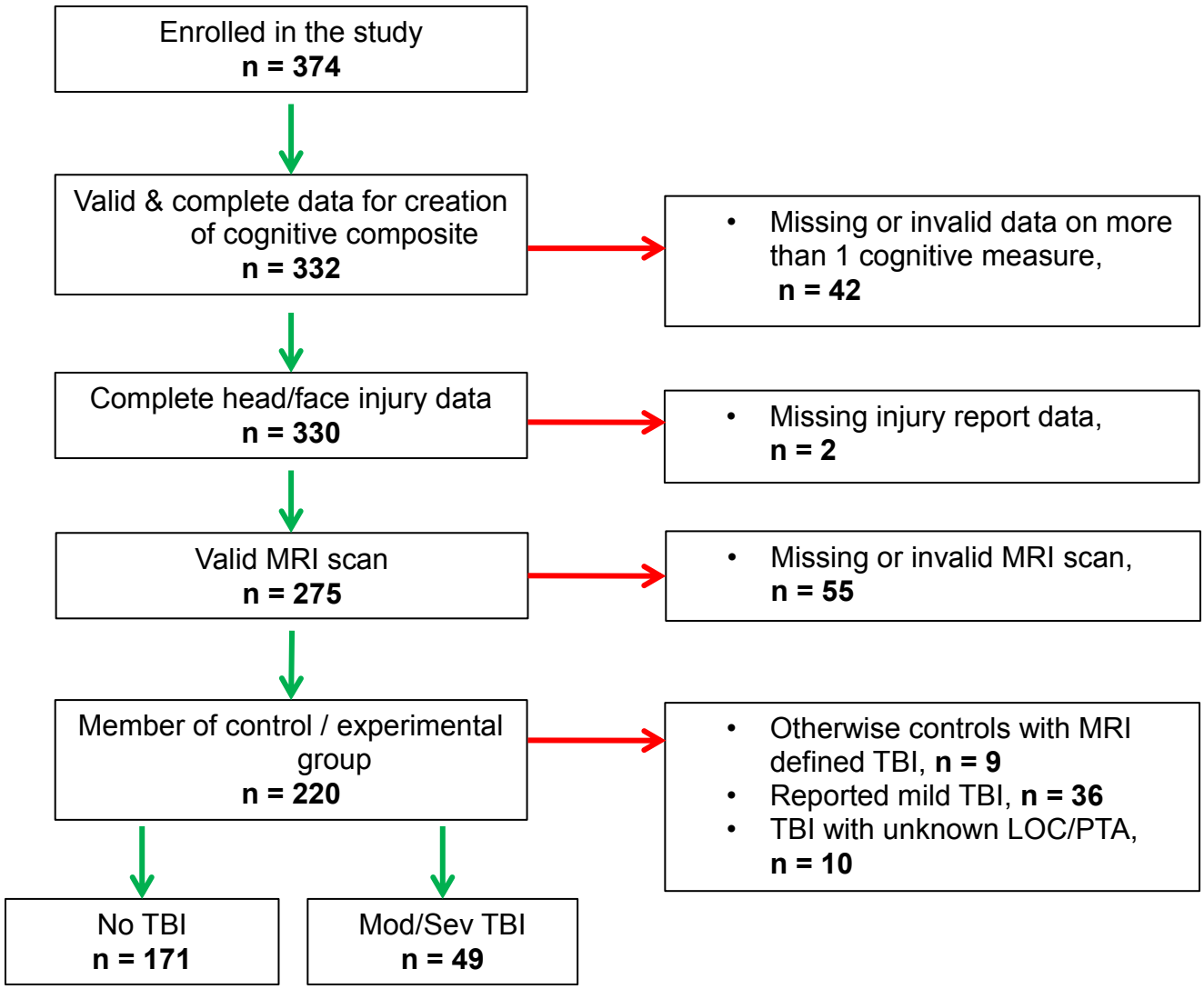
Appendix A

Participant Flow Chart



Appendix B.

Medical Review Questionnaire

This questionnaire was used as a screening tool for traumatic brain injury. Question 8 A to F contains all relevant questions pertaining to possible head or face injury.

Past Medical History:			
INTERVIEWER: First we want to discuss any health issues you may have had in the past.			
1) Did you have any health problems as a child/while growing up?	❑ NO ❑ YES ➡	IF "YES", PLEASE HAVE PARTICIPANT SPECIFY: _____ _____ _____	
2) In school, were you ever told you had a learning disability?	❑ NO ❑ YES ➡	Were you ever in special education classes?	❑ NO ❑ YES
3) Were you ever diagnosed with anything like:			
a) Attention Deficit Disorder		❑ NO ❑ YES	
b) Dyslexia		❑ NO ❑ YES	
c) Eating problems	❑ NO ❑ YES ➡	Anorexia	❑ NO ❑ YES
		Bulimia	❑ NO ❑ YES
4) Have you ever been in the hospital because of serious illness in the past?		❑ NO (PROCEED TO Q5) ❑ YES (PROCEED TO Q4a)	

a) Have you ever had surgery?	❑ No (PROCEED TO Q4b) ❑ Yes ➡		What type of surgery was it? ❑ OPEN-HEART ❑ TO CLEAR ARTERIES TO THE BRAIN ❑ ABDOMINAL ❑ OTHER_____	
	Were you under general anesthetic?	❑ NO ❑ YES ➡	How long were you unconscious?	❑ < 1hr ❑ > 1hr
b) Have you ever had a heart attack/heart disease?	❑ NO ❑ YES ➡	Have you ever been resuscitated?		❑ NO ❑ YES
5. Have you ever had a heart murmur or a problem with your heart valves?	❑ NO ❑ YES			

		Type	When	Treatment
6. Have you ever had cancer?	❑ NO ❑ YES ➡	1.		❑ Chemotherapy ❑ Radiation ❑ Surgery
		2.		❑ Chemotherapy ❑ Radiation ❑ Surgery

7. Have you ever had:	
a) Pneumonia	❑ NO ❑ YES
b) Asthma	❑ NO ❑ YES

c) Emphysema	❑ NO ❑ YES
d) Bronchitis	❑ NO ❑ YES

Current Medical Conditions

INTERVIEWER: Now we want to discuss any health issues that may be affecting you right now.

1. Do you have any allergies?	❑ NO ❑ YES	
2. In general, do you have any problems sleeping?	❑ NO ❑ YES	
3. Do you get regular exercise?	❑ NO ❑ YES	
4. Has your weight changed lately?	❑ NO ❑ YES ➡	A) By how much has your weight changed? _____
5. Do you frequently have to stay in bed because of illness?	❑ NO ❑ YES	

INTERVIEWER: Now we'll go through the body from the head down to find out about any problems.

6. Do you have any problems with:

a) Your vision	❑ NO ❑ YES ➡	Do you have:	
		Trouble with your vision that prevents you from reading ordinary print even when you have glasses on	❑ NO ❑ YES
		Glaucoma	❑ NO ❑ YES
		Cataracts	❑ NO

			❑ YES
b) Your hearing	❑ NO ❑ YES ➡	Do you have a hearing aid?	❑ NO ❑ YES

7. Have you ever had/do you have problems with:			
a) Your sinuses	❑ NO ❑ YES		
b) Headaches	❑ NO ❑ YES		
c) Dizziness or fainting	❑ NO ❑ YES		
d) Seizures, fits or Epilepsy	❑ NO ❑ YES ➡	Date of most recent? _____	For how long do the seizures or fits last? (MARK ALL THAT APPLY) ❑ Seconds ❑ Minutes ❑ Hours ❑ Days
	Have you ever been treated for Epilepsy?		❑ NO ❑ YES
e) Your memory	❑ NO ❑ YES ➡	Dementia	❑ NO ❑ YES
		Alzheimer's Disease	❑ NO ❑ YES
f) A stroke	❑ NO ❑ YES		

8. Have you ever had a serious head/face injury?		❑ NO (PROCEED TO Q.9) ❑ YES ➡	
a) What was your age at the time of the injury? IF SUBJECT ENDORSES MORE THAN ONE INCIDENT REPORT MOST SEVERE.		_____ YEARS OLD	
b) Please describe the event that caused injury: _____ _____		Please explain what the injury was: _____ _____	
c) Did you lose consciousness?	❑ NO ❑ YES ➡	For how long? _____	❑ Seconds ❑ Minutes ❑ Hours ❑ Days
d) Were you hospitalized for this injury?	❑ NO ❑ YES ➡	Where? _____ For how long? _____	
e) Did you have dizziness, headache, blurred vision, or other problems relating to the injury?	❑ NO ❑ YES ➡	For how long? _____	
f) Did you suffer from confusion or loss of memory?	❑ NO ❑ YES ➡		
9. Do you have problems with your metabolism, such as Thyroid problems, Diabetes or High Cholesterol?	❑ NO ❑ YES ➡	Thyroid	❑ NO ❑ YES
		Diabetes	❑ NO ❑ YES
		High Cholesterol	❑ NO ❑ YES

10. Do you have any problems with your chest/lungs?	❑ NO ❑ YES ➡	Are you ever short of breath?	❑ NO ❑ YES ➡	Do you experience shortness of breath when you are sitting still?	❑ NO ❑ YES
b) Do you use home oxygen?		❑ NO ❑ YES			
11. INTERVIEWER: Now I'm going to ask some questions about heart problems. Do you have any:					
a) Chest pain	❑ NO ❑ YES				
b) Blood pressure problems	❑ NO ❑ YES ➡	❑ High blood pressure	❑ NO ❑ YES		
		❑ Low blood pressure	❑ NO ❑ YES		
12. Any problems with your digestion or bowels?	❑ NO ❑ YES				
13. Any problems with your liver?	❑ NO ❑ YES				
14. Any problems with your bladder or kidneys?	❑ NO ❑ YES ➡	Are you receiving kidney dialysis?	❑ NO ❑ YES		
15. Any problems with your bones or joints?	❑ NO ❑ YES ➡	❑ Arthritis	❑ NO ❑ YES ➡	How severe is your Arthritis? ❑ Mild ❑ Moderate ❑ Moderate-severe ❑ Severe	
		❑ Osteoporosis	❑ NO ❑ YES		

		❑ Back pain that interferes with your everyday functions	❑ NO ❑ YES	
16. Do you have varicose veins in your legs?		❑ NO ❑ YES		
17. INTERVIEWER: Finally, I want to ask you about infections. Have you ever had/do you have:				
a) Scarlet/ Rheumatic Fever	❑ NO ❑ YES			
b) Tuberculosis	❑ NO ❑ YES			
c) An MRSA infection	❑ NO ❑ YES			
d) HIV	❑ NO ➡	Have you ever been tested for HIV?	❑ NO ❑ YES ➡	First test date: _____ Most recent test date: _____
	❑ YES ➡	What date did you test positive? _____		
e) Hepatitis	❑ NO ➡	Have you ever been tested for Hepatitis?	❑ NO ❑ YES ➡	First test date (Hep A): _____ Most recent test date (Hep A): _____
				First test date (Hep B): _____ Most recent test date (Hep B): _____
				First test date (Hep C): _____ Most recent test date (Hep C): _____
	❑ YES ➡	❑ Hep A ➡	What date did you test positive? _____	

		❑ Hep B ➡	What date did you test positive? _____		
		❑ Hep C ➡	What date did you test positive? _____		
f) Meningitis or Encephalitis	❑ NO ❑ YES ➡	Age of infection: ____	Were you hospitalized?	❑ NO ❑ YES ➡	Which Hospital? _____ For how long? _____

Appendix C.

Traumatic brain injury and all risk factors for neurocognitive burden included in screening of their impact on composite cognition

Effect sizes marked with an asterisk denotes those with a *d* of at least 0.2 in the appropriate direction (i.e. negatively associated with cognition); risk factors for neurocognitive burden with an asterisk were included in the neurocognitive burden index.

Variable	Description	Effect Size (*d*)	Coding
Traumatic Brain Injury			
TBI	Self-report measure with controls verified by MRI	-.019	[0,1] where no MRI verified history of TBI, and either no reported head/face injury, injury with no symptoms, or possible TBI = 0, reported history of moderate/severe TBI = 1
Demographic Variables			
Age	Age in years	-.398*	Continuous variable
Cognitive reserve	Composite of reading ability and years of education attained	-.863*	Continuous variable made into negative association with cognition
Vascular Health Variables			
History of Stroke	Ever had stroke	-.161	[0,1] where no history = 0, history = 1
Cholesterol Level	Current low versus high cholesterol level	-.046	[0,1] where low (less than or equal to 5 mmol) = 0, high (greater than 5 mmol) = 1
History of Heart Attack/Disease	Ever had a heart attack or heart disease	-.305*	[0,1] where no history = 0, history = 1
History of Diabetes	Ever had diabetes	-.584*	[0,1] where no history = 0, history = 1
Pulse Pressure	At risk for cardiovascular disease versus normal levels	.191	[0,1] where normal (less than 60) = 0, at risk (60 or higher) =1

Variable	Description	Effect Size (*d*)	Coding
Body Mass Index	Obese versus normal/overweight index	.026	[0,1] where normal or overweight (less than 30) = 0, obese (30 or higher) = 1
Substance Dependence Variables			
Alcohol dependence	Diagnosed using the BECED according to DSM-IV criteria	-.056	[0,1] where diagnosis absent = 0, present = 1
Cocaine dependence	Diagnosed using the BECED according to DSM-IV criteria	-.067	[0,1] where diagnosis absent = 0, present = 1
Methamphetamine dependence	Diagnosed using the BECED according to DSM-IV criteria	.117	[0,1] where diagnosis absent = 0, present = 1
Heroin dependence	Diagnosed using the BECED according to DSM-IV criteria	.212	[0,1] where diagnosis absent = 0, present = 1
Methadone dependence	Diagnosed using the BECED according to DSM-IV criteria	.040	[0,1] where diagnosis absent = 0, present = 1
Cannabis dependence	Diagnosed using the BECED according to DSM-IV criteria	.047	[0,1] where diagnosis absent = 0, present = 1
Mental Illness Variables			
Depression	Diagnosed using the BECED according to DSM-IV criteria	-.194	[0,1] where diagnosis absent = 0, present = 1
Schizophrenia	Diagnosed using the BECED according to DSM-IV criteria	-.557*	[0,1] where diagnosis absent = 0, present = 1
Schizoaffective Disorder	Diagnosed using the BECED according to DSM-IV criteria	.464	[0,1] where diagnosis absent = 0, present = 1
Bipolar I Disorder	Diagnosed using the BECED according to DSM-IV criteria	.551	[0,1] where diagnosis absent = 0, present = 1
Psychosis Not Otherwise Specified	Diagnosed using the BECED according to DSM-IV criteria	-.347*	[0,1] where diagnosis absent = 0, present = 1
Viral Infection Variables			
HIV	Human immunodeficiency virus	-.290*	[0,1] where antibody negative = 0, positive = 1
HepB	Hepatitis B virus	-.311*	[0,1] where antibody negative = 0, positive = 1
HepC	Hepatitis C virus	-.146	[0,1] where antibody negative = 0, positive = 1
CMV	Cytomegalovirus	-.055	[0,1] where antibody negative = 0, positive = 1
HSV	Herpes simplex virus	-.164	[0,1] where antibody negative = 0, positive = 1

Variable	Description	Effect Size (*d*)	Coding
Neurological Illness Variables			
Lesion/Trauma due to Infection	Based off of MRI reading	-.317*	[0,1] where no lesion/trauma = 0, present = 1
Stroke with Hemorrhage	Based off of MRI reading	-.241*	[0,1] where no hemorrhage = 0, present = 1
Hemorrhage not due to stroke	Based off of MRI reading	.588	[0,1] where no hemorrhage = 0, present = 1
Infarct	Based off of MRI reading	.010	[0,1] where no infarct = 0, present = 1
Lacune	Based off of MRI reading	-.281*	[0,1] where no lacune = 0, present = 1