Biomarkers of autonomic regulation for predicting psychological distress and functional recovery following road traffic injuries: protocol for a prospective cohort study

Ilaria Pozzato, Ashley Craig, Bamini Gopinath, Yvonne Tran, Michael Dinh, Mark Gillett, Ian Cameron

ABSTRACT

Introduction Psychological distress is a prevalent condition often overlooked following a motor vehicle crash (MVC), particularly when injuries are not severe. The aim of this study is to examine whether biomarkers of autonomic regulation alone or in combination with other factors assessed shortly after MVC could predict risk of elevated psychological distress and poor functional recovery in the long term, and clarify links between mental and physical health consequences of traffic injury.

Methods and analysis This is a controlled longitudinal cohort study, with follow-up occurring at 3, 6 and 12 months. Participants include up to 120 mild to moderately injured MVC survivors who consecutively present to the emergency departments of two hospitals in Sydney and who agree to participate, and a group of up to 120 non-MVC controls, recruited with matched demographic characteristics, for comparison. WHO International Classification of Functioning is used as the framework for study assessment. The primary outcomes are the development of psychological distress (depressive mood and anxiety, post-traumatic stress symptoms, driving phobia, adjustment disorder) and biomarkers of autonomic regulation. Secondary outcomes include indicators of physical health (presence of pain/fatigue, physical functioning) and functional recovery (quality of life, return to function, participation) as well as measures of emotional and cognitive functioning. For each outcome, risk will be described by the frequency of occurrence over the 12 months, and pathways determined via latent class mixture growth modelling. Regression models will be used to identify best predictors/biomarkers and to study associations between mental and physical health.

Ethics and dissemination Ethical approvals were obtained from the Sydney Local Health District and the research sites Ethics Committees. Study findings will be disseminated to health professionals, related policy makers and the community through peer-reviewed journals, conference presentations and health forums.

Trial registration number ACTRN12616001445460.

Strengths and limitations of this study

- This study will comprehensively describe the risk of developing psychological distress and poor functional recovery in people involved in a motor vehicle crash and sustaining mild-to-moderate injuries.
- Identifying biomarkers of mental health risk and poor functional recovery adds novelty to this field. Easy-to-measure biomarkers of autonomic regulation hold promise in preventing serious mental disorders, reducing patient-related barriers to mental healthcare and improving recovery rates among crash survivors.
- The use of the International Classification of Functioning standard framework and validated measures will assure an in-depth analysis of complex needs of the injured person, which are often studied in isolation, and will promote comparability with other research.
- Findings may be useful to primary care clinicians in the early diagnosis and referral of at-risk individuals for a better management of mental health and a more integrated form of care.
- Findings may also assist changes in compensation processes and policies towards a more holistic approach to injury recovery.

INTRODUCTION

Around 50 million people worldwide are injured annually in non-fatal motor vehicle crashes (MVC).1 Surviving a crash can lead to a number of physical and psychological consequences, and many individuals develop long-term disability.2–4 While improved outcomes are shown for severe injuries,5 evidence suggests that minor-to-moderate injuries are a challenge.6,7 With traffic injuries remaining the 10th leading cause of disability-adjusted life years in 2010,8 minor-to-moderate injuries (ie, Maximum Abbreviated Injury Score [MAIS] of less than 3) account for 46% of...
injury-related disability. Therefore, consequences and costs of minor-to-moderate traffic injuries such as whiplash, mild traumatic brain injury and musculoskeletal injury are serious public health concerns.

A recent longitudinal study from Europe reported that minor-to-moderate (MAIS <3) traffic injuries hospitalised for more than 24 hours result in higher average costs, both direct and indirect, compared with severe injuries. On the other hand, in Australia, it is estimated that around US$1b is spent each year only on traffic injuries admitted to hospital for less than 24 hours, with an average cost by casualty of US$14,183. Furthermore, when psychological problems are involved, care costs have been shown to escalate alarmingly and time to recovery to increase fourfold.

Psychological distress is prevalent in people surviving an MVC and has been demonstrated to be a substantial contributor to long-lasting morbidity and disability, affecting up to one in two MVC survivors, according to a recent meta-analysis. Although there is some variability in estimates, the proportion of MVC survivors (up to 50%) who experience psychological problems appears to be many times greater than the proportion of people with mental health in the Australian community (20%), and global population (25%), often resulting in serious mental disorders, such as post-traumatic stress disorder (PTSD), major depressive disorder, driving phobias and other anxiety disorders.

Unlike physical consequences that ideally receive appropriate and timely medical care following an MVC, early clinical management of psychological consequences associated with mild-to-moderate physical injury rarely occurs since, for example, psychological distress is often normalised as a common response to the trauma. Hence, it is not surprising that mental health-related quality of life of MVC survivors is more resistant to improvement over time than physical-related outcomes, as for instance demonstrated by Kenardy et al. This is pertinent given failure to address psychological distress will have a significant detrimental impact on functional recovery, supporting the hypothesis that there is ‘no health without mental health’.

Some underlying circumstances may lead to delayed recognition of psychological distress. First, a clear diagnostic framework is lacking for detecting psychological distress symptoms that include clinically elevated anxiety and depressive mood and high levels of arousal, and which often co-occur following an MVC. It is argued that these symptoms may be all manifestations of one construct of general distress. However, previous studies on MVC survivors typically focused on a single mental disorder, particularly PTSD. The second and more significant fact is the absence of empirical evidence for reliable biomarkers of vulnerability to psychological distress following an MVC.

Vulnerability to psychological distress and poor functional recovery draws on the broader concept of psychological resilience as the unique ability of an individual to adapt to adversity, which develops throughout the lifespan. Following an MVC, individual vulnerability to poor psychological adjustment and functional recovery, has been linked to a number of biological (eg, preinjury health, injury severity), psychological (eg, prior traumatic experiences, perceptions) and environmental factors (eg, social support, compensation); however, biological responses, in particular autonomic responses, to traffic injury remain an underinvestigated area.

Unlike other traumatic or pathological conditions, there have been very few studies examining the predictive value of biomarkers of autonomic regulation, such as traditional vital signs measured early after an MVC, to investigate long-term outcomes, and only one study, to our knowledge, has attempted to use heart rate variability (HRV). The main focus of these studies was the association between heart rate at the scene or during hospitalisation and the development of PTSD following an MVC. However, there was lack of consistency between findings, highlighting differences in methodology and confirming that substantial interindividual variability exists in psychological responses to physical threat.

Biological responses to potential threats involve activation of neural substrates such as the stress response system. The autonomic nervous system is the first to respond to stressors by a transitory withdrawal of the parasympathetic ‘brake’ and modulation of sympathetic activity for a rapid control of body functions critical for survival, that is, changes in heart rate, blood pressure and breathing rate, and later re-engagement of the parasympathetic system during recovery, by inhibition of sympathetic control.

Studying the sympathetic–parasympathetic balance is rather complex, and one marker is often not enough to convey the complexity of stress regulatory processes. Therefore, more research is needed to assess autonomic resting level, reactivity and recovery in a comprehensive manner, by using several markers to increase predictive ability and investigating their relationship with other psychological, social and biological factors. There is emerging evidence of associations between negative affect, perseverative cognition and physiological over-reactivity to stress, as introduced, for example, by the perseverative cognition hypothesis. The most common autonomic markers include vital signs (ie, heart rate, respiratory rate, blood pressure, peripheral skin temperature), skin conductance (SC), peripheral blood circulation and HRV. While SC and peripheral skin temperature have been widely used as an index of sympathetic activity, HRV, the variation in the beat-to-beat interval, is recommended as a reliable, non-invasive index for assessing cardiac vagal tone. Higher levels of vagally mediated resting-state HRV and faster cardiovascular recovery have been shown to be associated with better self-regulatory capacity to environmental demands.

Different theoretical models have linked vagally mediated HRV to individual differences in adaptation to external and internal stressors, suggesting that poor...
Open access


autonomic regulation is an indicator of poor self-regulatory capacity in managing stress levels, that can be associated with poor psychological health, physical health, cognitive performance and social functioning. Thus, sympathetic–parasympathetic balance, measured early after an MVC, is regarded as a promising biomarker of vulnerability to develop dysfunctional responses, such as elevated psychological distress and stress-related disorders that can affect a person’s capacity to recover following traffic injury.

There is substantial evidence that supports the co-occurrence of psychological and physical consequences post-MVC, for example, anxiety, depression, chronic pain, fatigue, sleep disturbance and other somatic conditions, for which physical evidence is often missing, hinting at the possibility of shared psychological and biological factors in stress vulnerability. However, the majority of evidence for these associations comes from cross-sectional studies, especially from the relationship between chronic pain and PTSD in whiplash injuries. Therefore, prospective research is now needed to investigate links between mental and physical health in recovery from traffic injuries.

Full functional recovery is a combination of a person’s physical and mental well-being, often measured as health-related quality of life, and social functioning, such as resumption of work/usual level of activities and social participation. In the current study, WHO International Classification of Functioning (ICF) will be employed as the biopsychosocial framework to assess mental health and functional recovery outcomes following MVC-related injury, and to build comprehensive prognostic models for the identification of the at-risk cohort. Early detection is crucial for preventing disease and progression to chronicity; therefore, this study has the potential to prevent the development of serious mental health conditions and disability among thousands of MVC survivors in Australia and worldwide annually.

**Study aims**
The study objectives are:
1. To determine prevalence estimates and trajectories of psychological distress (ie, depressive mood and anxiety, PTSD symptoms, driving phobia, adjustment disorder) and functional recovery (ie, health-related quality of life, return to work/activities, social participation) post-MVC.
2. To determine the efficacy of autonomic biomarkers (ie, post-MVC vital signs and autonomic measures 1-month post injury), alone or in combination with other biopsychosocial factors, in predicting psychological distress and poor functional recovery post MVC.
3. To investigate associations and shared biopsychosocial predictors/biomarkers, between mental health (ie, psychological distress, emotional and cognitive functioning) and physical health (ie, pain, fatigue, physical functioning) consequences post MVC.

**METHODS AND ANALYSIS**

**Conceptual framework**
The conceptual study framework, drawing on WHO ICF model, is outlined in figure 1. WHO ICF Disability and Health model is widely recognised as the most recent and comprehensive framework for assessing health and disability. Therefore, it provides an effective framework for describing consequences of road traffic injuries, such as psychological distress and poor functional recovery.

---

**Figure 1** International Classification of Functioning-based on the impact of psychological distress on recovery from injuries sustained in a traffic crash (IMPRINT) study biopsychosocial assessment framework. *Primary outcomes; **secondary outcomes. QoL, quality of life.
Potential predictors will be biological, personal and environmental factors, with a focus on testing the predictive ability of autonomic biomarkers, which are simple and easy to measure. This is a prognostic study where event prediction will follow a data-driven approach and careful consideration will be given to the issue of overfitting. There are also plans of exploring causal effects that will come as a separate proposal.

Design
A controlled longitudinal cohort design will be undertaken to assess risk of psychological distress and poor functional recovery among mildly to moderately injured MVC survivors (Injury Severity Score ≤15). Baseline assessment will occur around 1 month (3–6 weeks) of their injury, with follow-up assessments occurring at 3, 6 and 12 months post injury. Results will be compared with a control group who have not sustained an MVC or severe injuries in the past 5 years, and who will be assessed at the same time periods.

Setting
The emergency departments (ED) of two of the seven adult major trauma services in NSW, Australia, will be involved in the recruitment of MVC survivors: Royal North Shore Hospital and Royal Prince of Alfred Hospital. These are large public hospitals located in Sydney metropolitan area, providing care to trauma patients across the whole spectrum of severity.

Participants’ eligibility and identification
The study inclusion and exclusion criteria for MVC survivors and control participants are presented in table 1. These include exposure status (ie, injury vs non-injury) and factors related to the outcomes being studied (ie, mental health, autonomic function, disability and physical health). At the time of their enrolment, both cohorts will be free of severe mental health disorders or major disabling conditions due to very severe injury like spinal cord injury. The non-injured cohort will include normally healthy individuals with no active medical concern or serious comorbid conditions (ie, chronic disease, degenerative neurological disease). Medications or other factors that could potentially influence autonomic function/outcomes investigated, as well as differences between the two cohorts, will be adjusted for in the analysis.

The identification of MVC survivors will begin following their presentation to the ED of the two hospitals. Participants will be consecutively identified and assessed for eligibility by a research nurse from the information management system, FirstNet.

The non-MVC control group, matched by sex and age (±5 years) to the MVC sample on a case-by-case basis, will be recruited through advertising. Study eligibility will be assessed using an online self-reported screening interview.

Recruitment process
Participants’ recruitment flow chart is illustrated in figure 2. Eligible survivors will be invited to participate by: (1) being approached at the time of ED presentation, or (2) receiving an invitation letter to their postal address from the ED-treating clinician. After written consent is obtained (opt-in approach), participants will be requested to complete the baseline interview-based assessment by accessing an online secure website, and otherwise by completing a paper based or phone interview. As part of their enrolment, within 6 weeks of their

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Inclusion and exclusion criteria of motor vehicle crashes (MVC) participants and non-MVC controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MVC participants</strong></td>
<td><strong>Non-MVC controls</strong></td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td></td>
</tr>
<tr>
<td>► Age ≥18 years,</td>
<td>► Age ≥18 years.</td>
</tr>
<tr>
<td>► Sustained in last 6 weeks, a minor-to-moderate injury due to MVC in NSW, Australia.</td>
<td>► No history of MVC, serious injury or traumatic event (ie, w/perceived threat of injury to self or others) in the previous 5 years.</td>
</tr>
<tr>
<td>► A driver, motorbike rider, passenger, pillion passenger, pedestrian and bicyclist (only collision involving a motorised vehicle).</td>
<td>► Sufficient English proficiency.</td>
</tr>
<tr>
<td>► Presented to RNSH or RPAH emergency departments, Sydney, Australia.</td>
<td></td>
</tr>
<tr>
<td>► Sufficient English proficiency.</td>
<td></td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td></td>
</tr>
<tr>
<td>► Catastrophic injury as defined by NSW are lifetime care, that is, a very severe traumatic brain injury, a spinal cord injury, extensive burns to the body (&gt;60%), major amputation or blindness.</td>
<td>► Catastrophic injury: severe brain injury, spinal cord injury, extensive burns to the body, major amputation or blindness.</td>
</tr>
<tr>
<td>► Serious injury (ISS &gt;15).</td>
<td>► Severe mental health condition.</td>
</tr>
<tr>
<td>► Localised, superficial soft-tissue injuries.</td>
<td>► Dementia or cognitive impairment affecting ability to consent.</td>
</tr>
<tr>
<td>► MVC due to intentional self-harm or MVC survivors with severe mental health condition.</td>
<td>► Chronic disease such as severe heart disease, stroke, cancer, chronic respiratory diseases, obesity and advanced complicated diabetes.</td>
</tr>
<tr>
<td>► Death of a family member in the MVC.</td>
<td>► Degenerative neurological disease.</td>
</tr>
<tr>
<td>► Dementia or cognitive impairment affecting ability to consent.</td>
<td></td>
</tr>
</tbody>
</table>

ISS, Injury Severity Score; RNSH, Royal North Shore Hospital; RPAH, Royal Prince of Alfred Hospital.
accident, participants will also be asked to attend a 30 min hospital visit for the collection of autonomic biomarkers. An overall reimbursement up to US$100 in vouchers will be provided to cover participant travel cost and time.

**Sample size**

A sample size of up to 120 MVC participants and an equivalent number of non-MVC controls will be employed to test the study aims. Assuming a loss to follow-up of 20%–30%, a moderate effect size of 0.2 (eta-squared or $\eta^2$) at $\alpha=0.05$, two groups and four time periods, statistical power using repeated measures analyses was calculated to be 83%. For the logistic regression, assuming an $\alpha=0.05$, 10 predictors, a moderate effect size of 0.2 (eta-squared or $\eta^2$), the power to measure the strength of relationship was calculated to be 90%.

**Assessments and outcome measures**

Assessment time points, study outcomes and details of the validated measures used within each ICF domain are provided in table 2.

**Primary outcomes**

The primary outcome is the development of psychological distress as any psychological discomfort that interferes with daily living functioning following the MVC. Psychological distress is defined as the presence of at least one of the following psychological symptoms over the 12 months after the MVC, including elevated depressive mood and anxiety (Depression, Anxiety and Stress Scale) and PTSD symptoms (Impact of Events Scale), evaluated using these two validated psychometric assessments, as well as the presence of driving phobia and adjustment disorder using diagnostic interview (MIM-International Neuropsychiatric Interview based on Diagnostic and Statistical Manual of Mental Disorders, 5th Edition). Another key outcome are biomarkers of autonomic regulation by means of HRV and other autonomic measures of sympathetic–parasympathetic balance as described below.

**Secondary outcomes**

Secondary outcomes include indicators of physical health (ie, pain, fatigue and physical functioning measures such as somatic symptoms and/or new clinical diagnosis) and functional recovery (ie, health-related quality of life, return to work/usual activities, social participation) up 12 months post MVC. Other outcomes of interest are measures of emotional (ie, emotional balance, self-reported valence and arousal of affect) and cognitive functioning (ie, perceived cognitive health, selective attention and processing speed ability).

**Predictors**

Biopsychosocial predictors include a comprehensive regimen of biological (eg, injury details), personal (eg, demographic, health history, perceptions/reaction to the injury/expectations, coping skills, self-efficacy, cognitive styles) and environmental factors (eg, crash circumstances, economic factors, social life, compensation, healthcare use and satisfaction) that may predict risk of elevated psychological distress and poor recovery, in association with autonomic biomarkers.

**Biomarkers of autonomic regulation**

**Measures and procedures**

Biomarkers of autonomic regulation consist of vital signs (heart rate, respiratory rate, blood pressure) on the day
<table>
<thead>
<tr>
<th>Domain</th>
<th>Outcome category</th>
<th>Outcome measures</th>
<th>Assessment points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body functions and structures</strong></td>
<td><em>Psychological distress (mental health)</em></td>
<td>Depressive mood and anxiety (DASS21[^58]); PTSD symptoms (IES-R[^59]); driving phobia (MINI[^60]); adjustment disorder (MINI[^60]);</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td><strong>Emotional functioning (mental health)</strong></td>
<td>Emotional balance (PANAS[^56]); self-reported valence and arousal dimension of emotions (Self-Assessment Manikin Scale[^56]);</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td><strong>Cognitive functioning (mental health)</strong></td>
<td>Perceived cognitive health (WHODAS II—Domain 1[^68]); selective attention and processing speed ability (Stroop test[^63]);</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td><em>Autonomic regulation (biomarkers)</em></td>
<td>Sympathetic–parasympathetic balance (postcrash vital signs; HRV; heart rate; respiration rate; skin conductance; peripheral body temperature; blood volume pulse).</td>
<td>X</td>
</tr>
<tr>
<td><strong>Pain (physical health)</strong></td>
<td>X X X</td>
<td>Pain intensity (NRS[^59]); risk of persistent pain and disability (OMPO, short form[^70]).</td>
<td>X</td>
</tr>
<tr>
<td><strong>Fatigue (physical health)</strong></td>
<td>X X X</td>
<td>Fatigue intensity (VAFS[^71]).</td>
<td>X</td>
</tr>
<tr>
<td><strong>Physical functioning (physical health)</strong></td>
<td>X X X</td>
<td>Stress-related physical symptoms (sleep disturbance, loss of sex drive, frequent infections, upset stomach, constipation); lifestyle habits (physical activity, smoking, alcohol use); medications; postcrash new clinical diagnoses.</td>
<td>X</td>
</tr>
<tr>
<td>Injury</td>
<td>X X X</td>
<td>Injury type; injury severity (abbreviated injury severity[^52]; Glasgow Coma Score[^72]); hospital admission, length of hospital stay, surgery.</td>
<td>X</td>
</tr>
<tr>
<td>Activities</td>
<td><strong>Quality of life (functional recovery)</strong></td>
<td>Health-related physical and mental quality of life (SF-12[^73]).</td>
<td>X</td>
</tr>
<tr>
<td>Participation</td>
<td><strong>Social functioning (functional recovery)</strong></td>
<td>Return to work and activities; social participation (WHODAS II—Domain 6[^68]).</td>
<td>X</td>
</tr>
<tr>
<td>Personal factors</td>
<td>Demographic</td>
<td>Sex; age; primary language; education; marital status.</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Trauma and stressors</td>
<td>Prior and postcrash stressors. Traumatic events following the crash (MINI[^60]).</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Physical health history</td>
<td>Clinical and medication history; body composition (BMI); past chronic pain or fatigue diagnosis; prehealthcare utilisation.</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Mental health history</td>
<td>Prior trauma (MINI[^60]); previous mental health problems and mental health treatment.</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Coping skills</td>
<td>Coping responses (COPE inventory[^74]).</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Perceptions</td>
<td>Perceived life threat; perceived helplessness; blame versus self or others; perceived injustice; perceived resilience; perceived sense of safety and life balance.</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Cognitive bias</td>
<td>Pain catastrophising, rumination, magnification (PCS[^59]); self-efficacy beliefs (GSE[^53]); expectations to return to work (OMPQ[^70]) and expectations to recover.</td>
<td>X</td>
</tr>
</tbody>
</table>

Continued
of the accident (at the scene and ED triage) and autonomic measures around 1 month (3–6 weeks) of the injury, non-invasively and simultaneously acquired using a BiosemiTM Active-Two System at a 2480-Hz native sampling rate. Autonomic assessment will include respiration rate (sensitive band around chest), SC level and responsiveness, that is, absolute SC and number/amplitude of non-specific SC fluctuations (surface electrodes on second and fourth fingers of non-dominant hand), peripheral body temperature (clip-on sensor on fifth finger of non-dominant hand), blood volume pulse amplitude (light sensor on third finger of non-dominant hand), heart rate and HRV (ECG recording). For the ECG recording, three Ag/AgCl electrodes will be placed in modified Einthoven I and II configurations (beneath the right and left clavicles, and on the fourth intercostal space on the left side of the sternum).

Experimental design and structure
The chosen design allows examination of within and between subject changes between phases. For an in-depth investigation of autonomic regulatory processes, a 3R protocol will be employed that allows examination of tonic resting level (baseline) and phasic autonomic control, including autonomic reactivity (change between baseline and task) and recovery (change between task and post-task, percentage/time of return to baseline).

On the morning prior to the autonomic assessment, participants will be asked to follow a normal sleep routine and to abstain from eating, drinking caffeinated and alcoholic beverages, smoking and intense physical activity. Recording will be conducted under constant conditions, between 08:00 and 13:00 to control circadian influences. Participants will sit in a relaxed position with eyes open. The protocol includes four phases, throughout which autonomic biomarkers will be measured continuously: (1) 5 min resting baseline, after a 2 min acclimatisation; (2) 5 min response inhibition task, using the validated Stroop Color-Word test; (3) 5 min resting post-task; (4) 2 min slow-paced breathing (6 breaths/min), using a breath pacer application providing visual feedback for breathing cycle control. Before every phase change, participants will be asked to rate pain and fatigue intensity, and their emotional state (Self-Assessment Manikin Scale).

Data manipulation
After appropriate data cleaning to remove noise and artefacts and resampling (512-Hz sampling rate), biosignals analysis will be performed using Kubios (V.2.0 beta 2, Department of Applied Physics, University of Kuopio, Finland) and other Analysis Software. For HRV, time-domain, frequency-domain (LF: 0.04–0.15 Hz; HF: 0.15–0.4 Hz) and non-linear indices will be analysed.

Hypotheses and data analysis
It is hypothesised that:

a. People sustaining mild-to-moderate injuries in an MVC will continue to suffer high rates of psychological

<table>
<thead>
<tr>
<th>Table 2 Continued</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assessment points</strong></td>
</tr>
<tr>
<td><strong>Baseline (within 6 weeks)</strong></td>
</tr>
<tr>
<td><strong>Outcome category</strong></td>
</tr>
<tr>
<td><strong>Social life</strong></td>
</tr>
<tr>
<td><strong>Healthcare use/quality</strong></td>
</tr>
<tr>
<td><strong>Compensation status</strong></td>
</tr>
<tr>
<td><strong>Compensation status</strong></td>
</tr>
</tbody>
</table>

Outcome categories marked in bold are primary (I) and secondary (II) study outcomes. The remaining measures are biopsychosocial predictors. BM: Body Mass Index; DASS: Depression, Anxiety and Stress Scale; GSE: General Self-Efficacy Scale; HRV: Heart rate variability; IIP: Impact of Events Scale; MNI: Mini-International Neuropsychiatric Interview Version; NRS: Numeric Rating Scale; OMPS: Osteo Musculoskeletal Pain Questionnaire; PAIN: Positive and Negative Affect Schedule; SASS: Social Adjustment Scale; VAFS: Visual Analogue Fatigue Scale; WHODAS: World Health Organisation Disability Assessment Schedule.
distress, poor physical health (eg, high levels of pain and fatigue, poor physical functioning) and poor functional recovery (eg, poor quality of life, limited work/activities resumption and low social participation) 6–12 months post injury, though improvements in all outcomes are expected to occur over time compared with 1–3 months post injury.

b. Compared with non-MVC controls, MCV survivors will have significantly poorer autonomic regulation (ie, lower sympathetic–parasympathetic balance) at 1 month follow-up, and will exhibit poorer mental health (eg, higher psychological distress, poorer emotional and cognitive functioning), poorer physical health (eg, higher levels of pain and fatigue, lower physical functioning) and poorer social outcomes (eg, poorer health-related quality of life and social functioning) over the follow-up period, though to a lesser extent at long term (6 and 12 months) compared with short term (1–3 months) post injury;

c. Among MVC survivors, those with sustained elevated psychological distress over the first-year post injury will be less likely to recover and have significantly lower autonomic regulation early after the crash (ie, higher heart rate and respiratory rate on the day of the accident; poorer sympathetic–parasympathetic balance 1 month post injury) compared with those without psychological distress who will be more likely to recover;

d. Specific biological factors (eg, higher injury severity, longer hospital stay), personal factors (eg, older age, being female, poor preinjury health, poor coping skills, negative perceptions/reactions to the injury, catastrophic thinking, low self-efficacy, poor recovery expectations) and environmental factors (eg, preinjury unemployment, poor socioeconomic background, protected road users, poor social support, poor healthcare use and satisfaction, involvement in compensation) will predict increased risk of elevated psychological distress and poorer functional recovery in those injured in an MVC.

e. There will be similarities in factors predicting mental and physical health consequences of a traffic injury. Shared predictors/biomarkers will include biomarkers of poor autonomic regulation, and psychological/personal factors like preinjury health, psychological distress, thinking styles, coping skills and self-efficacy.

f. In both groups, there will be high correlations between states of low sympathetic–parasympathetic balance, reactivity to stress and negative emotions/perceptions. Those with balanced autonomic regulation will be more likely to exhibit better health (ie, both mental and physical health) and social outcomes (quality of life, social functioning).

All data analyses will be performed using SPSS software V.22. Descriptive statistics will define sociodemographic characteristics and other variables of interest of the study. First, risk will be calculated separately for each outcome by the frequency of occurrence and percentage over the 12-month post-MVC period, while latent class mixture growth modelling will determine outcome class pathways. In addition, repeated measures linear mixed models will be used to analyse differences between and within groups over time.

To identify biomarkers/predictors at 3, 6 and 12 months post MVC, multiple regression analyses will be conducted for each outcome of interest, after appropriate selection procedures (eg, univariate analysis, bootstrap), whereas adjustment for confounders will not be considered as priority given the non-etiologic nature of the study. Sensitivity/specificity analyses and constructing receiver operating characteristic plots will determine discriminative performance.

Subgroup analyses and multiple regression will study differences and shared predictors/biomarkers between mental and physical health outcomes following the MVC. Clinical significance of autonomic biomarkers will be also tested using cluster analysis and other exploratory analyses.

The same analyses will be conducted with control data, to describe differences in outcomes with the group of MVC survivors.

Bias
To reduce selective bias, the study will adopt the following strategies: a 6-week inception period, participant cost reimbursement, adequate statistical power, as well as consecutive recruitment from two hospitals with major catchments for traumatic MVC injury in Sydney that will provide a wide variety across ethnicity, culture, socioeconomic status and education levels.

To minimise loss to follow-up, multiple options will be given on assessment modality (online, paper based on phone interview) and date/time to schedule the hospital visit. Follow-up reminders via emails and phone calls will also increase adherence through the study.

Though experienced research staff will ensure quality and completeness of assessment, missing data are expected to occur. Imputation techniques will be used for missing values, considering comparison with non-missing cases. The study will also aim to assess a wide range of possible prognostic markers on their ability to identify people with poor outcomes, for ease of use when translating the research findings to clinical practice.

Patient and public involvement
Research question and outcome measures are developed with knowledge from our ongoing research into patient feedback, expectations and concerns following traumatic injury. However, the present study is not a clinical trial; therefore, participants are not directly involved in study design, conduct or assessment of intervention. Nevertheless, findings from this study, that is, peer-reviewed publications, will be shared with study participants via email communication.
ETHICS AND DISSEMINATION

Approvals, progress and timeframe
STROBE guidelines have been followed for this protocol. The first participant was recruited on 16 June 2017, and both sites are actively contributing towards the recruitment target. It is anticipated that the recruitment will last until the end of March 2019; thus, data collection is expected to be completed by early 2020.

Data storage and sharing
Eligible participants’ information will be stored on the local health server at the site, until informed consent is obtained. Signed consent forms will be stored in lockable cabinets. Data from consenting participants will be then entered and stored on a secure online platform (REDCap) at The University of Sydney, to which only designated research team will have access. Methodology details and deidentified data will be available on request once analyses have been completed, provided there is no breach of participant confidentiality.

Confidentiality and safety aspects
Written informed consent will be sought from participants and for publication of deidentified study findings. Participants will be reminded that their information will remain confidential and that consent can be withdrawn at any time, without interference with their usual care.

To minimise and manage any distress or anxiety they may experience completing assessments, the expertise of the principal investigators and follow-up care calls will be employed to identify potential critical situations and provide guidance or referral to further care.

Dissemination
Findings from this study will be disseminated through peer-reviewed publications and conference presentations to communicate results and clinical implications to health professionals and health policy makers. Presentations on research findings at local community forums will also occur.

DISCUSSION

This study intends to raise awareness about the risk of psychological distress and poor functional recovery following minor-to-moderate traffic injuries, and to develop processes for the early detection of at-risk individuals, the aim being to prevent disability in the long term.

This study, for the first time, will use biomarkers of autonomic balance, to detect this risk. If results of this study are positive, a non-invasive screening tool like HRV holds promise for providing a means of preventing serious mental health disorders and disability through detection and early treatment, as well as clarifying links between mental and physical health consequences post MVC.

It is expected that general and acute care clinicians would have a crucial role in early diagnosis and referral of at-risk individuals. Employing easy-to-measure ‘biological markers’ for those at risk of mental health disorders may facilitate timely access to care and help reduce patient-related barriers to mental healthcare.66

Adopting the ICF framework to assess consequences of minor-to-moderate injuries also represents a real shift in this field. For example, compared with severe injuries, recovery from these injuries is rarely accepted as a complex multidimensional experience and management often follows a biomedical care model. By contrast, the comprehensive study assessment using standardised measures will clarify the complex needs of people sustaining minor-to-moderate traffic injuries, assist compensation processes and policy changes towards a more holistic approach to injury recovery, and promote comparability with other research.

REFERENCES

Author affiliations
1 Sydney Medical School—Northern, John Walsh Centre for Rehabilitation Research, University of Sydney, St Leonards, New South Wales, Australia
2 Northern Clinical School, University of Sydney, St Leonards, New South Wales, Australia
3 Centre for Vision Research, University of Sydney, Sydney, New South Wales, Australia
4 Emergency Department, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia
5 Emergency Department, Royal North Shore Hospital, St Leonards, New South Wales, Australia

Acknowledgements The authors would like to acknowledge the support of Emergency Department staff at each of the study sites.

Contributors All authors provided inputs in study design. IP, YT and AC are involved in data analysis and data acquisition. IP, AC, BG and IC are responsible for publication writing. All authors reviewed and approved the final version of this manuscript.

Funding This study has received research grant support by the NSW State Insurance Regulatory Authority (grant: MAA 14/1433) and the Australian Rotary Health (Ian Scott Mental Health PhD Scholarship).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethical approval was obtained from the Sydney Local Health District Ethics, Australia (HREC/15/RPAH/423), and Site-Specific approvals obtained for each site (SSA/16/HAWKE/505; RESP/16/349). The study has been prospectively registered with the Australia New Zealand Clinical trial registry on 17 October 2016 (Registration number: ACTRN 12616001445460, IMPRINT study).

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.


Open access

9.

8.

7.

6.

5.

4.

3.

2.

1.

2011;26:508–12.

the acute aftermath of trauma can predict post-traumatic stress

Psychol Inj Law Trauma: pathways to disability.


Neurosci Biobehav

J Abnorm Psychol

Grant DM, Beck JG, Mar

crash.

Gopinath B, Jagnoor J, Harris IA, 


Geneva, Switzerland:

emerging evidence, practice: Summary report

Australian Bur Health and Wellbeing 2016

BMJ Open

Craig A, T

Nurs Stud

Int J

symptom severity on long-term functional recovery: A secondary

Arch Phys Med Rehabil


Psychol Med


Psychol Med


Mental Health: ICF

W

2005;67:783–90.

Psychosom Med

collision: integrating the potential role of stress response systems

Clin Psychol Rev


Kok BE, Fr

Phys Sportsmed


Prinsloo GE, Rauch HG, Deman WE, A brief review and clinical

appraisal of heart rate variability biomarkers: implications for sports, exercise, and rehabilitation medicine. 


Brosschot JF, Gerin W, Thayer JF. The perceptive cognition hypothesis: new insights into adaptive reactions of the autonomic nervous system. 


Kok BE, Fredrickson BL. Upward spirals of the heart: autonomic flexibility, as indexed by vagal tone, reciprocity and prospectively predicts positive emotions and social connectedness. 


Lu WC, Tzeng NS, Kao YC, et al. Reduced population responsiveness of motor vehicle accident survivors with chronic 


Berna G, Ott L, Nandrinio JL. Effects of emotion regulation difficulties on the tonic and phasic cardiac autonomic response. 


Laborde S, Mosley E, Mertgen A. Vagal tank theory: the three rs of cardiac vagal control functioning–resting, reactivity, and recovery. 


Prinsloo GE, Rauch HG, Deman WE. A brief review and clinical appraisal of heart rate variability biomarkers: implications for sports, exercise, and rehabilitation medicine. 


Brosschot JF, Gerin W, Thayer JF. The perceptive cognition hypothesis: new insights into adaptive reactions of the autonomic nervous system. 


Kok BE, Fredrickson BL. Upward spirals of the heart: autonomic flexibility, as indexed by vagal tone, reciprocity and prospectively predicts positive emotions and social connectedness. 


Lu WC, Tzeng NS, Kao YC, et al. Reduced population responsiveness of motor vehicle accident survivors with chronic 


Berna G, Ott L, Nandrinio JL. Effects of emotion regulation difficulties on the tonic and phasic cardiac autonomic response. 


71. Laborde S, Mosley E, Thayer JF. Heart rate variability and cardiac vagal tone in psychophysiological research—recommendations for experiment planning, data analysis, and data reporting. Front Psychol 2017;8:213.