Allostatic load and heterogeneity of outcome after head injury

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Abstract

Background

Outcome after head injury is heterogeneous; in particular, late outcome including disability and increased risk of mortality are only partly explained by the severity of the injury and demographic factors (McMillan et al., 2014; McMillan et al., 2012; Whitnall et al., 2006). The allostatic load model conceptualises how stressors can chronically elevate physiological activity and impact on health (McEwen, 1998b). Allostatic load has been shown to be associated with psychosocial functioning, morbidity, and mortality and can predict these outcomes at follow-up; however, it has never been investigated with outcome in the head injury population. The studies in this thesis explore the extent to which allostatic load is associated with cognitive and disability outcome, and change in disability over time after head injury.

Methods

A systematic search was conducted to inform how to measure allostatic load; 15 indicators of health were assessed representing immune, cardiovascular, anthropometric, metabolic, and neuroendocrine system functioning, and were combined using a summation z-score method to create allostatic load scores. Four empirical studies were conducted to investigate the relationship between allostatic load and outcome after head injury; at discharge from hospital in severe head injury participants (n = 35), at 6 month follow-up (n = 28), late (median 27 years) after head injury (n = 41), and late after repeat concussion in retired international rugby players (n = 48). Allostatic load was also compared with cognitive function late after head injury and repeat concussion and with change in disability between hospital discharge and 6 month follow-up, and from 6 months post-discharge to late after injury. In all the studies, the allostatic load scores of head injury participants were compared to that of non-head injured comparison participants.

Results

The studies within this thesis found limited evidence to suggest that allostatic load was associated with outcome after head injury. There was no association between allostatic load and disability outcome, change in disability over time, or cognitive function in the severe head injury studies. There was a significant relationship between higher neuroendocrine component scores at hospital discharge and worse disability outcome at 6 month follow-up, indicating possible pathophysiological consequences of neuroendocrine indicators early after injury. Also, the finding that head injury participants had higher anthropometric and metabolic component scores than comparison participants late after injury, and that greater disability over a median of 27 years was associated with higher metabolic component scores, indicates that brain damage causes an increase in secondary outcomes of allostatic load, which potentially has implications of an increased risk of morbidities over time. There was no association between allostatic load and frequency of concussions and therefore a number of outcomes in the retired international rugby player group; with the exception of an unexpected inverse relationship between allostatic load and time to complete a fine motor co-ordination task.

Conclusion

Findings from this thesis do not support the hypothesis that accumulated physiological dysregulation explain the heterogeneity after head injury. Some of the findings in this thesis require further study to investigate the pathophysiological consequences of higher neuroendocrine indicators at hospital discharge and metabolic indicators late after injury. Also it is important to understand the causes of increased metabolic and anthropometric component scores late after head injury to explore potential interventions to reduce possible increased risk of morbidities and mortality. The atypical findings in the investigation of allostatic load and repeat concussion indicate the accumulation of allostatic load in elite athletes is different to the general population. As none of the studies presented in this thesis found evidence for an association between allostatic load and disability outcome, there is a clear need for more research into factors that predict the heterogeneity of outcome after head injury.

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Poster presentation at the 10th International Brain Injury Association World Congress, San Francisco, 2014:

Wainman-Lefley, J., McMillan, T. M., Pell, J., Cavanagh, J. (2014). Association between allostatic Load and outcome following head injury. *Brain Injury*. Abstract, *28* (5-6), 793.

Poster presentation at the 11th International Brain Injury Association World Congress, The Hague, 2016:

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Author's Declaration

"I hereby declare that I am the sole author of this thesis, except where the assistance of others has been acknowledged.

It has not been submitted in any form for another degree or professional qualification."

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Chapter 1 **Introduction**

Background

This chapter provides an introduction to head injury (HI) and a review of the research investigating predictors of outcome at different time points after HI. This chapter outlines outstanding questions in the investigation of factors that explain outcome after HI, which this thesis aims to address.

Methods

In order to examine factors that predict outcome after HI, research investigating disability outcome in the first year and after a year post-head injury, change in disability outcome overtime, and mortality late after head injury are discussed in order to highlight evidence of what factors are known to predict outcome after HI, but also gaps in the outcome after HI literature.

Results

The HI literature discussed in this chapter demonstrates that outcome after HI is heterogeneous; in particular late outcome, including disability and increased risk of mortality, are only partly explained by the severity of the injury and demographic factors. Further exploration of factors that predict outcome after HI may improve interventions and thus recovery following HI.

Conclusions

The evidence from the HI literature about what factors predict outcome after HI is inconsistent. The literature points to an unhealthier lifestyle in those with poorer outcomes; however there is also great inter- individual variability in HI in terms of the mechanisms of injury, demographic, and lifestyle factors. Thus the studies in this thesis investigate the variability in outcome at different stages following HI, using the allostatic load model, which is a model of disease mechanism that focuses on the individual. This model may elucidate the heterogeneity in outcome after HI.

1.1 General overview of Chapter 1

This thesis explores whether allostatic load (AL) helps explain outcome, in terms of disability, after head injury (HI). This was achieved by investigating AL and disability outcome in HI populations at different time points after HI, as well as follow-up assessments of the same HI participants over time. This combination of cross-sectional and longitudinal cohort studies allowed a widespread exploration of any relationship between AL and HI, and change in disability over time. The aim of the studies in this thesis was to illuminate the current difficulty in explaining and predicting long term outcome after HI, using a model that describes the accumulated physiological consequences over time of the varied adaptive processes of the body when responding to stress in the environment (the AL model).

In order to understand why this research is important, this introduction begins with a general overview of what a HI is and of its effects. It then reviews research that has investigated outcome after HI, and the known predictors of: outcome early (within a year), and late (after a year) after injury, change in disability over time, and the increased risk of mortality late after HI. Although mortality is not an outcome in this thesis, the predictors of late mortality may be relevant to persisting disability or poor health after HI.

1.2 General overview of head injury

A systematic review of HI in Europe estimated an average incidence of 235 per 100,000, with approximately 6,246,400 people (330 million population in 2006) living with some disability (Tagliaferri, Compagnone, Korsic, Servadei, & Kraus, 2006). There are approximately 453 head injuries per 100,000 presentations to UK emergency departments each year (Yates, Williams, Harris, Round, & Jenkins, 2006). In Glasgow, there is an estimated annual incidence of 100-150 per 100,000 population of adults with disability following admission to hospital for a HI (Thornhill et al., 2000).

The incidence of mild HI is far more common than moderate or severe; most reports indicate moderate to severe HI in less than 10% of HI cases (Tagliaferri et al., 2006). In a cohort study of every HI patient admitted to the five general

hospitals in Glasgow in a year, 3.4 % were severe, 4.5% were moderate and the remaining 92.1% were mild (Thornhill et al., 2000).

HI is more common in individuals from more socially deprived areas (Dunn, Henry, & Beard, 2003; Yates et al., 2006). The demographics of the HI population are also closely linked to cause of injury. Men are more at risk of HI than women, particularly during adolescence and young adulthood when testosterone is particularly high, and causes of injury linked to risky behaviours such as road traffic accidents and violence (Bruns & Hauser, 2003). For example men aged 15–19 had the highest UK emergency department attending rates for moderate to severe HI; approximately 180 per 100,000 (Yates et al., 2006).

In adulthood, the male to female ratio is commonly found to be between 3:1 and 2:1 (Annegers, Grabow, Kurland, & Laws, 1980; Mushkudiani et al., 2007), progressing to 1:1 at the age of 65 (Mushkudiani et al., 2007), and later in life, elderly women are more at risk of HI than men (Annegers et al., 1980). Young children (0-4 years) and elderly adults (75 years and older) are at increased risk of HI due to falls (Faul, Xu, Wald, & Coronado, 2010). The link between cause of HI, gender and age at injury suggests HI is not necessarily a random event; it may be an indicator of lifestyle.

1.3 What is a head injury?

The Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health define HI as “an alteration in brain function, or other evidence of brain pathology, caused by an external force” (Menon, Schwab, Wright, & Maas, 2010). Altered brain function may include loss of consciousness, retrograde or post-traumatic amnesia, disorientation, or psychological or neurological deficits. Within Scotland, the Scottish Intercollegiate Guidelines Network (2009) use the broad definition of HI described by Jennett and MacMillan (1981); “a history of a blow to the head or the presence of a scalp wound or those with evidence of altered consciousness after a relevant injury”.

Head injuries range from minor, to profound and serious brain damage. Largely, head injuries can be divided into two groups; closed- or open- HI (Bešenski, 2002). A HI is closed if the head collided with an object, or a violent motion causes the brain to hit against the skull. An open HI occurs when the brain is penetrated by an object.

1.3.1 Effects of head injury

Head injuries are associated with a broad spectrum of impairments and disabilities that may include: memory failure, trouble concentrating, fatigue, headaches, dizziness, language and word-finding problems, sleep disturbance, anxiety, depression, being quick-tempered, mood swings, reduced interest in social and leisure activities, issues with emotional regulation, and lack of insight.

Head injuries range from mild to severe, depending on the damage to brain tissue. Mild HI is associated with short-lived symptoms, such as headache, dizziness, and nausea. Severe brain injury is associated with impairment of physical, emotional, and cognitive functioning. Typically patients with more severe head injuries require rehabilitation following hospital discharge for complex cognitive and physical impairments. Whilst many symptoms resolve within the first few months after injury, some remain for up to 30 years or more after injury (Himanen et al., 2006).

1.4 Outcome after head injury

Predicting outcome after HI is difficult due to the combination of inter-patient variability and the number and variety of factors associated with each incident. For example there are large individual differences in the initial brain injury, including possible contusions, shearing or lacerations at different sites of the brain, followed by possible secondary injury caused by hypoxia, hypotension, ischemia and other complex biochemical events, which lead to delayed tissue damage and cell death (Graham, McIntosh, Maxwell, & Nicoll, 2000; Reed & Welsh, 2015; Rigg & Zafonte, 2006).

The heterogeneity of outcome following HI has given rise to a mass of research that has attempted to understand factors associated with outcome, in the hope

of improving outcomes for HI patients. However, as this chapter will describe, the results of these studies are not consistent. One reason for this may be the variability in the definition of 'outcome' after HI between studies, ranging from; initial survival, late mortality, the presence of symptoms, impact on ability to live an independent life, employment, quality of life, effect on relationships, or specific emotional, cognitive or psychological factors.

The word 'outcome' is used in this thesis to describe the consequences or results of changes following a HI. The primary outcomes in the studies in this thesis were the Glasgow Outcome Scale- Extended (GOS-E; Wilson, Pettigrew, and Teasdale (1998); Appendix C) and a hospital- setting appropriate version of the GOS-E, the Glasgow Outcome at Discharge Scale (McMillan, Weir, Ireland, and Stewart (2013); Appendix C). The GOS-E is an extended and more sensitive version of the Glasgow Outcome Scale (GOS) (Jennett & Bond, 1975). It is the most widely cited assessment of outcome after HI (King, Carlier, & Marion, 2005; McMillan, Wilson, Ponsford, Levin, Teasdale, & Bond, 2015). For this reason, where appropriate this introduction will focus on literature that has used the GOS-E or GOS as measures of disability outcome.

What follows is a description of key research that has investigated disability outcome at different stages following HI, and what factors may predict these outcomes.

1.5 Disability outcome in the first year after head injury

There are many studies that explore early recovery after HI, and possible predictors up to one year after HI. A meta-analyses by Mushkudiani et al. (2007) investigated demographic characteristics and outcomes after HI using the International Mission for Prognosis And Clinical Trial (IMPACT) database (n = 8,720), which contains comprehensive data from most clinical trials and epidemiologic studies investigating moderate to severe (Glasgow Coma Scale (GCS) < 12) HI in the last 20 years (Marmarou et al., 2007). The main outcome was GOS rating between 3 and 6 months after injury. Factors that were associated with poorer GOS ratings included; increasing age (n = 8,719; OR 2.14; 95% CI: 2.00–2.28), Black race (compared with Caucasian: n = 5,320; OR 1.30; CI 1.09–1.56), and there was a weak relationship with number of years in education. Gender was

not associated with outcome; this finding is supported by an earlier meta-analysis of gender differences in outcome after HI (Farace & Alves, 2000). As this chapter will later describe, disability is known to change over time; Levin et al. (2001) demonstrated changes in GOS-E and GOS ratings between 3 and 6 months after HI, therefore a limitation of this meta-analysis is the assessment of outcome at different time-points post- HI.

A recent systematic review investigated early predictors of outcome 6 months after a moderate to severe HI (GCS 3-12) (Husson, Ribbers, Willemse-van Son, Verhagen, & Stam, 2010). A total of 28 prospective cohort studies were included; 2 studies used the GOS-E as the main outcome, 1 used the Disability rating Scale (DRS) and the remainder used the GOS to investigate outcome at 6 months. The results demonstrated evidence for a link between poorer outcome (lower GOS and GOS-E ratings and higher DRS ratings) and a high pulsatility index (difference between systolic and diastolic blood flow velocity divided by the mean velocity during the cardiac cycle) assessed within 24 hours of admission, evidence of midline shift on a CT scan, subdural haematoma, lower GCS on admission to hospital, and lower motor score on the GCS. Gender and intraventricular haemorrhage had no relationship with outcome, and the prognostic value of age was inconclusive, with most studies demonstrating no relationship between age and outcome. However this review and that by Mushkudiani et al. (2007) excluded any study that investigated outcome following mild HI, hence omitting most of the HI population (Tagliaferri et al., 2006).

Another meta-analysis of 26 studies (n participants = 21,050) investigated severity of HI as an indicator of recovery 1 year later (Cappa, Conger, & Conger, 2011). There were 87 combinations of injury severity (12 measures) and outcome measures (n = 25) investigated. Measures of injury severity focussed on different aspects of injury, including post-traumatic amnesia (PTA), DRS, GCS, length of hospital stay, simple motor command, the Functional Independence Measure, length of loss of consciousness, orientation log, abbreviated injury scale, revised trauma score, and the injury severity score. Outcome measure constructs were organised into categories: productivity (for example the Community integration questionnaire) global disability (for example the DRS), quality of life (for example Satisfaction with Life), independence (for example the Supervision Rating Scale), and global outcomes (Glasgow Outcome Scale).

Overall, the average relationship between injury severity and outcome at one year demonstrated a significant medium effect size (r = 0.257), although it only explained a modest proportion of the variance. Interpreting the findings of this study is difficult when the measures of HI severity and outcome after HI were pooled together in the absence of guidelines or standards (Donnan et al., 2016).

In contrast to the finding by Cappa et al. (2011), a large prospective cohort follow-up study of all severe, moderate and a representative sample of mild HI participants (n = 549/ 2,995) admitted to hospitals in Glasgow found that survival with moderate or severe disability on the GOS at one year was similar for mild (47%), moderate (45%), and severe HI (48%), assessed using GCS at arrival to hospital (Thornhill et al., 2000).

However a limitation of this study is that it did not investigate factors associated with disability outcome at 1 year in moderate or severe HI participants. It did investigate predictors of disability in a subgroup of 362 mildly injured patients (GCS 14-15) however death was also included as an outcome in this analysis, therefore these finding are not discussed further as predictors of disability alone cannot be separated from the results.

In conclusion, the evidence points to injury-related factors such as more severe head injuries, indicated by CT abnormalities, low GCS, and duration of coma or hospital admission, and biomarkers and physical measures of health assessed in the acute stages as being associated with disability outcome (Cappa et al., 2011; Husson et al., 2010), although these factors only explain a modest proportion of the variance. The role of patient characteristics and demographic predictors of outcome after HI is less clear. Increasing age appears to predict poorer outcome, and gender is not associated (Husson et al., 2010; Mushkudiani et al., 2007).

It remains difficult to derive predictions for individual HI patients as the evidence is not precise enough to inform or support clinical decisions (Johnston, Sherer, & Whyte, 2006; Mushkudiani et al., 2008). The variability in indicators of HI severity, and outcome measures after HI, may underpin the inconclusive and sometime contradictory research findings regarding outcome early after HI.

1.6 Disability outcome after a year post-head injury

Predicting disability outcome late after HI would be valuable for making treatment decisions and for managing the expectations of patients and families. Unfortunately, there are no systematic reviews or meta- analyses investigating recovery late after HI. The following section summarises and discusses the research evidence.

Ponsford, Draper, and Schonberger (2008) demonstrated that poorer outcome on the GOS-E 10 years after injury in 60 HI participants was significantly associated with: longer duration of PTA (Cohen's d = 0.8, p <0.01); fewer years in formal education, at the time of injury (d = 0.7, p <0.05), and at follow-up (d = 1.1, p <0.001) and higher anxiety on the Hospital Anxiety and Depression Scale (HADS) at follow-up (d = 0.8, p <0.05). Although as anxiety HADS scores were assessed at follow-up and the same time as the GOS-E, this limits the interpretation of this finding in terms of determining causality. Minimum GCS, age at injury, gender, preinjury employment and preinjury relationship status were not associated with, and therefore not helpful predictors of late outcome after HI (p >0.05).

In a Glasgow population, 5-7 years after HI, all participants from the Thornhill et al. (2000) study with a severe (GCS <8; n = 102) or moderate HI (GCS 9–12; n = 133) and a random sample with a mild HI (GCS 13–15; n = 507) were invited for a follow-up assessment (Whitnall, McMillan, Murray, & Teasdale, 2006). Global outcome was assessed using the GOS-E, and of the 219 survivors assessed, 47% (n = 104) had made a good recovery and 53% were disabled; 42 (19%) were severely disabled, and 73 (33%) moderately disabled. There was an association between those who were Disabled at 5-7 years (GOS-E rating <6) and severe HI at hospital admission (GCS score 3-8; p <0.05). However disability at 5-7 years was not associated with gender, age at injury, previous brain injury, and social deprivation at 5-7 year follow-up.

One hundred and twenty-one (55%) of the above cohort were successfully traced for a follow-up 12-14 years after HI (McMillan, Teasdale, & Stewart, 2012). Thirty-four (15.5%) participants died between 5-7 and 12-14 years follow-up, 87 were successfully followed-up. Disability was found in 51% of survivors using the GOS-E; 20% severely disabled, 31% moderately disabled. GOS-E ratings at 12-14 years were

not associated with self-report of a further HI (z = 1.334; p = 0.182), or hospital admissions for other reasons between 1 and 12-14 years (z = 0.424; p = 0.672), but greater disability at 12-14 years was associated with greater perceived stress (r_s = 0.393; p <0.005) and lower self-esteem (r_s = 0.540; p <0.001). The temporal relationship of these psychological associations is not known however as they were assessed at the same time as the GOS-E (12-14 years after injury). In this study, further investigation was conducted of pre-injury predictors of severe disability late after HI; although death was also included as an outcome therefore predictors of disability alone cannot be determined.

This study also compared outcome at 12-14 years with psychological variables assessed at 5-7 years in the Whitnall et al. (2006) study. Greater disability on the GOS-E at 12-14 years correlated with greater HADS anxiety (r_s= -0.402; p <0.005) and depression (r_s = -0.570; p <0.001), lower self-esteem (Rosenberg Self-Esteem Scale scores, r_s = 0.453; p <0.001), greater perceived stress (Perceived Stress Scale; r_s = -0.356; p <0.005) and Multidimensional Health Locus of Control perceived as 'Powerful other' (r_s = -0.299; p <0.05) and 'Chance' (r_s = -0.342; p <0.005). Although with a small sample size (n = 88), the interpretability of these findings is limited.

In conclusion several factors seem to be associated with disability late after injury. In terms of injury characteristics, more severe HI, (measured using lowest GCS scores at emergency department), predicted poorer outcome late after HI (Whitnall et al., 2006), however this was not found in other studies (McMillan et al., 2012; Ponsford et al., 2008), although these latter follow-ups were later after injury when more of the severe cases were likely to be dead. With demographic risk factors, there is evidence that lower education predicts poorer late outcome (Ponsford et al., 2008), however other measures of social deprivation (McMillan et al., 2012; Whitnall et al., 2006), or preinjury unemployment (Ponsford et al., 2008) were not helpful predictors. The evidence for age predicting increased disability later after HI is inconclusive with some studies arguing older age increases risk (McMillan et al., 2012), and others finding it not to be a risk factor (Ponsford et al., 2008; Whitnall et al., 2006), however this may be explained by more of those who were older at injury may have died in the later follow-up studies. One finding that was consistent was that gender did not predict outcome (McMillan et al., 2012; Ponsford et al., 2008; Whitnall et al., 2006). After injury,

poorer mental health (greater anxiety and depression, lower self-esteem, greater perceived stress and believing your health is controlled by 'powerful other' or by 'chance') were associated with poorer outcomes assessed at a later time-point (McMillan et al., 2012).

It remains difficult to predict outcome late after HI. It requires considering many demographic, injury and even pre-injury factors. This issue of predicting outcome late after injury is further complicated by the recent evidence that disability changes over time late after injury; something that will be explored in the next section.

1.7 Change in disability late after head injury

Recent evidence from a small number of longitudinal cohort studies suggests that disability following HI can be a dynamic process. For example, change in Glasgow Outcome Scale (GOS) was assessed between discharge from inpatient rehabilitation and 6-15 years follow-up (mean time since injury = 10 years) in a sample of 88 HI participants in Northern Sweden (Jacobsson, Westerberg, Soderberg, & Lexell, 2009). The results demonstrated 44% (n = 39) had improved in GOS rating between rehabilitation discharge and follow-up 6-15 years later. Only two participants deteriorated in GOS rating; one had a history of psychiatric illness and the other a previous brain injury. However factors that were associated with change in GOS ratings were not investigated in this study. This study is further limited by a small sample size, which may not represent the HI population of Northern Sweden as participants were recruited from a rehabilitation centre. Therefore the percentage of change in disability for those who did not receive rehabilitation is unknown. Also, the GOS is not valid for use in an inpatient setting, as was done at the first time-point in this study, because it evaluates independence in the community (McMillan et al., 2013).

In a larger follow-up study of 219 (7.3%) individuals 5-7 years after injury from a cohort of 2,995 adults admitted with a HI to hospitals in Glasgow (Thornhill et al., 2000), ratings on the GOS-E deteriorated (from Good recovery to Disabled) from 1 year follow-up in 26%, improved (from Disabled to Good recovery) in 31% and were unchanged in 43% (Whitnall et al., 2006). At the 5-7 year follow-up, improvement from Disabled to Good recovery on the GOS-E was not associated with severity of

injury assessed using GCS scores at hospital admission, having a previous HI, age at injury, gender, or having other brain illnesses. Similarly, deterioration from Good recovery to Disabled was not associated with these factors.

There were associations between emotional and cognitive factors at 5-7 years and change in GOS-E rating from 1 year to 5-7 years after HI. Improvement in GOS-E rating was strongly associated with higher self-esteem (Rosenberg's Self-Esteem scale; p <0.05), and lower scores for self-rated perception of stress (Perceived Stress Scale; p <0.005) and HADS scores of anxiety (p <0.01) and depression (p <0.005). Deterioration in GOS-E rating from Good recovery to Disabled between these two time points was associated with lower ratings of self-esteem (p <0.001), and higher self-ratings of stress (p <0.001), anxiety (p <0.001), depression (p <0.001), and an assessment of alcohol intake (p <0.005). However, these cognitive and emotional factors were assessed at the 5-7 year follow-up therefore the temporal relationship between these factors and change in disability is unknown based on this research.

When 87 survivors from the above study were followed-up 12-14 years post injury, 55% had a change in ratings on the GOS-E from 5-7 years; 32% deteriorated and 23% improved (McMillan et al., 2012). The proportion changing between 5-7 and 12-14 years post injury (55%) was similar to that between 1 and 5-7 years (57%). Stronger perceptions of health locus of control as being 'powerful others' on the Multidimensional Health Locus of Control at 5-7 years, were moderately associated with deterioration on the GOS-E between 5-7 and 12-14 years (r_s = 0.259, p <0.05). Change in disability was not associated with normal or high AUDIT ratings, assessed at 5-7 years or 12-14 years, or with change in measures of perceived stress or self-esteem between these two time points, however the interpretation of these findings are limited by the modest sample size (McMillan et al., 2012).

It is important to consider survival bias in longitudinal studies, something that may affect all of the above studies; the disability of those who died, and those who were not followed up from the original cohort is unknown, which limits the interpretation of the findings. However despite there being only a few studies, with limited sample size, it is clear that disability following HI can change over time; nonetheless why these changes occur late after injury is not so clearly understood. Change in disability has been most significantly associated with

measures of mental health assessed at follow-up, but these do not inform future projections of change in disability. Without the knowledge of what factors predict improvement or deterioration in disability over time, it is difficult to intervene, or prepare HI patients for the potential future of their health. Further, recent research has illustrated that HI causes an increased risk of mortality late after injury, which adds further uncertainty. This is explored in the next section.

1.8 Mortality late after head injury

It is well established that there is an increased risk of mortality early after HI (De Silva et al., 2009); however only recently has research demonstrated that the risk of mortality after HI is long-lasting. HI patients are vulnerable to developing epilepsy following their injury (Annegers & Coan, 2000), and the increased risk of death late after injury due to epilepsy compared to the normal population is well documented (Roberts, 1979; Shavelle, Strauss, Whyte, Day, & Yu, 2001). What is not so commonly known is that there is an increased risk from common causes of death, not specific to the HI, which lasts for years after injury.

For example, mortality was investigated in 2,178 American HI participants who had completed inpatient rehabilitation, compared with the general population (Harrison-Felix, Whiteneck, Devivo, Hammond, & Jha, 2004). There were 161 deaths (7.4%) following inpatient rehabilitation; the Standardised Mortality Ratio (SMR) was 2.00 (95% CI: 1.69–2.31), demonstrating that individuals with HI were two times more likely to die than age, gender, and race comparable members of the general population. Cause of death was investigated for 124 deaths after 1 year post-injury, in a sample of 2,140 HI participants recruited from the same rehabilitation centre (Harrison-Felix, Whiteneck, Devivo, Hammond, & Jha, 2006). HI participants were 37 times more likely to die of a seizure, 12 times more likely to die from septicaemia, 3 times more likely to die of digestive conditions, 3 times as likely to die due to external causes/ poisoning, more than twice as likely to die of respiration related conditions, and 4 time more likely to die of pneumonia. These findings are important as they indicate an increased risk of mortality from general causes for HI participants later after injury and the importance of continual observation of the health of HI patients after discharge from hospital. However, a limitation of this study is that socioeconomic status was not controlled

for in the comparison of mortality between HI participants and the general population.

Later Harrison-Felix et al. (2009) followed up 1,678 HI patients from a rehabilitation hospital between 381 days to 25 years since injury (median 11 years). There were 130 deaths; the SMR for HI participants was 1.51 (95% CI: 1.25–1.78), indicating they were one and half times more likely to die than an age, gender, and race comparable member of the general population. Again, the causes of death in the HI group that were significantly higher than for the general population included: aspiration pneumonia (SMR 48.64, 95% CI: 23.32-89.44), pneumonia (SMR 4.33, 95% CI: 1.98-8.22), suicide (SMR 2.95, 95% CI: 1.42-5.43), and deaths related to seizure (SMR 22.48, 95% CI: 8.25-48.93).

Although the above studies do not fully report the range of severity of head injuries, patients who attend rehabilitation for HI are more likely to be receiving it for moderate to severe disabilities in the acute stage, most likely as a result of a more moderate to severe HI. However mild HI and minimal disabilities at the acute stage have also been demonstrated to have an increased risk of mortality late after injury (Brown et al., 2004). For this reason mortality follow-up studies based on samples from rehabilitation or clinic populations, such as those described above, have been criticised as being unrepresentative of the wider HI population, who do not all receive rehabilitation (McMillan, Teasdale, Weir, & Stewart, 2011).

Retrospective studies are also vulnerable to bias; in order to avoid this, a prospective cohort study was conducted to investigate survival 13 years after injury in a cohort of 757 HI patients from the Thornhill et al. (2000) investigation of outcome at one year after HI (McMillan et al., 2011). Survival of the HI cohort was compared with two control groups; the first group were hospitalised for an injury other than HI, matched for the same length of stay in hospital, and a second community control group. Both the other injury and community control group were matched for age, gender, and social deprivation. Scottish Index for Multiple Deprivation (SIMD) 2006 quintiles were used to determine the degree of socioeconomic deprivation of the neighbourhoods in which participants lived.

Results demonstrated 40.3% (n = 305) of the HI group had died within 13 years of injury. Death rate was high within the first year after injury, however the rate of

death after one year (n = 229, 33.6%; X^2 65.35; p <0.0001) was significantly higher than the other injury group (n = 168, 23.7%) and the community control group (n = 116, 15.7%). Death rates were significantly higher more than one year after injury in younger adults (15-54 vs. >54 years) in the HI group (OR 9.40; 95% CI: 5.35-16.50) and other injury group (OR 4.32; 95% CI: 2.40-7.80), than community controls. The six main causes of death in the Greater Glasgow population accounted for 92-94% of deaths in each group; circulatory, neoplasm, respiratory, digestive, mental/behavioural, and external. Increased risk of death was similar 2-13 years after injury for mild (32.4%) moderate (37.9%) and severe (32.4%) HI. Mortality later after HI was not associated with social deprivation, gender, or previous HI.

Therefore in McMillan et al. (2011), HI participants were more than twice as likely to die as members in the community control group, and significantly more likely to die than the other injury control group. This increased risk of death was not explained by gender, social deprivation or the severity of HI and sustaining an injury as a younger adult was associated with an especially high risk of death in later life compared with the general population.

As a result of the finding of increased risk of death in the mild, younger HI adults in this study, a follow-up was conducted of the 2,537 adults admitted with a mild injury (GCS 13-15) from the original Thornhill et al. (2000) cohort, 15 years after injury (McMillan, Weir, & Wainman-Lefley, 2014). A total of 2,428 (96.5%) mild HI participants were traced and a community control and other injury control matched for age, gender, and SIMD (2006) quintile. Over the 15 year follow-up period, 36.7% (n = 891) of the mild HI group had died, with 93% of those deaths being from the 6 major categories of cause of death as in the general population described above. Mortality per 1,000 per year in the mild HI group (24.49; 95% CI: 23.21-25.79) was higher than in community controls (13.34; 95% CI: 12.29-14.44; p <0.0001), and other injury controls (19.63; 95% CI: 18.43-20.87; p <0.0001). Again, younger mild HI adults (aged 15– 54 years) were most at risk of death with a 2.4-fold greater risk of death than community controls.

Health history information demonstrated the mild HI cohort had significantly more admissions to hospital with systemic disease pre-injury and post-injury, but for shorter periods that the other injury group. Both injury groups were admitted

more often and for longer periods of time than the community control group. Also both the mild HI (OR 1.21; 95% CI: 1.07-1.37; p <0.005) and other injury groups (OR 1.23; 95% CI: 1.07-1.41; p <0.005) had significantly more admission post-injury than pre-injury, whereas this increase over time was not seen in the community control group. However it remains unknown what it is about the lifestyle or general health of the mild HI group that increased the frequency of hospital admissions and risk of mortality late after injury.

In conclusion, the above evidence demonstrates there is an increased risk of death after HI compared with age, gender, and social deprivation matched comparison participants, and this increased risk of death is present as late as 25 years after injury (Harrison-Felix et al., 2006; McMillan et al., 2011). Causes of death vary widely, and are similar to those for the general population of the respective population, indicating there are health consequences for the whole body, not just those immediately associated with HI (Harrison-Felix et al., 2006; McMillan et al., 2011; McMillan et al., 2014). Further, evidence of significantly increased number of admissions to hospital pre- and post-injury compared with control groups, point to an unhealthier lifestyle being the cause of the increased risk of mortality (McMillan et al., 2014). Still, further research is required to understand why HI patients are at an increased risk of early mortality.

1.9 Explanation of poor outcome after head injury

The research detailed above shows that it remains difficult to predict disability outcome after HI, both in the acute stages and the long-term. For some, disability changes over time, and there is an increased risk of mortality late after HI. However who is more vulnerable to change in disability or early death is unknown. The recent finding of increased number of admission to hospital pre- and post-injury in a HI cohort compared with a community control group, point towards lifestyle as an important factor, which might help explain these poor outcomes in a percentage of HI patients (McMillan et al., 2014).

It has been argued that HI may accelerate disease pathways as survival after HI can be associated with chronic illness (Masel & DeWitt, 2010). For example severe HI is associated in the long-term with systemic disease, in particular cardiovascular and respiratory disease (Zygun, Kortbeek, Fick, Laupland, & Doig,

2005). Mild HI is also associated with poorer cardiovascular health; Ahmadi et al. (2012) demonstrated significantly higher coronary artery calcium, which is associated with coronary artery atherosclerosis, in 543 single mild HI veterans compared to comparison veterans without history of mild HI, and reduced autonomic cardiovascular modulation has been reported in adults 20 months after mild HI in the absence of cardiovascular complaints (Hilz et al., 2011).

The finding of significantly more hospital admissions with systemic disease after mild HI than pre-injury, might suggest that the HI has a pivotal effect on the frequency of hospital admissions (McMillan et al., 2014). There may be lifestyle changes following HI that increase the risk of systemic disease. Some unhealthy lifestyle factors are more prevalent in the HI population, for example there is a high risk of excess habitual alcohol drinking pre- and post-injury (Corrigan, 1995).

Recent evidence from neuroimaging and post-mortem studies has demonstrated long-term neuropathological consequences of HI. Post-mortem studies showed tauopathy and amyloid beta plaques were more widely distributed and abundant in long-term survivors of a single HI, than age-matched controls (Johnson, Stewart, & Smith, 2012). There is also evidence of persistent inflammation and continual loss of white matter for many years following a single moderate to severe HI (Adnan et al., 2013; Johnson et al., 2013).

There is also evidence that mild HI can be associated with neuropathology, for example McKee et al. (2013) demonstrated neurofibrillary tangles and astrocytic tangles in sports players with history of repeat mild HI (N = 68). This neuropathology was linked to clinical symptoms ranging from a cluster of non-specific complaints such as depression, irritability, poorer concentration, and memory impairments to more widespread and severe cognitive complaints and personality change that are consistent with dementia In addition, mild HI patients who experienced cognitive impairment showed a higher number of amyloid accumulation and allele frequency of apolipoprotein E epsilon 4 (APOE4) using amyloid-positron emission tomography (Yang et al., 2015). Thus, even a single HI is now viewed as a risk factor for dementia and Alzheimer's disease (Sivanandam & Thakur, 2012; Wang et al., 2012). However other research in a larger clinical outcome study did not find that late cognitive decline after HI was associated with carrying APOE4 (Millar, Nicoll, Thornhill, Murray, & Teasdale, 2003). Nonetheless,

there may be biological processes that are provoked by the HI, which cause late development of pathology that in turn lead to comorbidity and early mortality.

In addition to the above evidence of neuropathological effects of HI, a meta-analysis of outcome late after self-report of mild HI evidenced long-term effects on cognition including executive functioning and delayed memory (Belanger, Spiegel, & Vanderploeg, 2010). Persistent cognitive deficits and disabilities are reported throughout the range of severity of HI but are more prevalent after moderate or severe than after mild HI (Colantonio et al., 2004; Schulz-Heik et al., 2016). Cognitive impairments arise in many cognitive domains, and especially executive functioning, memory (verbal and visual), and attention but can also affect general intellect and visuospatial abilities (Carlozzi, Kirsch, Kisala, & Tulsky, 2015; Marsh, Ludbrook, & Gaffaney, 2016; Rabinowitz & Levin, 2014). In Chapters 7 and 8, cognitive outcome is considered as a secondary outcome late after moderate-severe hospitalised HI (Chapter 7) and late after repeat concussion (Chapter 8).

It remains unknown whether the comorbidity and increased risk of mortality following HI is a result of chronic neuropathology, or is a lifestyle change caused by reduced physical or cognitive functioning. In the investigation of heterogeneity of outcome after HI it seems important to look at HI individuals holistically and to consider health given the recent findings of increased hospital admissions for systemic disease post- HI (McMillan et al., 2014).

1.10 Summary

Head injury is a major cause of life-long disability and death often affecting young and previously healthy adults (Corkin, Rosen, Sullivan, & Clegg, 1989; Thornhill et al., 2000). HI is heterogeneous, in terms of patient characteristics, cause of injury, resulting pathophysiology, treatment access, and outcome, and this makes assessment of factors associated with recovery and comparison between studies challenging.

This chapter describes research investigating outcome after HI, relevant to the studies in chapter 5-8. It is not possible to provide a comprehensive account of all studies that have looked into all potential outcomes after HI. Research

investigating pre- and post-injury factors, injury characteristics, and demographic information that may predict outcome, report associations with a different combination of these factors. Yet when these findings are compared across studies, results often contrast, and there is no agreement about what factors predispose HI patients to a better or worse outcome. This makes it difficult to know how intervention can best be staged after HI.

Given the potential to intervene and to maximise improvement from disability, reduce deterioration and associated cost to social, emotional and cognitive function, and rates of mortality, we need to understand more about factors that influence outcome at different stages following HI. There is great inter-patient variability in HI in terms of the mechanisms of injury, demographic, and lifestyle factors; a measure that can capture this may elucidate the heterogeneity in outcome after HI. Generally, the literature points to an unhealthier lifestyle in those with poorer outcomes, particularly the recent finding of a higher incidences of pre- and post-injury hospital admission with systemic disease in those surviving late after HI, compared to matched control groups (McMillan et al., 2014). Thus, the studies in this thesis attempt to contribute to the understanding of variability in outcome at different stages following HI, using a model of disease mechanism that focuses on the individual, known as the allostatic load model, which is discussed in chapter 2.

Chapter 2 **The allostatic load model**

Background

This chapter provides an introduction to the allostatic load (AL) model and a review of literature that uses AL to predict functioning, disease and mortality in healthy populations. A systematic search was conducted to evaluate whether (1) AL studies have used and evaluated different methods to construct an AL score in adult samples, and (2) any AL studies have evaluated different combinations of indicators of AL to predict or be associated with health outcomes

Methods

This chapter discusses, the theory associated with AL and key studies investigating AL and health outcomes in the general population. Following this, a systematic search of AL is presented. Initially, a keyword search of three major psychological and medical databases (PubMed, Embase, Cochrane, PsycINFO, and CINAHL) was conducted. The search for the first research question yielded 1,114 papers, and 557 remained after the removal of duplicates (n = 557). A manual search of a previous systematic review added 4 further papers (n = 561). Following screening for inclusion criteria, 3 papers remained and were quality assessed. The search for the second research question yielded the same n = 561 papers as the first systematic search. Following screening for inclusion criteria, 1 paper remained and was quality assessed.

Results

The AL model conceptualises how stressors can chronically elevate physiological activity and have a negative impact on health (McEwen, 1998b). Allostatic load has been demonstrated to be associated with psychosocial functioning, morbidity, and mortality and can predict these outcomes at follow-up. However the findings of the systematic search indicated that the evidence base on the methodology associated with measurement of AL is limited. More specifically no AL studies have evaluated different combinations of indicators as predictors of AL or of associated health outcomes. The few that compare methods of calculating a total AL score found no significant difference between them.

Conclusions

The systematic search highlights the paucity of evidence for a valid and reliable method for measuring AL, and the importance of future AL research to aim fill this gap in the literature. The theory of AL is presented as a framework for investigating various health outcomes in the general population. Previously, AL has not been investigated in the head injury population, but it may help to explain the heterogeneity in outcome described in Chapter 1.

Chapter 1 highlighted the lack of agreement about factors that predispose head injury (HI) patients to a better or worse outcome in the HI literature. Recent findings indicate that the prevalence of pre- and post-injury hospital admissions with systemic disease is higher in those surviving late after HI, than in matched control groups (McMillan et al., 2014), suggesting health and lifestyle factors may play a role in poor outcomes late after HI. The allostatic load (AL) model is an objective, yet person-focussed model of disease mechanism, which if measured in a HI population, may be helpful in understanding the development of poor outcomes after HI. This chapter introduces the AL model and following this, a systematic search is conducted to investigate the evidence base for a valid and reliable method of measuring AL. The stress response

When threat is detected, a coordinated physiological response occurs in the brain involving the activation of metabolic, immune, neuroendocrine and autonomic system component (McEwen & Gianaros, 2010). This complex range of responses is known as the stress response, the activation of which triggers a number of physiological and behavioural changes that are essential for survival. The severity of threat caused by an external challenge, whether perceived or real, regulates the degree of the stress response (Lazarus, 1966). Immediate physiological changes in response to a challenge include increased respiratory rate, cardiovascular tone and core temperature and the inhibition of appetite, which are closely regulated by a number of anatomical, endocrine, and neuronal systems (Charmandari, Tsigos, & Chrousos, 2005; Habib, Gold, & Chrousos, 2001; Smith & Vale, 2006). Behavioural adaptations include increased vigilance and alertness, enhanced cognition, and focused attention (Charmandari et al., 2005). The stress response is an adaptive process with a number of potential successful adaptations but also pathogenic effects, both acute and chronic. The physiological basis and short and long-term consequences of stress have been widely studied in order to understand the complex nature of the stress response. The following section gives a brief overview of this research.

2.1.1 Stress: a brief history

Human physiological responses to stress are associated with health. Stress is known to predispose many diseases such as coronary heart disease, diabetes, the common cold and gastrointestinal disorders (McEwen, 1998b). The understanding

of human physiology and the adaptive regulation of the stress response system has developed and advanced enormously over the last 140 years. What follows is a brief description of the development in understanding of how stress affects the human body.

In the theory of the Milieu Intérieur, Claude Bernard developed the idea of bodily fluids maintaining the constancy of the internal environment of the body (Bernard, 1879). It was later recognised that organisms must sustain internal consistency, changing diet and fluid intake in the face of environmental conditions (Starling, 1923).

Later, Walter Cannon first introduced the term 'homeostasis', which defined the principle of the human physiology adaptive mechanisms. He described how a healthy system is sustained in the body by using restorative feedback mechanisms to reduce variability and maintain constancy (Cannon, 1932). Cannon (1932) suggested disease was caused by the failed homeostatic mechanisms and the regulation of these parameters.

Hans Selye was the first to describe the idea that chronic stress could result in cumulative damage on the body (Selye, 1956). Homeostasis is integral to his account of the General Adaptation Syndrome (GAS), where physiological systems respond to environmental stressors in three stages to maintain life; alarm, resistance, and exhaustion (Selye, 1950). During the alarm stage, rapid physiological changes occur immediately in response to a challenge, such as change in heart rate and blood pressure (Berkman & Kawachi, 2000). If the stressor does not diminish, the body enters a resistance stage during which the physiological adaptation is more intense. During this stage the body is more vulnerable to illness and more susceptible to damaging physiological effects of other stressors. If exposure to the stressor persists for a longer period, the body enters the exhaustion stage, where it is less able to adjust and combat the stress or to moderate damaging effects. Serious changes in the immune system can result in severe illnesses if not resolved promptly. Over time, repeated cycles of physiological systems responding to environmental stressors have cumulative damaging effects.

The GAS theory was the first to link stress and illness. It was important as it defined the crucial roles of the hypothalamus and pituitary glands, and the hormones they release, in meditating the stress response. However the GAS did not consider differences in the perception of stress or individual differences in lifestyle behaviour.

In 1966, the psychologist Richard Lazarus described a new theory of stress, emphasising individual differences in the interpretation and perception of a stressful event. The theory describes the experience of stress as resulting from two stages of cognitive appraisal: 1) primary appraisal- deciding if there is a significant threat; whether it is a positive encounter or is it harmful, and 2) secondary appraisal- assessing what resources are available to combat the stress (Lazarus, 1966). In the 'transactional model of stress and coping', stress is experienced when "demands exceed the personal and social resources the individual is able to mobilise" (Lazarus & Folkman, 1984). Therefore the effect that stress has on an individual is a result of their interpretation of the event and of their ability to cope. This theory contributed to the understanding and consideration of the appraisal process as a moderator between a stressor and the biological stress-response.

The research of Bernard, Cannon, Selye, and Lazarus laid the foundations for decades of further research, and theory development of an understanding of the physiological basis and consequences of stress.

2.1.2 Allostasis

Elaborating on the theory of homeostasis, the concept of 'allostasis' was proposed to describe the process of achieving stability through change (Sterling & Eyer, 1988). Specifically, allostasis is the ability of the body to adapt to fluctuating environmental demands and stressors through multiple, nonlinear and dynamic physiological networks and neuroendocrine systems (figure 1). The process of allostasis supports homeostasis; it is the active process of physiologically adapting and maintaining bodily systems, returning them to homeostasis and ultimately aiding in sustaining the health of an individual (Carlson & Chamberlain, 2005). Healthy functioning requires systems such as the autonomic nervous system, hypothalamic–pituitary–adrenal (HPA) axis, and immune system to adjust in

response to external stressors such as fatigue, or extreme heat or cold (McEwen, 1998b).

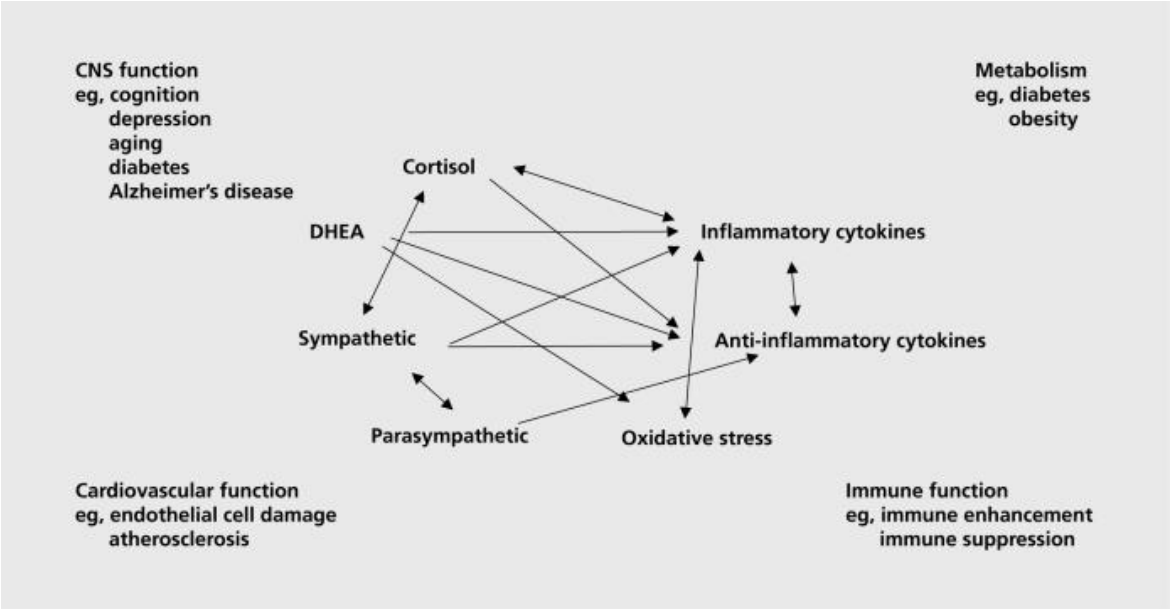

Figure 1 - The non-linear network of mediators of allostasis involved in the stress response. Arrows indicate systems that regulate others; some are reciprocal, forming a nonlinear network (McEwen, 2006a), permission obtained (see appendix A).

The theory of allostasis explains individual differences in physiological reactions to the same environmental stressor as being due to variation in the subjective interpretation of the stressor and in personal coping mechanisms (McEwen & Wingfield, 2003). Allostasis considers the impact of genetic predisposition, early life events, lifestyle behaviours, habits and health-related choices, stressful events, and social relationships, on the ability of the body to cope with physiological adaptation (figure 2). The primary mediators of allostasis, such as cytokines, catecholamines, and hormones in the HPA axis, adapt quickly in the short-term in response to an external challenge (McEwen, 1998b; McEwen & Seeman, 1999; McEwen & Wingfield, 2003), however this dynamic process is theorised to have long-term physiological consequences.

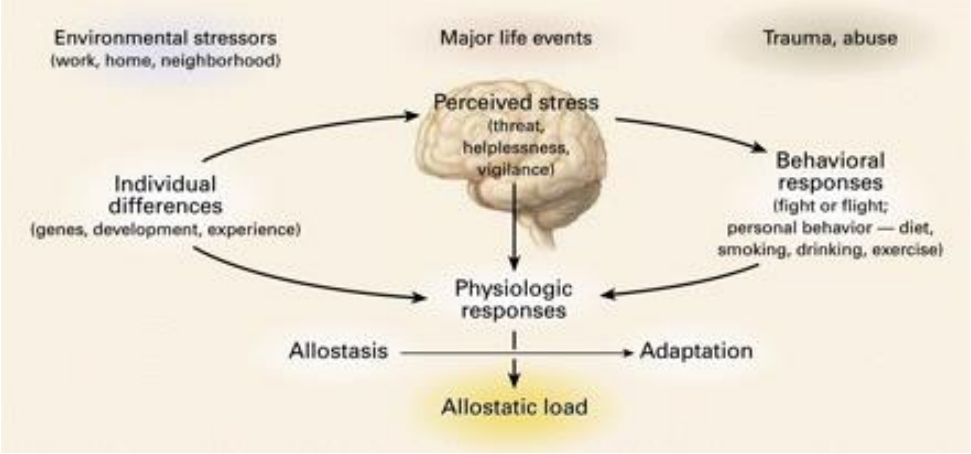

Figure 2 - The theory of allostasis and allostatic load model.
How the physiological response to stress depends on individual differences, perceived stress and the behavioural responses (McEwen, 1998a), permission obtained (see appendix A).

2.1.3 Allostatic state and allostatic load

McEwen & Stellar (1993) described 'allostatic state' as a chronic imbalance of the primary mediators of allostasis, resulting from the combined effects of repeated cycles of the physiological response, raised physiological activity and changes in metabolism (McEwen & Stellar, 1993).

The normal allostatic response is demonstrated in diagram A, figure 3. The stress response is initiated by a stressor, continued for an appropriate amount of time, and then switched off. Four situations have been described when elevated or deregulated activity of the primary allostatic mediators occur (McEwen, 1998a):

1. Repeated challenges or 'hits' when an individual is repeatedly exposed to a novel challenge or stressor, returning to normal in-between (figure 3, diagram B).

2. Failure to adapt or adjust to chronic exposure (figure 3, diagram C).

3. A prolonged physiological response and failure to shut off the response to a challenge once it has ceased (figure 3, diagram D).

4. Failure to create an adequate response to a challenge or stressor, for example, one physiological component of the allostatic response does not employ fully and other components will compensate (figure 3, diagram E).

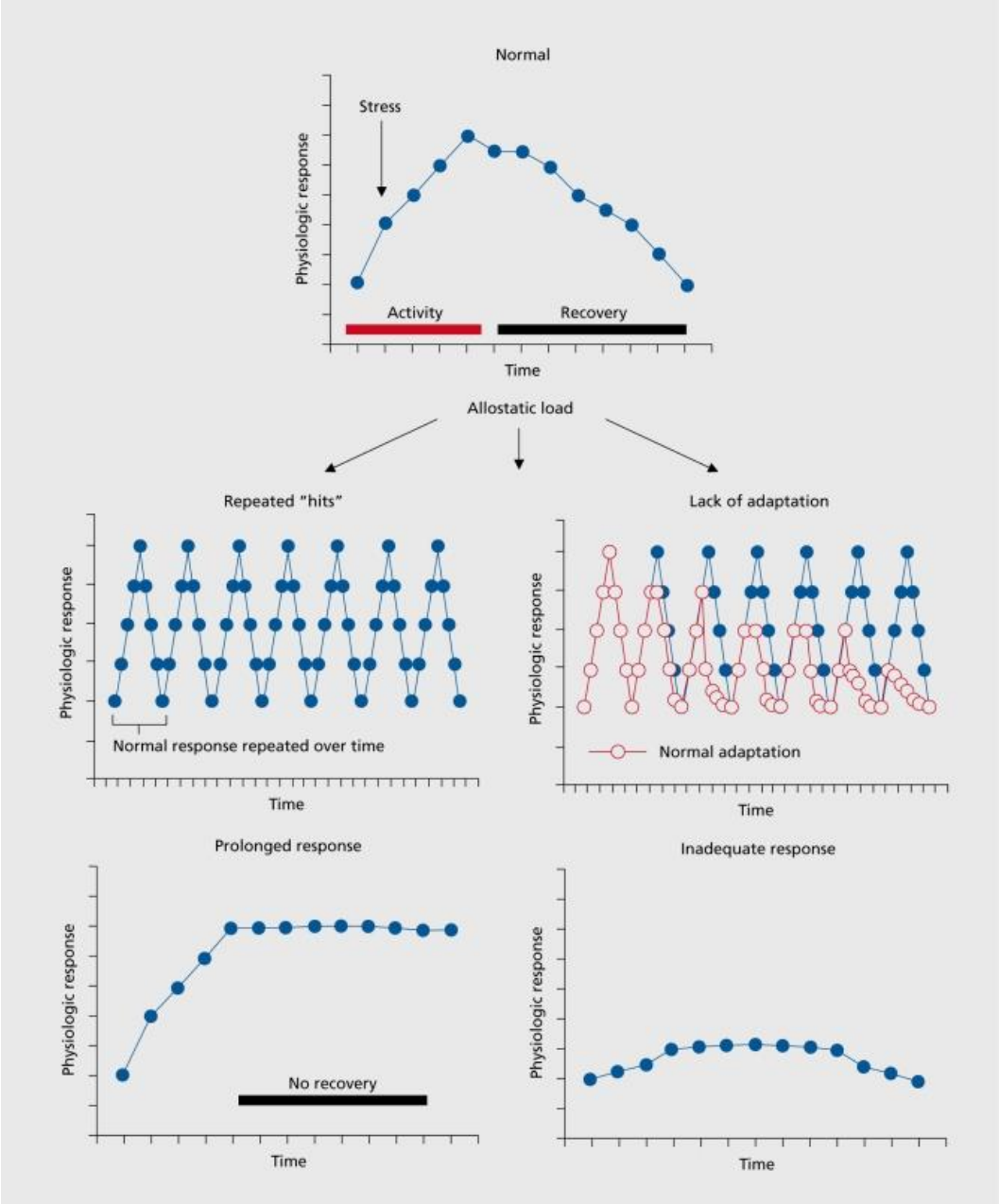

Figure 3 – Conditions that facilitate atypical production of primary allostatic mediators. There are four conditions that deviate from the normal allostatic response (top panel) and lead to allostatic load: repeated hits from multiple stressors (B); lack of adaptation to stressors (C); a prolonged response due to impaired shutdown (D); and inadequate response that causes other mediators to compensate with hyperactivity (E) (McEwen, 1998a, 2006a), permission obtained (see appendix A).

These response profiles of atypical production of primary allostatic mediators could take place alone or in combination. They overlap in their theme of ineffective or overactive management of the primary allostatic mediators. McEwen (2002) argued that these scenarios alter the typical production of primary allostatic mediators, and over time, this modifies the normal regulation boundary, after which they continue to be produced either at an increased or inadequate level, based on an abnormal sequential pattern. Allostatic states, also known as the secondary outcomes of the allostatic load (AL) model, refer to changes from

typical to maladaptive allostatic processes. In this model, metabolic, immune, and cardiovascular parameters reach sub-clinical levels and this deregulation becomes a chronic condition (Juster, McEwen, & Lupien, 2010).

The concept of AL describes the cumulative physiological damage resulting from these secondary outcomes; from prolonged exposure to primary mediators of allostasis (McEwen & Stellar, 1993). AL is the consequence of the over or underactivity of allostatic systems as the HPA-axis, sympathetic nervous system, metabolic, immune, and cardiovascular systems respond to environmental stressors (McEwen, 1998b). It is the inevitable natural damage to organs and tissues, which accumulates over time, and predisposes individuals to serious pathophysiology, morbidity, and mortality. This is the final stage of the AL process known as 'allostatic overload', when the cumulative physiological damage leads to tertiary outcomes such as disease and death (Juster et al., 2010).

The model implies that in measuring relevant blood biomarkers and physical measures of health representing the primary mediators and secondary outcomes (consequences of primary meditators) of the AL process, individuals who are at high risk of the tertiary outcomes may be detectable (McEwen & Seeman, 1999). Some blood biomarkers and physical measures of health, along with guidelines of normative levels, are routinely used by clinicians in medical practice, supporting diagnosis and treatment of illnesses. However by measuring primary mediators as well as secondary outcomes, the aim of the AL model is to identify pre-clinical information to better predict those at risk of developing disease.

2.1.4 Operationalising allostatic load

The concept of allostasis and AL provides a theoretical framework for exploring the effects of chronic stress exposure on health. Empirical literature has developed methods for measuring AL that reflects information on levels of physiological activity across a range of important regulatory systems that are affected by stress; neuroendocrine, immune, metabolic, cardiovascular and anthropometric (Juster et al., 2010). AL scores aim to assess the primary mediators and secondary outcomes of the maladaptive allostatic processes, reflecting change in typical operating ranges and risk of pathology (McEwen, 1998b).

2.1.4.1 Allostatic load, functioning, disease, and mortality research

A large body of scientific literature has used the AL model and AL scores to determine and explore demographic and environmental precursors of several adverse health outcomes and mortality. The following is a summary of this literature. The terminology 'indicator' is used for single biomarkers or physical measures of health such as blood pressure. An 'AL score' is the measure of accumulated physiological damage, calculated in a variety of ways by combining the data from the indicators.

The first studies were the longitudinal MacArthur Studies of Successful Aging, which investigated health outcome in approximately a thousand healthy American older-adults (aged 70-79) (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). These studies created an AL score using 10 indicators, for each, participants were organised into quartiles based on the distribution of the scores for the whole group for that indicator. The number of indicators for which the participant was in the highest-risk quartile (such as highest quartile for systolic blood pressure, and lowest quartile for high density lipoprotein cholesterol, for which low scores indicate high risk) were summed in order to create the AL score. This study also examined other methods of creating AL scores, including using 90%/10% indicator distribution cut-offs for more extreme health risk, and averaging and summing the z-scores of each indicator.

Higher AL scores were associated with lower baseline functioning: weaker physical performance (indicated by timed measure of foot taps, chair stands, gait, balance, and manual ability; r = -0.09; p <0.05) and poorer overall cognitive performance using a composite measure of language, abstraction, spatial ability, delayed spatial recognition, incidental recall of confrontation naming, and delayed recall of a story, (r = -0.13; p <0.001). Comparing the three different ways of creating an AL score, the constructs yielded approximately the same results, although the z-score method yielded the strongest associations.

A 2.5 year follow-up of the same cohort, using the high-risk quartile count method of measuring AL and the same 10 indicators, showed that higher baseline AL scores were associated with declines in cognitive (memory performance, r = -0.08; p <0.05, and verbal memory, r = -0.09; p <0.05), and physical functioning and (r = -

0.12; p <0.005) (Seeman et al., 1997). This was independent of baseline health status and socio-demographic characteristics.

Higher baseline AL scores also predicted all-cause mortality in the same population at 7 and 12 year follow-up using an AL score derived from 10-16 indicators, and calculated using 75%/25% cut-offs based on the group distribution or clinical guidelines for each indicator (Gruenewald, Seeman, Ryff, Karlamangla, & Singer, 2006; Seeman, Crimmins, et al., 2004; Seeman, McEwen, Rowe, & Singer, 2001). A 7.5-year follow-up of 171 participants from this cohort found that a reduction in AL scores (constructed from 10 indicators, scored using a system based on continuous values of risk factors assessed at baseline and follow-up) were associated with decreased risk of all-cause mortality (Karlamangla, Singer, & Seeman, 2006).

A 3 year follow-up of this population of older adults, using a 13 indicator AL score, based on the highest-risk quartile of the distribution of indicators, found high baseline AL scores were also associated with frailty assessed by slow gait, exhaustion, weight loss, weak grip and low physical activity (Gruenewald, Seeman, Karlamangla, & Sarkisian, 2009). A one unit increase in AL scores was associated with a 10% increased risk of frailty.

In a 7-year follow-up study of the same older adults from the above cohort, baseline AL scores derived from the sum of highest risk quartile of 10 indicators, predicted functional decline (Karlamangla, Singer, McEwen, Rowe, & Seeman, 2002). This included physical functioning (gait, hand dexterity, balance, lower extremity strength and lower extremity dexterity) and cognitive functioning (naming, construction, delayed spatial recognition, abstraction and memory).

The link between cognition and AL was also demonstrated by Karlamangla et al. (2014) using AL scores (the sum of highest risk quartile of the distribution of 24 indicator) in 1,076 healthy American participants aged between 49 and 66 (mean = 57 years). Higher AL scores were associated with poorer executive functioning (p <0.001) and episodic memory (p <0.001) after adjusting for age explaining 4.9% and 7.3% of the variance, respectively.

In a different population, a study using data from the Taiwanese Social Environment and Biomarkers of Aging Study (SEBAS), a national sample of around 1,500 adults aged 54 and over, found a 13 indicator AL score (evaluating the explanatory value of the indicators using logistic regression) predicted increased all-cause mortality at 3-years follow-up (Goldman, Turra, Glei, Seplaki, et al., 2006). In follow-up assessments of the same population, but using a 16 indicator AL score (constructed using decile cut-offs (90%/10%), viewing risk as two-tailed, in both low and high scores), higher AL scores were associated with more depressive symptoms (a 10-item version of the Center for Epidemiologic Studies Depression Scale; p <0.001), poorer health (assessed by activities of daily living, self-assessed health, temporal orientation and mobility limitations) and higher cognitive impairments (12 items adapted from three tests: the Short Portable Mental Status Questionnaire, the Rey Auditory Verbal Learning Test, and the Digits Backward test) (Goldman, Turra, Glei, Lin, & Weinstein, 2006; Seplaki, Goldman, Weinstein, & Lin, 2006).

Further evidence of the utility of AL scores in predicting poor health outcomes in a group of adults from a wider age range was demonstrated using data from almost 14,000 participants aged 20 years and over in the National Health and Nutrition Examination Survey (NHANES), linked to the National Death Index (Borrell, Dallo, & Nguyen, 2010). After controlling for education, income, age, gender and ethnicity, high AL scores (summed high risk quartiles of 9 indicators) were associated with a 40-88% greater risk of all-cause mortality compared to those with low AL score.

Using a 13 indicator AL score (summed high risk quartiles) and a 22,000 sample of the same cohort, researchers illustrated that AL increased sharply between the ages of 20 and 60, and then levelled off (Crimmins, Johnston, Hayward, & Seeman, 2003). Data from 12,000 participants from the same cohort established that those with higher AL scores (a continuous score assessed using 9 indicators, summing the number of indicators above a high-risk clinical cut-off) had a life expectancy that was 6 years shorter compared to those with lower AL scores, matched for gender and poverty status (Crimmins, Kim, & Seeman, 2009).

In each of these studies described above, increased AL was associated with poorer outcomes over time, in terms of poor health, cognitive and physical functioning and mortality. This trend persisted across socioeconomic and ethnic groups.

2.1.4.2 Evidence for combining scores

Measures of multi-system physiological damage, or AL, are not used in clinical practice. However there is evidence from the AL literature that individual blood biomarkers and physical measures do not explain tertiary outcomes as well as total AL scores, supporting the use of a multi-system composite approach. In Karlamangla et al., (2002) total AL scores were superior to individual indicators in predicting functional decline in older adults in a 7-year follow-up study. Also AL scores were a better predictor of mortality and decline in physical functioning than individual indicators in a population of relatively high-functioning older adults (Seeman et al., 2004).

However, despite the evidence that summary measures of AL provide important explanatory information in research investigating health outcomes, functioning, and mortality in different populations, there is no agreed method for measuring AL.

2.1.4.3 Methods of constructing an allostatic load score

A recent review detailed the full range of algorithmic formulations and statistical techniques used in the AL literature (Juster et al., 2010). One popular method dichotomises individual indicators into high and low risk categories, based on either the distribution of the sample, or recommended clinical cut-offs. The MacArthur Healthy Aging studies were the first to construct an AL score count-based method based on the distribution of the sample (Seeman et al., 1997). Single measures of indicators that fell above the 'high risk' 75th percentile, with respect to the overall indicator distribution of the sample, were dichotomised as '1', and those below the 75^{th} percentile within normal ranges as '0' (Seeman et al., 1997). If the indicator had a positive association with health, such as high density lipoprotein, the lowest quartile corresponded to the highest risk. These values were then summed to give a total AL score, with higher scores indicating greater AL and cumulative physiological deregulation.

However this approach has been criticised as dichotomising scores reduces variation and may not capture the full range of AL (Loucks, Juster, & Pruessner, 2008; Mair, Cutchin, & Kristen Peek, 2011). Disregarding 75% of the blood biomarker or physical measure data (by scoring as 0) reduces the power and precision available for later analysis (Vie, Hufthammer, Holmen, Meland, & Breidablik, 2014). Also the cut-off values used to define 'at risk' will vary depending on the health of the population being studied (Gersten, 2008; McDade, 2008).

Another commonly used method to create a total AL score is to create a z-score where each indicator has a mean of 0 and a standard deviation of 1. AL scores are created by summing the z-scores of indicators. This method of standardising values enables indicators of different natures to be compared to one another whilst maintaining the continuous disposition of the blood biomarkers and physical measures, and of AL. However this method can attribute unequal weights across the five biological components of AL (neuroendocrine, immune, metabolic, cardiovascular, and neuroendocrine Juster et al. (2010)), if the number of indicators within the components is unequal. To compensate for this, studies can create a mean score of blood biomarkers and physical measures for each of the five components, and then summate the five means to create a total AL score (Hickson et al., 2012). This produces an equal weight for the five health system components that contribute to overall AL.

Research comparing these two methods of constructing AL scores have not shown that either is superior in predicting health outcomes (Hampson, Goldberg, Vogt, Hillier, & Dubanoski, 2009; Langelaan, Bakker, Schaufeli, van Rhenen, & van Doornen, 2007; Mair et al., 2011; Seeman et al., 1997). However, some have argued that as the z-score method uses the full continuum of indicators, it more accurately reflects the continuous nature of the indicators and of cumulative AL, than the cut-off method (Hawkley, Lavelle, Berntson, & Cacioppo, 2011; Hickson et al., 2012; Mair et al., 2011).

In addition to the lack of consensus over the method for combining biomarker scores to construct an AL score, there is little agreement about how many and which indicators to include in the composite measure of AL (Gersten, 2008; Loucks et al., 2008; McDade, 2008). A recent review of 58 papers found a total number

of 51 indicators have been used in varying numbers and combinations across the AL literature (mean 10.6; SD 3.1; range 4-17) (Juster et al., 2010).

In order to decide what indicators of health to include, and how to combine them to create an AL score in this research, it was necessary to conduct a systematic search of the AL literature to investigate whether any studies have evaluated indicator inclusion and AL score construction.

2.2 Systematic Search

2.2.1 Introduction

A systematic review published in October 2012 examined literature that measures AL, to evaluate its predictive utility for a variety of health outcomes (Beckie, 2012). PubMed (1966–2011), CINAHL (1994–2011), and PsycINFO (1985–2011) databases were searched using the key terms 'allostasis' or 'allostatic load'. Titles, abstracts, and full papers were searched, resulting in a total of 148 English-language published abstracts. An additional manual search of references of all the manuscripts and websites, added 37 publications, producing a final total of 185. The review included human studies, those exploring age, ethnicity, socioeconomic status and gender differences in AL and studies investigating the association between AL and health outcomes. It excluded commentaries, book chapters, editorials, review articles, studies lacking multisystem physiological AL measures, experimental stress response studies and studies involving children or adolescents.

The review did not assess the quality of the studies. However, the author concluded that there was "considerable heterogeneity in the operationalisation of AL and the measurement of AL biomarkers, making interpretations and comparisons across studies challenging". Despite this, there was evidence for an association between AL scores and mental and physical health, and all-cause mortality.

This review did not search for studies that evaluated the predictive value of blood biomarkers and physical measures, used to represent AL, in predicting poor health outcomes or mortality. Nor did it examine papers that compared methods of constructing an AL score. Furthermore, there are alternative phrases used

repeatedly by some researchers to describe AL, such as 'cumulative biological risk' (Hickson et al., 2012; Merkin et al., 2009; Seeman, Glei, et al., 2004), 'multisystem biological risk' (Booth, Starr, & Deary, 2013; Carroll et al., 2015; Seeman et al., 2010), and 'physiological dysregulation' (Dich et al., 2015; Milot et al., 2014; Wu et al., 2015) that were not included as search terms.

Therefore, the literature review by Beckie et al., (2012) was repeated and updated using the same databases, and two additional databases (Embase and Cochrane), and adding the search terms: 'cumulative biological risk' 'multisystem biological risk', and 'physiological dysregulation'. The initial search took place on the 9th July 2015 and the last date the search was updated was 30th January 2016.

My review addresses two research questions:

Review question 1: Have studies used and evaluated different methods to construct an AL score in a population of adults?

Review question 2: Have studies evaluated different combinations of indicators of AL to predict or be associated with health outcomes?

2.2.2 Methods

2.2.2.1 Eligibility criteria

Studies were included if they measured an AL score in adults aged 18 or over. Studies that included participants over the age of 65 years, and did not report data separately for participants younger than 65, were not included. This is because previous literature has shown that AL scores plateau during the 6th decade and beyond, therefore inclusion of older participants is not informative in relation to the review questions (Crimmins et al., 2003). Studies that measured AL in children or animals were not included as this thesis concerns AL in adults. AL was first described in 1993 so the earliest date that was searched was 1985 (McEwen & Stellar, 1993). Only papers written in English were included.

2.2.2.2 Sources

CINAHL, Medline (Ovid), Embase (Ovid), Cochrane and psycINFO were searched via the Glasgow University library online services (http://eleanor.lib.gla.ac.uk/search~S0/y).

2.2.2.3 Search

The search within the main five databases (CINAHL, Medline (Ovid), Embase (Ovid), Cochrane and psycINFO) consisted of the key terms 'allostasis', 'allostatic', 'cumulative biological risk', 'multisystem biological risk' and 'physiological dysregulation' using the OR function. For the search of Embase and Medline, these key terms were mapped to medical subject headings (MESH headings), helping to find relevant official medical subject headings for the terms ('allostatic' and 'cumulative biological risk' mapped to 'allostasis'). There were two searches, one searched titles and the other searched abstracts. These searches were then combined using the OR function. Additional search limits were added to restrict articles to human participants, written in English, published since January 1985 and on adults over the age of 18.

2.2.2.4 Study selection

After the initial search, duplicate articles were deleted using EndNote software (http://endnote.com/). The articles included in the systematic review by Beckie et al., (2012) were manually checked, generating 4 additional articles. These 4 studies were manually checked, they were not generated in the search because they did not use any of the search terms in the title or abstract. Of the remaining articles, titles, abstracts and, if necessary, full texts were read and the exclusion criteria applied to exclude irrelevant papers (see Figure 4).

2.2.3 Search question 1

"Have studies compared methods of how to construct an allostatic load score?"

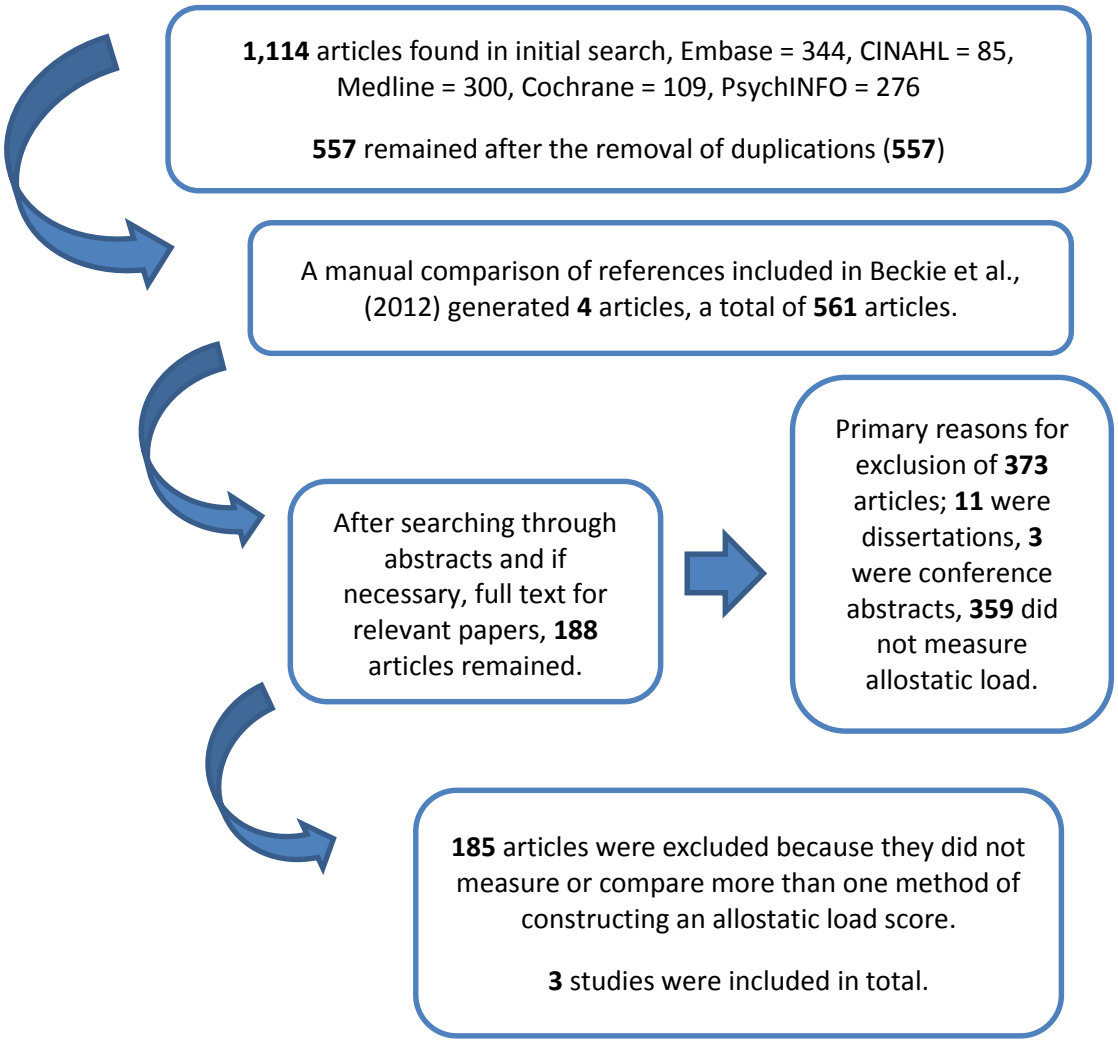

Figure 4 – Flowchart of the study selection process and results for search question 1

2.2.3.1 Results

2.2.3.1.1 Study selection

Figure 4 is the flowchart showing details of the search process and results.

2.2.3.1.2 Study characteristics

Table 1 displays details of the methods used to construct an AL score in the three articles reviewed. They all assessed at least two methods of AL score construction. The number of indicators ranged from 8 to 16; no study included indicators from all five recommended components (Juster et al., 2010).

Table 1- Studies that compare methods of constructing an AL score

Author	Purpose and Design	Sample size	Population: Gender, ethnicity	Method: z-score	Indicators of health	Finding	Covariates	Method conclusion
Hampson, 2009	A cross-sectional study examining the relationship between allostatic load and self-reported health and depressive symptoms s in 40-50 year follow-up of longitudinal Hawaii Personality and Health Cohort.	470	Adults from Hawaii Personality and Health Cohort (Men = 227, Women = 243, Japanese = 198, native Hawaiian = 80, European American = 56, Other = 136). Mean age = 50.	Folded z Linear z-scores Count-based cut point: two tailed 10/90 and 25/75 one tailed >75 and >90	N = 11: Systolic blood pressure, Diastolic blood pressure, total cholesterol, triglycerides, fasting blood glucose, total-to-High Density Lipoprotein cholesterol and urinary protein, Body Mass Index, Waist- to-hip ratio, cholesterol medication, blood pressure medication	Allostatic load in men was greater using one-tailed count and linear Z, but not two tailed count or folded z-scores. Higher allostatic load predicted lower self-rated health for both men and women. Depression associated with higher allostatic load for female linear z-score.	Education	The linear z makes maximal use of the available variance, thus yielding more power; it is recommended over one-tailed count scores.
Langelaan, 2007	A cross-sectional study exploring whether allostatic load mediates the relationship between burnout and physical health in male Dutch telecom managers	290	Dutch managers (All men). Mean age = 43	Sum of Z-scores for each indicator. Sum of number of physical indicators which fell into highest quartile based on group's distribution	N = 8: C-reactive protein, Systolic blood pressure, Diastolic blood pressure, cholesterol. High Density Lipoprotein cholesterol, glucose, Glycated haemoglobin, Body Mass Index	Burned-out managers did not differ from healthy managers with regard to their scores on either allostatic load composite.	Physical activity, smoking	No difference in results found between the two methods of constructing allostatic load scores.
Mair, 2011	A cross- sectional study examining the relationships between allostatic load, gender and stressors (environmental risks) in residents of Texas	1,072	Texas city Stress and Health Study (2004-2006) (Women = 526, Men = 445, Mexican American-US born = 400, Mexican American-Foreign Born = 130, Black = 116). Mean age 51.6	Sum of Z-scores for each blood biomarker and physical measure. Cut-offs (not reported)	N = 16: C-reactive protein, Interleukin-6, Tumor necrosis factor α, Interleukin-1, Interleukin-10, Latent EBV-capsid antigen, Early antigen EBV nuclear antigen HSV-1, Systolic blood pressure, Diastolic blood pressure, Ratio of Total/HDL cholesterol, Glycated hemoglobin, Triglycerides, High Density Lipoprotein cholesterol, Body Mass Index	Stressors (residential proximity to petrochemical plants, perceived poor neighbourhood conditions, and daily hassles) was associated with higher allostatic load in men and women.	Education, perceived stress, chronic health conditions, marital status, income, social support, smoking, health insurance, physical activity	No differences between methods, however dichotomised cut-offs method reduces variation and may not capture the full range of allostatic load therefore authors opted to use z-score method.

The outcomes in the three studies ranged from self-reported health (SF-36), depressive symptoms (modified version of the Center for Epidemiological Studies Depression scale), burnout in workers (Maslach Burnout Inventory- General Survey), to gender and environmental stressor (subjective assessment of exposure to petrochemical plants and concern about petrochemical health risks, neighbourhood perception assessed using the Perceived Neighbourhood Scale, negative life events measured using the Life Events Stressor Scale, and daily hassles assessed using the Daily Hassles Scale).

2.2.3.1.3 Description of allostatic load construction methods used

Hampson et al. (2009) constructed six scores for AL. Four were count-based AL scores, defined using the sample distributions of the indicators. Of these four, two included both tails of the distribution of the indicators (systolic and diastolic blood pressure, total cholesterol, triglycerides, fasting blood glucose, BMI and waist/hip ratio); one used the 10th and 90th centiles, and one used the 25th and 75th. The remaining two count-based AL scores were one-tailed and used a cut-off for each indicator; one used 75^{th} centile and the other 90^{th}. To create a total AL score for each of the four count-based methods, the number of scores falling at the extremes of the distribution for each indicator was summed. An additional point was added for medications for high blood pressure and for high cholesterol because the measures of blood pressure and cholesterol scores could be reduced as a result of taking this medication.

For the two continuous summary measures, two scores were created. The first was a two-tailed count score; this was a folded z-score summary with the sum of the absolute standardised distances of each indicator from its respective mean (i.e. z-scores and 'folded' in respect of treating deviations above and below the mean as the same for systolic and diastolic blood pressure, total cholesterol, triglycerides, fasting blood glucose, BMI and waist/hip ratio but only deviations above the mean were included for the ratio of total-to-HDL cholesterol and urinary protein). Finally, one-tailed count linear z-scores were created by summing the standard deviations from the mean of all the indicators (positive deviations above the mean plus negative deviations below the mean). Again, if participants were taking medications for high cholesterol or blood pressure, this was accounted for by creating a z-score for these dichotomous variables and adding them to the total

summary z-scores. For all of the summary measures, higher scores indicated higher AL.

Langelaan et al. (2007) created two AL scores. The first was the sum of z-scores for each indicator of health (n = 8). The other was a count based measure, summing the indicators that fell into the highest risk quartile based on the distribution of the sample.

Mair et al. (2011) opted to create two AL scores, the first by summing z-scores of the 16 indicators of health. The data were stratified by gender in order to generate gender-specific z-scores. Total scores were also created for cardiovascular, metabolic, inflammatory, and immune components of AL by summing the z-scores of the indicators within those components. A count based measure of AL was also constructed, identifying high risk cut-offs for each indicator of health and summing the resulting binary scores. The value and source of the cut-offs were not reported.

2.2.3.1.4 Study results and conclusions

Hampson et al., (2009) correlated AL scores and two health outcomes in 445 men and 627 women: self-rated health and depressive symptoms (see table 2). All six constructs of AL correlated significantly with self-rated health, in both genders, and the linear z-score construct only correlated with depressive symptoms in women.

	Correlations between allostatic load and self-rated health		Correlations between allostatic load and depressive symptoms	
Count measures	Men	Women	Men	Women
Count 10/90	−0.23, p <0.01	−0.15, p <0.05	0.05, p >0.05	0.03, p >0.05
Count 25/75	−0.23, p <0.01	−0.11, p >0.05	−0.02, p >0.05	−0.05, p >0.05
Count >90	−0.31, p <0.01	−0.18, p <0.01	0.05, p >0.05	0.06, p >0.05
Count >75	−0.32, p <0.01	−0.16, p <0.05	−0.00, p >0.05	0.10, p >0.05
Continuous measures				
Folded z-scores	−0.29, p <0.01	−0.12, p <0.05	0.06, p >0.05	−0.00, p >0.05
Linear z-scores	−0.32, p <0.01	−0.18, p <0.01	0.05, p >0.05	0.14, p <0.05

Table 2 – Correlations between constructs of AL and self-rated health and depressive symptoms from Hampson et al. (2009)

All but the two-tailed count measure in women correlated significantly with self-rated health and the only significant association with depressive symptoms was with the linear z-score measure in women; demonstrating concurrent validity of those measures of AL with the respective outcomes. However the strength of the associations with self-rated health are not distinguishable between the different measures of AL; mostly moderate in men and small in women. Thus, it is not clear from these results which measure of AL is better.

The authors argue that because linear z-scores allow maximal use of the variance within each indicator, there is more power to detect an effect, and they recommend z-scores rather than one-tailed count-based scores for this reason. However this conclusion appears to be based on theory rather than the results from this study as the strength of association is only slightly different for the one-tailed and two-tailed constructs. It is important to note that overall, the correlations are small to medium, indicating that these constructs only explain a modest amount of variation in the outcome measures.

It is difficult to base solid conclusions on this study due to the limited choice of outcomes. Even though these findings demonstrate concurrent validity for the use of continuous and two-tailed methods of constructing AL scores with self-rated health, they cannot be generalised to the study of other outcomes. Also, to test

the concurrent validity of a construct, it should be associated with a previously established measure of the same construct (Stangor, 1998). It is not well evidenced that self-reported health correlates with AL; therefore concurrent validity of the AL constructs cannot be confirmed from these findings. It is also important to emphasise the weakness in measuring self-reported health, which may be vulnerable to systemic self-serving bias; a cognitive process of viewing oneself, in this case self-rated health, overly favourably. The design of the study (cross-sectional) and the analyses used also limit the conclusions that can be made because test-retest reliability or predictive validity of the AL scores cannot be established from these findings.

Langelaan et al., (2007) established individuals in the 'burned-out' group showed no significant difference from a healthy control group on two AL constructs (z-score construct: multivariate $F(290) = 0.02$, $p > 0.05$; quartiles construct: multivariate $F(290) = 1.04$, $p > 0.05$). From these limited results and given the cross-sectional nature of the study, conclusions cannot be drawn regarding the reliability or validity of the two different AL constructs.

Finally, using the z-score method of constructing AL scores, Mair et al., (2011) demonstrated that men had higher AL than women ($p < 0.05$), and higher AL was associated with self-report of more 'daily hassles' ($p < 0.05$). After controlling for education, smoking behaviour, income, chronic health conditions, exercise behaviour, social support, perceived stress, marital status and health insurance, AL was also associated with more negative life events ($p < 0.05$), and greater concern about petrochemical health risks ($p < 0.05$). The authors state that "results from this z-scored summation variable creation method did not differ significantly from results using the dichotomous summation method". However they do not report the values for the dichotomous summation method making conclusions difficult with regard to AL constructs used in this study.

These studies suggest that there is some evidence for the concurrent validity of the z-score measure of AL in self-report of perceived 'daily hassles', the number of negative life events, and concerns about petrochemical health risks; the strength of this is the use of more than one validated outcome to test the validity of the AL constructs. However, similar to Hampson et al. (2009) none of these measures are established as being strongly associated with AL. Therefore it is

difficult to conclude if the z-score method of AL used in Mair et al. (2011) has concurrent validity. In addition, the lack of reporting of the dichotomised AL score results makes it impossible to compare the validity and reliability of the two different constructs.

2.2.4 Discussion

Systematic search question 1: Have studies compared methods of how to construct an allostatic load score?

There is evidence from these studies that some of the constructs of AL demonstrated concurrent validity; however it is difficult to make any solid conclusions regarding which construct is better. Mair et al. (2011) found a z-score measure of AL correlated with higher self-report of 'daily hassles', negative life events, and greater concern about petrochemical health risks, however they did not report the findings from the dichotomous measure of AL. Langelaan et al. (2007) found no association with 'burn-out' and no differences between the two different methods tested in their study. Hampson et al., (2009) was the only study to report associations using six constructs of AL with self-rated health (and a z-score measure was associated with depressive symptoms in women); however the strength of the associations was similar for all constructs of AL, therefore it is ambiguous from these results if one method is better than the others.

Importantly, the outcomes in the papers in this review are not relevant to the outcomes in the studies in this thesis (e.g. disability outcome); therefore it is difficult to make conclusions about which construct of AL would be best to use in the research in this thesis. Further, not only were the outcome measures in the three studies few and specific, which would also make it difficult to generalise the findings to the investigations of other outcomes with AL, but the choice of outcome measure is questionable if the aim of the studies was to test the validity of the constructs of AL. None of the outcome measures were selected based on theoretical or scientific evidence that they would have strong associations with AL e.g. illnesses, cognitive or physical functioning; therefore, even if strong associations were found, concurrent validity of the constructs of AL cannot be concluded with confidence. In order to fully test the validity of a construct of AL, it should be compared with a previously validated outcome or measure of that

same variable (Stangor, 1998). For example, AL is well evidenced as being associated with cognitive (Goldman et al., 2006; Karlamangla et al., 2014; Seeman et al., 1997; Seplaki et al., 2006) and physical functioning (Gruenewald et al., 2009; Karlamangla et al., 2002; Seeman et al., 1997). Therefore future research attempting to test methods of constructing AL scores should look towards using outcome measures such as cognitive or physical functioning in order to be able to make strong conclusions regarding concurrent validity.

All three papers are cross-sectional studies and as such are limited in their ability to evaluate the AL constructs because they do not test the predictive validity of these constructs over time, or examine test-retest reliability by repeating the assessments in the same sample, in a different sample, or with different outcome measures. Hence, there is little evidence in the literature to guide the construction of AL scores.

Ideally to test the validity of AL constructs, a study would use a large cohort, representative of a wide span of ages, equal number of genders and a mix of ethnicities in order to be able to generalise the results to multiple populations. The study would be longitudinal with multiple samples taken at different time points in order to assess predictive validity, and test-retest reliability. A multitude of outcomes (for example different measures of cognitive and physical functioning) would be assessed that are known to be affected by of high AL. Finally, the study would compare all the known methods for constructing AL scores. With these data, analyses could be conducted to elicit the most reliable and valid construct of AL to be used in future research. Also, in terms of the internal consistency of a construct, the decision to use one- or two- tailed measures of risk should be informed by the nature of indicators being measured; for instance, high scores on some indicators of health have negative health consequences and others have positive consequences.

2.2.5 Search question 2

"Have studies evaluated different combinations of indicators of allostatic load in predicting or being associated with health outcomes?"

2.2.5.1 Method

The sources, search, and study selection method used for the first systematic search were repeated.

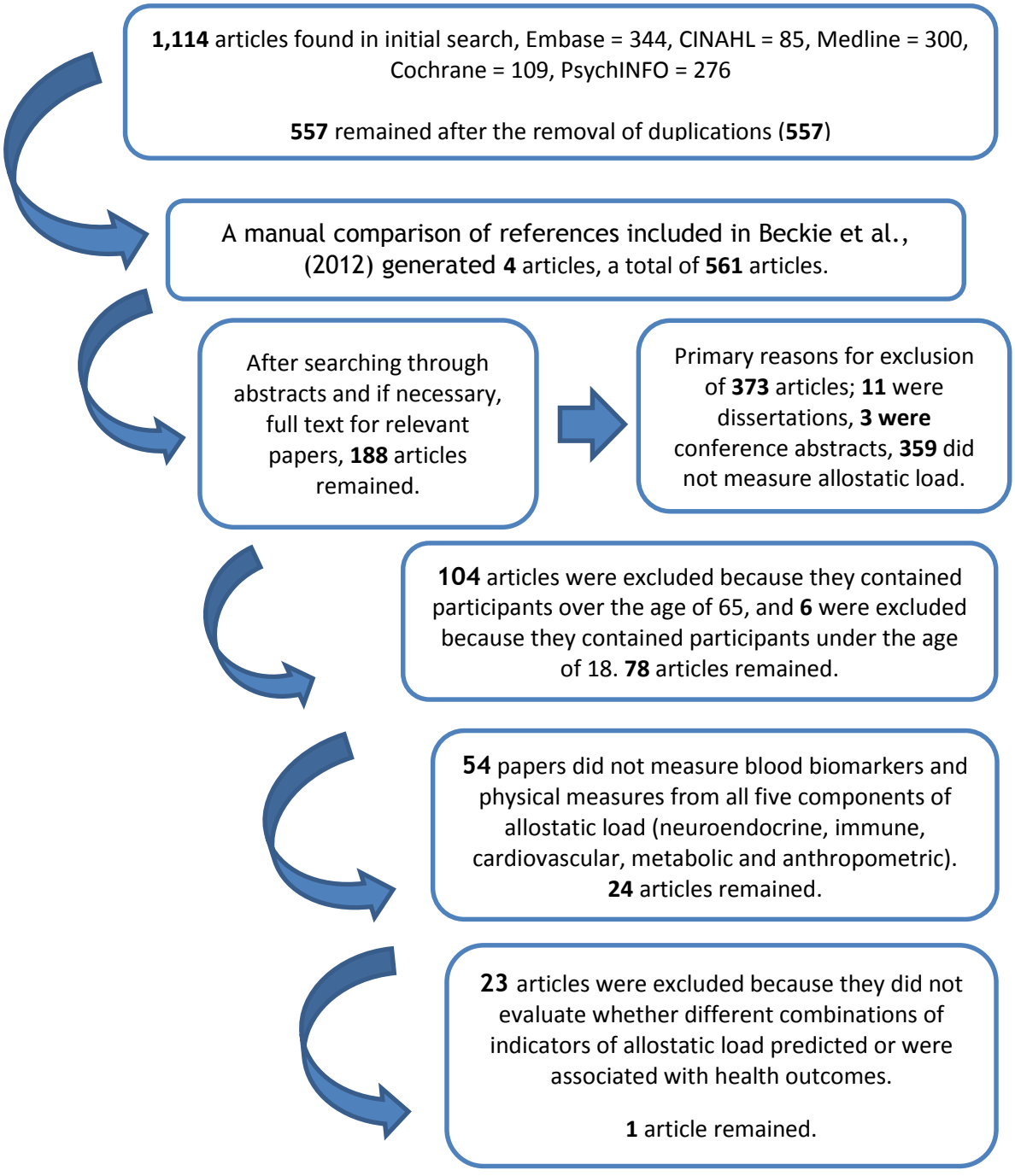

Figure 5 – Flowchart of the study selection process and results for search question 2

2.2.5.2 Results

2.2.5.2.1 Study selection

Figure 5 is a flowchart showing details of the search process and results.

2.2.5.2.2 Study characteristics

Table 3 displays details of the only study that evaluated the indicators used to construct an AL score. Seeman et al. (2010) used structural equation modelling to support the existence of an overarching AL factor comprising physiological dysregulation across 6 six biological systems (inflammation, blood pressure, heart rate variability, metabolism, sympathetic nervous system activity, and HPA activity) and 18 indicators of health (see table 3). The 6 biological systems loaded onto a total AL construct, reflecting a shared variance of 84%. This evidence supports the idea that there is a core of common or shared variance and therefore inter-relationships between the six biological systems, providing support for a multi-factor model of AL (Seeman et al., 2010).

However this study did not evaluate individual or groups of indicators in association with or predicting health outcomes. Therefore no studies were generated in the systematic search that evaluated the association or predictive value of individual or combinations of indicators that represent AL, with health outcomes. Thus, there is no evidence base to distinguish strong from weak indicators of AL.

Author	Purpose and design	Study population	Mean age (range)	Methods for creating total score	Mediators / confounders	Biomarkers (N)	Evaluate biomarkers?	Justify markers?	Finding
Seeman et al, 2010	A cross-sectional study: structural equation modelling used to test a hypothesised meta-factor model of allostatic load composed of a number of biological system factors, and to investigate model invariance across gender and ethnicity	Adults from American sites of the Coronary Artery Risk Development in Young Adults Study (n = 782; Female = 453, Men = 329, Black = 428, Caucasian = 354)	40 (32-47)	Structural equation modelling (SEM) analyses was employed to estimate alternative models of the "structure" of AL and to test for factorial invariance of the final structural model across gender and ethnicity.	NR	18 Immune (3): CRP, IL6, fib Neuroendocrine (4): Cort x 2, EPI and NE Cardiovascular (5): SBP, DBP, HR, low freq and high freq HR Metabolic (5): HDL, LDL, trig, insulin, fasting Gluc Anthropometric (1): waist circumference	no	Selected to reflect the activity and functioning of major biological regulatory systems known to affect health	A "meta-factor" model of allostatic load as an aggregate measure of six underlying latent biological sub-factors (blood pressure, metabolic parameters, markers of inflammation, heart rate variability, sympathetic nervous system activity and hypothalamic-pituitary-adrenal axis activity) was found to fit the data, with the meta-factor structure capturing 84% of variance of all pairwise associations among biological subsystems. There was little evidence of model variance across sex and/or ethnicity. The correlated six-factor model provided a much better fit to the data. Loadings similar in 4 gender/ethnicity groups.

Table 3 - Study that investigates the shared variance of 6 biological systems of AL
Cort = cortisol, CRP = C-reactive protein, DBP = diastolic blood pressure, EPI = epinephrine, Fib = fibrinogen, Gluc = glucose, HDL = high-density lipoprotein cholesterol, HR = heart rate, IL-6 = interleukin 6, LDL = low-density lipoprotein cholesterol, NE = norepinephrine, SBP = systolic blood pressure, Trig = triglycerides.

2.2.6 Discussion

No papers evaluate the use of single, or combinations of indicators of AL, in association with or predicting poor health outcomes or mortality.

Further research is needed to understand which indicators of health best represent AL, using a wide variety of indicators, and comparing them with multiple health outcomes. It is also important to measure these indicators from a large and diverse population, to understand how indicators of health vary by gender, race, and age. A longitudinal cohort study would also inform about change in association between indicators and outcomes over time. Valuable knowledge could be obtained regarding the predictive, construct, and content validity of groups of indicators following analyses of these data, which may assist the development of evidence for a standardised set of indicators for measuring AL.

2.2.7 Conclusions

The findings of this systematic search demonstrate that no AL studies have evaluated different combinations of indicators of AL in predicting or being associated with health outcomes, and the few that have compared more than one method of calculating a total AL score found no significant difference between them (Hampson et al., 2009; Langelaan et al., 2007; Mair et al., 2011). These results are novel and they make a unique contribution to the field of AL. It highlights a lack of evidence base for how to create a valid and reliable measure of AL, and the importance of future AL research to aim fill this gap in the literature.

Currently, a full meta-analyses or systematic review of the AL literature may not be meaningful because of variation in the language, choice of indicators, method of constructing AL scores, the population tested, outcomes assessed, and covariates adjusted for in the analysis. A longitudinal study is required in order to assess AL scores over time, using a large and representative sample, measuring a wide number of indicators, all the known methods for constructing AL scores, and a multitude of outcomes known to be consequences of high AL such as illness or mortality. These data would enable statistical analysis such as principal component analysis or factor analysis in order to test the validity, reliability and

predictive models of AL, which can be generalised to the study of other populations. With these issues resolved in the field of AL, researchers can take guidance from a gold-standard method for measuring AL and utilise this potentially helpful tool in other clinical populations.

2.3 Implications for the allostatic load algorithmic formulation in this research

Despite the lack of agreement about how AL should be measured, the Juster et al., (2010) review concluded that it is more important to have biomarkers that represent each of the AL components (cardiovascular, immune, metabolic, neuroendocrine, and anthropometric systems) than the precise indicators used within each component. The findings and conclusions from the Beckie et al., (2012) review are consistent with this view; there is no agreement for the recipe of biomarkers, except to have representatives from each component.

It has been argued that using 'cut-offs' to calculate AL scores may reduce sensitivity when measuring AL (Langelaan et al., 2007; Loucks et al., 2008). For this reason, the z-score method is used in the present research to preserve the continuous nature of the indicators of health, and AL, in order to increase sensitivity and to obtain as much information as possible about AL in the head injury population. The direction of risk for the z-scores (high/low) will depend on the nature and direction of risk for each indicator and is explored in Chapter 3.

In order to obtain a measure of AL that encapsulates accumulated physiological damage over multiple health systems, this research used a range of indicators that represent the five biological components of health in the AL model (cardiovascular, immune, metabolic, neuroendocrine, and anthropometric) (Beckie, 2012; Juster et al., 2010; McEwen, 2003). There is no evidence base to suggest that any AL component score would predict disability outcome in the studies in Chapters 5-8. The overall AL score was therefore used as the primary measure in this research. However given the limitations of the evidence base, it is possible that component scores (described in detail in Chapter 3), may be associated with disability outcome (Seeman et al., 1997), hence given the novel and exploratory nature of the research presented here, the relationships between the five component scores and disability outcome were explored. The

measurement of AL is described in detail in Chapter 3, along with the other assessments of the relationship between AL and outcome after HI.

Chapter 3 **Methods**

Background

The relationship between allostatic load (AL) and outcome after head injury (HI) has not previously been investigated. Thus, due to the exploratory nature of this research, the relationship was investigated in four different studies, on participants with different severities and time points since HI.

Methods

Four empirical studies were conducted on the relationship between AL and outcome after HI; these were at discharge from hospital after severe HI (n = 35), at 6 month follow-up (n = 28), late (median 27 years) after HI (n = 41), and late after repeat concussion in retired international rugby players (n = 48). Allostatic load was also compared with cognitive function late after moderate-severe HI and repeat concussion and with change in disability between hospital discharge and 6 month follow-up, and from 6 months post-discharge to late after injury. In all the studies, the AL scores of HI participants were compared to those of non-HI comparison participants. The measure of AL representing immune, cardiovascular, anthropometric, metabolic, and neuroendocrine system functioning was created using 15 indicators of health that were combined using a summation z-score method to create AL scores.

Conclusions

Assessing AL using the same measure in 4 different HI samples, at different time points since HI, enabled the research to more systematically investigate potential relationships between AL and outcome after HI.

Chapter 1 highlighted the inconsistency in head injury (HI) literature of factors that have been shown to predict outcome at different time points after HI. Chapter 2 described the allostatic load (AL) model, which may explain the differences in health, lifestyle and outcome previously observed in a HI population late after injury, compared with community controls (McMillan et al., 2014). Yet previously the relationship between AL and outcome after HI has not been examined. This chapter describes how this relationship was explored in a series of 4 empirical studies.

To investigate whether outcome after HI is explained by AL, a number of variables were assessed. These are categorised into group characteristics, main outcomes (measures of disability after HI and AL), and confounders. The following describes these variables in detail and how they were assessed.

3.1 Group characteristics

As described in Chapter 1, HI is heterogeneous in nature. For this reason, it is important to describe the characteristics of the HI group, in order to compare the studies in this thesis to other research, and for future researchers to be able to compare the findings in this thesis to new research.

3.1.1 Demographics of head injury and comparison participants

Information about age, gender, social deprivation (postcode: see below) for HI and comparison participants were obtained by interviewer-completed questionnaire. These factors were used to match HI and comparison groups in Chapters 5 and 6, and any differences between groups in these characteristics in Chapters 7 and 8 were controlled for in the analysis. The ethnicity of participants in this research reflects the Scottish population and is largely Caucasian (Chapter 5: 94%; Chapter 6: 93%; Chapter 7: 100%; Chapter 8: 100%), therefore meaningful analyses could not be conducted into differences in AL or outcome after HI in relation to ethnicity.

3.1.1.1 Social deprivation

The Scottish Index for Multiple Deprivation (SIMD) 2012 was used to determine socioeconomic deprivation in Chapters 5 to 8. SIMD is derived from a ranking of

postcodes (http://www.scotland.gov.uk/Topics/Statistics/SIMD/) and is recommended as an indicator of deprivation in Scotland by the Information Services Division of NHS Scotland and the Scottish Government (Bishop, Clark, Harris, Stockton, & Sutton, 2004). Postcodes are organised into 6,505 datazones, each datazone contains around 350 households. The characteristics of each datazone, (employment, education, skills and training, income, housing, health and crime, are used to attribute a SIMD score, which is ranked from 1 (most deprived) to 6,505 (least deprived). The characteristics of the data are derived from several sources, including; the Work and Pensions Longitudinal Study, NOMIS (a web-based database of labour market statistics), National Records of Scotland, local authorities and managers of mainstream grant-aided schools, General Register Office for Scotland, National Public Transport Data Repository, and Scottish Police Forces. SIMD 2012 was used for this research; it is the most recent SIMD dataset available, based on postcodes in the year 2012. SIMD (2012) quintiles for the general population were used, ranging from 1 (most deprived) to 5 (most affluent).

3.1.1.2 Health information

In order to understand the health of participants, they were asked how many physician diagnosed chronic illnesses they had, how many and what medications they took, and to subjectively rate their health on a Likert scale as 'Very Good', 'Good', 'OK', 'Poor', or 'Very Poor' scored from 1 to 5. This information was obtained by interviewer-completed questionnaire. These data enabled the investigation of differences in these secondary indicators of health between HI and comparison groups in Chapters 5 to 8.

3.1.2 Alcohol use of head injury participants

Substance and/or alcohol misuse is common after HI; one study reported that 25% of 121 HI participants were drinking at hazardous levels on the Alcohol Use Disorder Identification Test (AUDIT) two years post-injury (Ponsford, Whelan-Goodinson, & Bahar-Fuchs, 2007). Alcohol abuse post- HI might potentiate neuropsychological impairments and impede successful rehabilitation (Corrigan, 1995; Solomon & Malloy, 1992).

The AUDIT (Saunders, Aasland, Babor, Delafuente, and Grant (1993); Appendix C) was used to screen for alcohol intake in the 6 months prior to assessment in Chapter 6, and in the 12 months prior to assessment in Chapters 7 and 8. It is a 10 item self-completed questionnaire that assesses alcohol consumption, alcohol dependence and alcohol related problems. Each question is scored on a 0-4 point scale. Total scores range from 0 to 40; a score of 8 or more indicates a strong likelihood of hazardous or harmful alcohol consumption and scores of 20 or above suggest alcohol dependence (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001).

3.2 Main outcomes

3.2.1 Assessment of disability after head injury

3.2.1.1 The Glasgow Outcome Scale- Extended

Disability outcome in the HI participant group was a primary outcome in this thesis. The Glasgow Outcome Scale is an assessment of global disability following HI (Jennett & Bond, 1975) and is the most widely cited assessment of outcome after HI (King et al., 2005; McMillan et al., 2015). The original GOS was developed into the Glasgow Outcome Scale-Extended (GOS-E; Wilson et al. (1998); Appendix C), which enables more detailed categorization of outcome after HI. The GOS/GOS-E is for use in the community (Chapters 6, 7, and 8): the scale ranges from 8 (Upper Good Recovery) to 1 (Dead), and is based on the ability of participants to care for themselves, return to work, engage socially and in leisure activities, and on symptoms of HI and whether they have an impact on daily life. Outcome is determined by structured interviews with the participant and care/ nursing staff or relatives, and from information in the medical records. The GOS-E is quick to administer and is a valid and reliable measure of disability following HI (Hudak et al., 2005; Wilson et al., 1998).

The GOS-E showed good interrater reliability (Kappa of 0.85) in a sample of 50 mild-severe HI participants 5-17 months post-injury (Wilson et al., 1998). Later in 135 mild-severe HI participants assessed 5-10 months post-injury, the GOS-E established high concurrent validity with two measures of severity of HI (GCS: r_s = 0.32; p <0.01, and PTA: r_s = -0.52; p <0.01), and the Disability Rating Scale (r_s = -0.89; p <0.01), an assessment of sequelae of injury (Wilson, Pettigrew, & Teasdale, 2000).

3.2.1.2 The Glasgow Outcome at Discharge Scale

If the participant was in hospital or inpatient rehabilitation at the time of assessment (Chapter 5 and 6), the Glasgow Outcome at Discharge Scale (GODS) was used (McMillan et al. (2013); Appendix C). The GODS is a measure of functional outcome after HI designed to be used in an inpatient setting, and was developed from the GOS-E using the same outcome categories (Appendix D, table 1). It is a reliable and valid tool, which has high concurrent validity with the Disability Rating Scale in hospital (r_s = -0.728; 95% CI: - 0.819, - 0.601) and good predictive validity with GOS-E scores (r_s = 0.512; 95% CI: 0.281, 0.687) at follow-up within a few weeks of discharge from hospital (McMillan et al., 2013). Change in disability post-discharge, (leading to lower predictive validity), was a result of unexpected deterioration in 4 participants (7%; 2 deteriorated neurologically and needed CT, 1 had a heart attack and 1 developed severe anxiety post discharge) and 4 improved (7%) with resolution of impaired balance in 3 and symptoms of vomiting in 1. Despite this, the sensitivity of the GODS in predicting outcome after discharge was high (89%; (95% CI: 75% to 97%). Given these results, scores on the GODS and the GOS-E can be interpreted as equivalent (Appendix D, table 1), even though the assessments are in different environments.

To improve statistical power (Narayan et al., 2002), occasionally scores on the GODS and GOS-E were dichotomised into two categories 'Good Recovery', defined as scores of 7 (Lower Good Recovery) and above, and 'Disabled', for scores of 6 (Upper Moderate Disability) and below (see also McMillan et al. (2015)).

3.2.2 Allostatic load

The other main outcome was AL. As described in Chapter 2, there is no single agreed method for creating an AL score. As concluded after the systematic search of relevant literature, selecting a broad range of indicators of health seems ideal for representing all five components of health in the AL model; cardiovascular, immune, metabolic, neuroendocrine, and anthropometric, and the z-score method of constructing an AL score best preserves the continuous nature of the data. The following describes which indicators of heath were selected, and how AL scores were constructed.

3.2.2.1 Indicators of health

In the studies described in Chapters 5 to 8, AL is a composite measure derived from 15 indicators: 9 blood biomarkers and 6 physical measures of health. The indicators of health were selected to represent primary mediators and secondary outcomes of neuroendocrine, immune, anthropometric, cardiovascular and metabolic system functioning (see Chapter 2), based on the AL theory and supported by recent reviews (Beckie, 2012; Juster et al., 2010; McEwen, 1998b; McEwen & Seeman, 1999; McEwen & Wingfield, 2003). These systems are affected by stress and the selected indicators of health are associated with tissues and organs that are affected by AL; cardiovascular disease and atherosclerosis, inflammation and the immune system, metabolic process and adipose tissue deposition (Maselko, Kubzansky, Kawachi, Seeman, & Berkman, 2007). Indicators of health were also chosen on the basis of their use in previous AL research (Appendix D, tables 2 and 3).

Some blood biomarkers used in AL research impose restrictions on venepuncture conditions, such as time of day restrictions for biomarkers with diurnal variation (cortisol) and biomarkers that are affected by food intake requiring participants to fast (insulin and glucose). These restrictions could not be met for HI participants recruited as inpatients or followed-up in the community. Therefore, practicality of sample collection was a factor considered in the selection of the indicators.

Neuroendocrine	
Dehydroepiandrosterone sulphate (DHAS)	DHAS is the sulphated end product of dehydroepiandrosterone, a specific marker of adrenal androgen production. It has a role as a hypothalamic–pituitary–adrenal (HPA) axis antagonist; decreasing insulin resistance, improving lipid metabolism and suppressing inflammatory cytokines.
Aldosterone	Aldosterone is a steroid hormone produced by the adrenal gland. It is important for maintaining water and salt balance in the body and regulating blood pressure.
Anthropometric	
Body mass index (BMI)	BMI is derived from the height and weight of an individual. The index is created by dividing weight in kg by height in metres squared.
Waist-to-hip ratio (WHR)	WHR is the circumference of the waist divided by the circumference of the hips.
Metabolic	
High density lipoproteins (HDL)	HDL is synthesized in the liver. It is known as 'good cholesterol' because it absorbs cholesterol, and transports it from tissue to the liver, where it is excreted in bile.
Creatinine	Creatinine is a chemical waste product from normal muscle contractions. It is used as a marker of renal function; as renal function decreases, serum creatinine rises.
Albumin	Albumin is used as a marker of liver function; it decreases under bodily stress e.g. infection or elective operation.
Triglycerides	Triglycerides are lipids found in the blood and stored in fat cells, and are released by hormones between meals to provide energy.
Immune	
Tumor necrosis factor-alpha (TNFα)	TNFα is a cytokine produced primarily by macrophages in response to immunological challenges such as viruses, bacteria, and other cytokines.
C-reactive protein (CRP)	CRP is a protein synthesized by the liver. CRP levels rise at the start of an infection and in response to tissue injury. Release is triggered by inflammatory cytokines.
Interleukin-6 (IL-6)	IL-6 is both a pro- and an anti-inflammatory cytokine. It is produced by T cells and macrophages and assists as an acute reaction in the immune response. It is triggered by to tissue damage and infection.
Cardiovascular/ Respiratory	
Heart rate (HR)	HR (pulses of the heart within a unit of time) reflects variation in cardiac output in relation to metabolic needs, and is associated with coronary blood flow, myocardial oxygen demand and myocardial performance.

Systolic blood pressure (SBP)	SBP is the maximal force exerted by circulating blood upon the walls of blood vessels, during the systolic ventricular contraction period of the cardiac cycle.
Diastolic blood pressure (DBP)	DBP is the minimal force exerted by circulating blood upon the walls of blood vessels, during the diastolic ventricular contraction period of the cardiac cycle.
Forced expiratory volume (FEV)	FEV measures the volume exhaled during the first second of a forced breath. It quantifies the airflow through the bronchi, and therefore, any obstruction.

Table 4 - The 15 indicators of health used to represent AL in this research

3.2.2.2 Data transformation

All data were analysed using the statistical software package SPSS version 22. The raw scores of the 15 indicators were entered into an SPSS data file in preparation for AL score construction and analysis. As discussed in Chapter 2, the z-score method was adopted to create the total AL scores. In combining several indicators of health, it is important that all of the z-scores have the same directional relationship, with higher z-scores indicating greater 'risk' of physiological damage, disease and/or death.

3.2.2.3 Direction of indicators of health in relation to all-cause mortality

The directional relationship between the indicators of health in Chapters 5 to 8, and all-cause mortality are well established.

3.2.2.3.1 Positive, linear relationship with all-cause mortality

The following indicators have a positive, linear relationship with all-cause mortality: aldosterone (Pitt et al., 2003), waist/hip ratio (Srikanthan, Seeman, & Karlamangla, 2009; Welborn & Dhaliwal, 2007) creatinine (Irie, Sairenchi, Iso, & Shimamoto, 2001; Walsh, O'Donnell, Camargo, Giugliano, & Lloyd-Jones, 2002), triglycerides (Langsted et al., 2011; Shankar, Mitchell, Rochtchina, & Wang, 2007), tumor necrosis factor-alpha (Baune, Rothermundt, Ladwig, Meisinger, & Berger, 2011; Bruunsgaard, Andersen-Ranberg, Hjelmborg, Pedersen, & Jeune, 2003; Schulz, Aker, Belosjorow, & Heusch, 2004), C-reactive protein (Man et al., 2006; Zacho, Tybjærg-Hansen, & Nordestgaard, 2010), Interleukin-6 (Baune et al., 2011; Harris et al., 1999; Volpato et al., 2001), heart rate (Kristal-Boneh, Silber, Harari, & Froom, 2000; Okin et al., 2010; Rambihar et al., 2010; Vatten, Holmen,

Krüger, Forsén, & Tverdal, 1995) and systolic blood pressure (Pastor-Barriuso, Banegas, Damián, Appel, & Guallar, 2003)

3.2.2.3.2 Inverse, linear relationship with all-cause mortality

An inverse linear relationship with all-cause mortality is known for: dehydroepiandrosterone sulphate (Glei & Goldman, 2006; Ohlsson et al., 2010), high density lipoproteins (Okamura et al., 2006), albumin (Herselman, Esau, Kruger, Labadarios, & Moosa, 2010), and forced expiratory volume (Almagro et al., 2014; Schünemann, Dorn, Grant, Winkelstein, & Trevisan, 2000). For these indicators, z-scores were reversed (multiplied by -1), as in previous AL studies (Hawkley et al., 2011; Seplaki, Goldman, Glei, & Weinstein, 2005).

3.2.2.3.3 Non-linear relationship to all-cause mortality

Baseline body mass index has a 'J' shaped association with mortality, as shown in an 8 year follow-up of 66,552 participants from all over the world (Whitlock et al., 2009). Body mass index of values above and below the reported optimum of 22.5-25 were associated with mortality (30,416 vascular; 2070 diabetic, renal or hepatic; 22,592 neoplastic; 3,770 respiratory; 7,704 other) after adjusting for age, gender, and smoking status. Therefore body mass index data were transformed by subtracting participant data from a 'healthy range'; 22.5-25 (Whitlock et al, 2009). Values falling within the healthy range were given a value of '0'; the remaining scores were transformed to reflect 'body mass index risk' by squaring them to ensure that they were all positive; higher values indicate greater risk to health.

The direction of association between diastolic blood pressure and all-cause mortality is flat then a sharp increase above 80 mm Hg, in younger participants (<65 years) and J-shaped in elderly participants (aged > 65 years: increased risk below 80mm Hg and a sharp increase above 90 mm Hg) (Pastor-Barriuso et al., 2003). Therefore for participants aged <65 years, all values at 80 mm Hg or below were scored '0' and values above had 80 subtracted, to leave a residual value for diastolic blood pressure that reflected 'diastolic blood pressure risk'. For participants aged >65 years, the same calculation was performed except the cut-off was 90 mm Hg or below. Previous AL literature has dealt with data in a similar

way in considering that for certain indicators, only values above or below a cut-point reflect greater risk of disease or death (Seplaki et al., 2005).

3.2.2.4 Assumptions of normality and z-scores

In order to create a z-score, data must be normally distributed. A Kolmogorov-Smirnov test was performed to check the distribution of each indicator. Those that were not normally distributed were transformed using the common logarithm (base 10). Following this, normally distributed (naturally or by transformation) indicators were converted into z-scores so that each measure or biomarker had a mean of '0' and a standard deviation (SD) of 1.

To create z-scores, the mean for the total sample is subtracted from a target data point and then divided by the sample SD. When creating z-scores, it is good practice to use as large a sample as possible; increasing the number of scores in a sample produces smaller standard error (Gravetter & Wallnau, 2016). The smallest sample used to create z-scores in the present research was n = 265; this combined participant data from all four research studies. Data were also available for high density lipoproteins, interleukin-6, C-reactive protein, waist/hip ratio, body mass index, systolic blood pressure and diastolic blood pressure from 602 individuals from the Psychological, Social and Biological Determinants of Ill health (pSoBid) study. This cross sectional study of a Glasgow population aimed to investigate the psychological, behavioural and biological determinants of ill- health (Packard et al., 2011; Velupillai et al., 2008) and was demographically similar to the HI groups in the present studies. The pSoBid data were combined with data in the present research when possible to produce z-scores, giving a maximum sample of 867. Combining the two data sets to make a larger sample for z-score creation, produced a more valid SD for those indicators and made the z-scores more robust.

3.2.2.5 Creating an allostatic load score

Some studies simply sum the z-scores of every indicator to create the AL score (Hampson et al., 2009; Langelaan et al., 2007; Mair et al., 2011). However in the present studies, the number of indicators comprising each component ranged from two to four, so summing the z-scores is not valid because it would give different weightings to the components depending on the number of indicators in each

component. Therefore in this study, the z-scores of indicators were first summed within their respective component (immune, neuroendocrine, anthropometric, cardiovascular, and metabolic). Then, a further z-score was created from the sum of z-scores for each of the five components. The purpose of this was to reduce the variation of standard deviations between component scores (caused by creating means for varying numbers of indicators). The five component z-scores were then summed to produce the total AL score.

However summing different biological components, as described above, to provide an overall measure of AL, may obscure atypical values within each component (Seeman et al., 1997), therefore the z-scores for each of the five components (immune, neuroendocrine, anthropometric, cardiovascular and metabolic) were also analysed separately.

3.3 Confounders

Confounders were selected on the basis of the literature on AL and that on outcome after HI.

3.3.1 Confounders of outcome after head injury

3.3.1.1 Age

Older age (>40 years) predicted outcome on the GOS at 1 year post discharge follow-up (Thornhill et al., 2000) and using the GOS-E at 12-14 year follow-up (McMillan et al., 2012). Similar findings were demonstrated in a Swedish study (Jacobsson et al., 2009). Therefore age was included in the analysis as a covariate if found to have a relationship with GODS ratings (Chapter 5) and with GOS-E ratings (Chapters 6-8).

3.3.2 Confounders of change in outcome after head injury

3.3.2.1 The Alcohol Use Disorder Identification Test

Alcohol misuse is associated with change in disability after HI. Individuals with a Good Recovery at one year who then deteriorated to Disabled at 5–7 years scored significantly higher on the AUDIT at 5-7 years, than others with a Good Recovery at both time points (p <0.005) (Whitnall et al., 2006). Therefore scores on the

AUDIT were included in the analysis as a covariate if they were found to have a significant relationship with change in disability.

3.3.3 Confounders of allostatic load

3.3.3.1 Age

AL increases with age (Crimmins et al., 2003; Dich, Doan, Kivimaki, Kumari, & Rod, 2014; Hasson, Von Thiele Schwarz, & Lindfors, 2009), therefore, where groups were not matched by age, if AL correlated with age in Chapters 5-8, it was adjusted for in the analysis.

3.3.3.2 Social deprivation

3.3.3.2.1 Current deprivation

Higher AL is associated with greater social deprivation among adults, in terms of type of occupation (Gustafsson, Janlert, Theorell, Westerlund, & Hammarstrom, 2011), low income, low education (Upchurch et al., 2015), marital status, and residence (large cities vs. villages) (Lipowicz, Szklarska, & Malina, 2014). Therefore where groups were not matched by social deprivation, if the assessment of deprivation in this study (SIMD (2012) quintiles) was associated with AL scores, it was adjusted for in the analysis.

3.3.3.2.2 Childhood social deprivation

Childhood deprivation correlates with AL in adulthood (Gruenewald et al., 2012; Singer & Ryff, 1999). This association was further evidenced using an inflammatory marker based AL construct in a Glasgow sample using questions about Father's occupation at the age of 11 and childhood home status (owner-occupier; overcrowding) (Packard et al., 2011). The questions were; "At the age of 11, what job did your father have?", "At the age of 11, did you parents own the house you lived in?" and "At the age of 11, what was the number of rooms in your house and how many people lived there at the time?" (a measure of over-crowding).

These three childhood deprivation questions were used in this research and the answers for each dichotomised into 0 (not deprived) and 1 (deprived). For the latter two questions 0 was defined as home-ownership and having a total number

of rooms greater than the total number of occupants respectively. Father's occupational category was initially classified using the National Statistics Socio-economic Classification (NS-SEC) Coding Tool (http://www.ons.gov.uk/ons/guide-method/classifications/current-standard-classifications/soc2010/soc2010-volume-3-ns-sec--rebased-on-soc2010--user-manual/index.html#7) into: 1 Higher managerial, administrative and professional occupations; 2 Intermediate occupations; 3 Small employers and own account workers; 4 Lower supervisory and technical occupations; 5 Partly skilled occupations and 6 Unemployed. Consistent with previous studies (Packard et al., 2011), these categories were collapsed to derive: 1 (deprived), defined as occupational groups 4-6, and 0 (not deprived), defined as occupational groups 1-3.

The three dichotomised replies were then summed to create a total score for childhood deprivation; ranging from 0 (not deprived) to 3 (very deprived). Childhood deprivation scores were included in the analysis as a covariate if they had a significant relationship with AL scores.

3.3.3.3 Medication

Participants were asked if they were taking anti-inflammatory or anti-hypertensive medication as these would affect the inflammatory blood biomarkers and blood pressure measurements. These binary answers 'yes' or 'no' were included as covariates in the analyses if they were significantly associated with AL scores (see appendix for lists).

3.4 Data collection and analysis

3.4.1 Assessment of allostatic load components

When measuring AL, the same procedures and equipment were used for every participant to standardize the process across the four studies.

3.4.1.1 Cardiovascular measures

To measure forced expiratory volume, a Wright's Spirometer was used with disposable mouthpieces for hygiene purposes. Participants were given three attempts using the Spirometer, and the highest value was used in the analyses. An

Omron Digital Blood Pressure Monitor was used to measure heart rate, systolic and diastolic blood pressures. All three were calculated as the mean of three readings, taken one minute apart, with the participant in a seated position. All physical measures of health were taken at the end of the assessment, to make sure readings were not affected by activities prior to arrival at the clinic such as climbing stairs to the appointment room (Omron Healthcare, 2010).

3.4.1.2 Anthropometric measures

Waist/hip ratio was calculated by dividing the circumference of the waist by that of the hips. Participants were asked to stand and relax, with their feet together, and to wear one layer of thin clothing during the measurement of their waist and hips. A two meter soft tape measure was used to measure the circumference of the waist and hips. The waist circumference was measured just above the umbilicus, and the hips circumference at the widest portion of the buttocks. Body mass index was calculated by dividing the weight of the participant in kilograms by the square of their height in metres. A measuring tape and ruler placed on the top of the head were used to measure height and Weiheng portable personal digital body scales were used to measure the weight of participants wearing one layer of clothes and no shoes. The weighing scales were always placed on a hard surface in order to obtain an accurate reading and the same scales used for all participants.

3.4.1.3 Blood biomarkers

The neuroendocrine, metabolic, and immune biomarkers were all assessed from a venous blood sample. A 12ml blood sample was taken using two yellow top blood tubes, containing anticoagulant citrate dextrose solution (ACD). ACD preserves blood by stopping it from coagulating, enabling it to be tested for the blood biomarkers described above. Immediately after the blood sample was taken, the tubes were inverted 4-5 times to mix the blood and the ACD.

3.4.2 Analyses of blood samples

One tube of blood was taken to the Clinical Research Facility, Glasgow Royal Infirmary, in order to measure tumor necrosis factor-alpha and Interleukin-6. A Sigma 4-16KS centrifuge machine was used to spin the blood and separate the

serum for analysis. It was important that the contents of the centrifuge were weighted within 2g on both sides of the machine; therefore a tube of water was added and the quantity of water altered in order to create an equal weight. The tubes were distributed equally in the centrifuge machine, and spun at 3,000 revolutions per minute (rpm) for 10 minutes at 4 degrees Celsius. Following the separation of serum from the red blood cells, the serum was pipetted into 1ml aliquot tubes of serum. Samples were stored in a -80^{o}C freezer until a batch of 40 could be processed at once.

Analysis of these samples was undertaken by the Human Nutrition Department at the University of Glasgow. Enzyme-linked immunosorbent assay (ELISA) analysis was performed on the serum in order to assess the levels of tumor necrosis factor-alpha and interleukin-6. The sensitivity, intra- and inter-assay coefficients of variation are shown in table 5. Ninety-six ELISA well plates were prepared by 'attaching' capture antibody to the wells to which the serum could bind, depending on which blood biomarker was being tested. Serum was added to each well, before the serum was incubated with the capture antibody. Excess was rinsed off to avoid background non-specific staining, before adding a secondary antibody, which bound to the primary antibody. This was incubated, and excess rinsed off. If the secondary antibody was not already conjugated, a horseradish peroxidase (HRP) conjugate was added at this time point, and the sample incubated. Finally a substrate was added that bound to the HRP-conjugated secondary antibody, which was bound to the primary antibody, which was bound to the specific antigen, and this produced a colour change that could be measured. This process was carried out in duplicate for each participant sample; to avoid pipetting errors and confirm the accuracy of results. A multiskan machine outputted optical densities readings, showing a numerical representation of the colour reaction of the samples. These figures were transferred to a spreadsheet and the concentration of the samples calculated by plotting the data on a graph to produce a standard curve. This process was carried out by the staff at the Human Nutrition Department.

The remaining 5ml tubes of blood were delivered to the MacEwan biochemistry department, at Glasgow Royal Infirmary. The biochemistry department extracted aldosterone, dehydroepiandrosterone sulphate, creatinine, albumin, C-reactive

protein, triglycerides, and high density lipoprotein data from the venous blood. Samples were delivered to the laboratory with an anonymised study form, where they were allocated a unique barcoded laboratory number in the reception area. The samples were then placed in a centrifuge and spun for 10 minutes at 3,000 rpm. Clerical staff took the request form and the sample details, and entered the laboratory number and list of tests requested into the laboratory computer system. The spun samples were placed onto an automated analyser tracking system whereby they were delivered to a multichannel analyser that read the bar code and analysed the requested tests.

When the analyses were completed a hard copy report was printed from the laboratory IT system. Biochemistry results were gathered along with the study ID from the IT system and organised onto an excel spreadsheet that included no identifiable information.

3.4.2.1 Out of range blood biomarker values

For non-detectable levels of plasma Interleukin-6 and tumor necrosis factor-alpha, data were imputed based on half the lower limit of detection (LOD/2), the absolute lowest sensitivity of the assay, shown in table 3, as suggested by Hornung and Reed (1990).

	Inter-assay coefficient of variation %	Intra- assay coefficient of variation %	Lowest standard	Level of detection
Interleukin-6	7.2	10.0	1.56pg/mL	0.33pg/ml
Tumor necrosis factor-alpha	11.6	9.6	3.9pg/mL	1.90pg/ml

Table 5 - The sensitivity, intra-and inter-assay coefficient of variations for interleukin-6 and tumor necrosis factor-alpha

3.4.2.2 Missing data

Occasionally, indicator information was missing, due to difficulties analysing the sample, relating to the quality of the blood sample. Z-scores for missing indicator data were imputed using the mean of the total z-scores of the other indicators within the same component, a method used by Crimmins et al. (2009). This procedure was only conducted for 4 missing indicator data.

3.4.3 Contributors to data collection and analysis

I collected all the data for studies 1 and 2. Studies 3 and 4 were part of a larger study in the Head Injury Research Group; therefore other members of staff collected some of the data. In study 3, Dr Maria Gardani and Dr Lin McLean assessed approximately two-thirds of participants. In study 4, Dr Lin McLean assessed approximately half of participants. To ensure consistent data collation processes and inter-observer reliability of data, multiple team meetings were held to practice and discuss administration of the study measures.

I underwent venepuncture training, and collected most of the blood samples in all the studies. When more experience was required; nurses on the ward or at the Clinical Research Facilities collected the blood. A blood protocol was supplied to team members, containing the above instructions about how to centrifuge and store blood samples. Blood samples were analysed by Dr Emilie Combet of the Human Nutrition Department, University of Glasgow, and Dr Karen Smith of the MacEwan Biochemistry Department, Glasgow Royal Infirmary.

3.5 Estimation of required sample size

There are no previous studies investigating AL after HI, therefore a specific power calculation for this new research could not be performed. A pragmatic decision was made to undertake an estimate of the required sample size to achieve power to detect an effect using AL data derived from participants recruited from the general population in a similar geographical area. The estimate of sample size was based on a sample of pSoBid participants (Packard et al., 2011): 310 from deprived areas and 336 from affluent areas of Glasgow as defined by SIMD (2012) datazones, the lowest 5% and highest 20%. Inflammatory AL scores were compared between these two groups; the mean (0.18) and standard deviation (0.6) for the deprived group and the mean (-0.16) and standard deviation (0.47) for the affluent group. The group difference had an effect size of 0.63. Using Gpower 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007), at least 32 participants per group were required to detect a significant difference at the 5% level with 80% power. Therefore, the aim was to recruit 32 participants to each study group as described in subsequent chapters. The data provided in Chapters 5 to 8 can be used by future studies repeating this study design, to calculate a more accurate power calculation.

3.6 Contributions of this research

The aim of this research was to further understand what factors explain outcome after HI. It is the first to investigate the relationship between AL and global functioning after HI, at different time points, and in different HI severity populations. Furthermore, the literature search in Chapter 2 demonstrated that the AL literature is impoverished in terms of an evidence base for guiding how to measure AL. Thus, as described above (section 3.2.2), each step of constructing the AL score in this research was carefully considered using evidence from the AL literature and broader biological and epidemiological research. Future AL literature should consider similar issues when constructing an AL score, such as the evidence for potential confounders of AL, the direction of the relationship between indicators of health and risk to health, and the importance of preserving the continuous nature of the indicators of health and AL. In Chapter 4 the concurrent validity of the measure of AL in this research.

Chapter 4 The measure of allostatic load

Background

Several studies have shown allostatic load (AL) to be associated with psychosocial functioning, morbidity, and mortality and that AL can predict these outcomes at follow-up; however AL has never been used to predict outcome after head injury (HI). Prior to investigating the hypothesis that HI affects the accumulation of AL in 4 empirical studies, it was important to assess the concurrent validity of the method of assessing AL in this research.

Methods

Data from the comparison groups, described in the following chapters, were used to test the concurrent validity of AL scores (n = 77). The concurrent validity of the AL measure was assessed by comparing it with factors known to correlate with AL; increasing age, higher levels of deprivation, and higher levels of childhood deprivation.

Results

Age and childhood deprivation had a moderate and statistically significant relationship with the measure of AL. Measures of deprivation (SIMD (2012) datazones and current occupation skill) did not correlate with AL scores.

Conclusions

Consistent with previous literature, the measure of AL in this research correlated with age and childhood deprivation scores, which supports its concurrent validity, however the hypotheses that SIMD (2012) datazone and occupation skill category would correlate with AL scores were not supported. Despite this, and even with a modest sample size, there is evidence of concurrent validity of the measure of AL in this research, particularly when compared with age and childhood deprivation scores.

Chapter 3 described in detail how AL was measured in this research. Prior to investigating the relationship between head injury (HI) and allostatic load (AL), it was necessary to check the concurrent validity of the measure of AL. Therefore in this chapter, the concurrent validity of the AL measure used in this research was assessed by comparing it with factors known to correlate with AL; increasing age (Crimmins et al., 2003; Dich et al., 2014; Hasson et al., 2009), higher levels of deprivation (Gustafsson et al., 2011; Lipowicz et al., 2014; Upchurch et al., 2015), and higher levels of childhood deprivation (Gruenewald et al., 2012; Singer & Ryff, 1999).

4.1 Participants

Data from the comparison groups, described in the following chapters, were used to test the concurrent validity of AL scores. The HI participants were not included as my hypothesis is that HI affects AL. The comparison groups were matched to the HI group by age, gender and Scottish Index for Multiple Deprivation (SIMD) 2012 datazone but recruited from the general public. The comparison group from study 1 (n = 49; Chapter 5) were combined with the comparison group from study 4 (n = 28; Chapter 8) to provide a sample of 77 on which to test the concurrent validity of the measure of AL used in this thesis.

4.2 Data

Demographic information, including age, SIMD (2012) datazone, current occupation, and childhood deprivation, was obtained by interviewer-completed questionnaire.

4.2.1 Social deprivation

4.2.1.1 Neighbourhood deprivation

SIMD (2012) datazones were used to determine area-based socioeconomic deprivation; they are ranked from 1 (most deprived) to 6,505 (least deprived) (Fischbacher, 2014). Chapter 3 details how SIMD (2012) datazones are measured.

4.2.1.2 Occupational category

Current occupation was also used as a measure of individual-level socioeconomic deprivation. Personal occupation was categorised in the same way as father's occupation (described in Chapter 3), into 6 categories: 1- higher managerial, administrative and professional occupations; 2- intermediate occupations; 3- small employers and own account workers; 4- lower supervisory and technical occupations; 5- partly skilled occupations and a 6th category was added for unemployment. Data for participants who identified as students or housemakers were unable to be classified on an ordinal scale so was treated as missing data.

4.2.2 Childhood deprivation

To assess childhood deprivation, participants were asked three questions; "At the age of 11, what job did your father have?", "At the age of 11, did you parents own the house you lived in?" and finally "At the age of 11, what were the number of rooms in your house and how many people lived there at the time?" (a measure of over-crowding). Chapter 3 contains a description of how the answers to these three questions were dichotomised and combined to create a composite measure of childhood deprivation. Higher scores indicated higher levels of childhood deprivation.

4.3 Hypotheses

1. High age is associated with higher allostatic load scores.

2. High social deprivation is associated with higher allostatic load scores:

   I) In terms of lower SIMD (2012) datazones.

   II) In terms of higher occupation skill category (lower skills).

3. High childhood deprivation scores are associated with higher allostatic load scores.

4.4 Data analysis plan

Data were analysed using SPSS v22. The distribution of AL scores was determined using the Kolmogorov-Smirnov test. Demographic information was considered descriptively initially. The relationship between AL scores and age, childhood deprivation scores, SIMD (2012) datazone, and current occupation, was investigated using correlations. If data violated the assumption of normality, they were analysed using non-parametric tests.

4.5 Results

4.5.1 Tests of normality

Table 6 displays the Kolmogorov-Smirnov test results, which demonstrated the distribution of all the variables deviated significantly from normal except for SIMD (2012) datazone.

	Kolmogorov-Smirnov	
Variable	Statistic	*p*
Allostatic load score	0.112	<0.05
Age	0.118	<0.05
Total of three childhood SES binary questions	0.318	<0.001
Employment category 6 categories	0.292	<0.001
SIMD (2012) datazone	0.096	0.079

Table 6 - Tests of normality for AL scores and demographic factors of 77 comparison participants

4.5.2 Demographic information

The sample of 77 included 63 (82%) men, and age ranged from 20 to 72 years old (median = 50; interquartile range (IQR) = 36.0, 57.5). SIMD (2012) datazones ranged from 74 (high deprivation) to 6,477 (low deprivation) (mean = 3,462; standard deviation (SD) = 2,034). With regards to occupation category, 48% (n = 37) were in group 1 (higher managerial, administrative and professional occupations), 22% (n = 17) were in group 2 (intermediate occupations), 5% (n = 4) were in group 3 (small employers and own account workers), 3% (n = 2) were in group 4 (lower supervisory and technical occupations), 10% (n = 8) were in group 5 (partly skilled occupations), and 1% (n = 1) were in group 6 (unemployed). Eight

(10%) occupation categories were missing; of these 1% (n = 1) were housemakers and 9% (n = 7) were students. Forty-eight percent of participants experienced some degree of deprivation in their childhood; 17% (n = 13) had a childhood deprivation score of 1, 21% (n = 16) a score of 2, and 10% (n = 8) a score of 3.

4.5.3 Hypothesis 1

"High age is associated with higher allostatic load scores"

Figure 6 displays a scatterplot of AL scores plotted against age. It shows a moderate, positive linear relationship between the two variables. A Spearman's rank correlation was used as both variables were not normally distributed and there was a moderate, significant correlation between age and AL (r_s = 0.294, p <0.05).

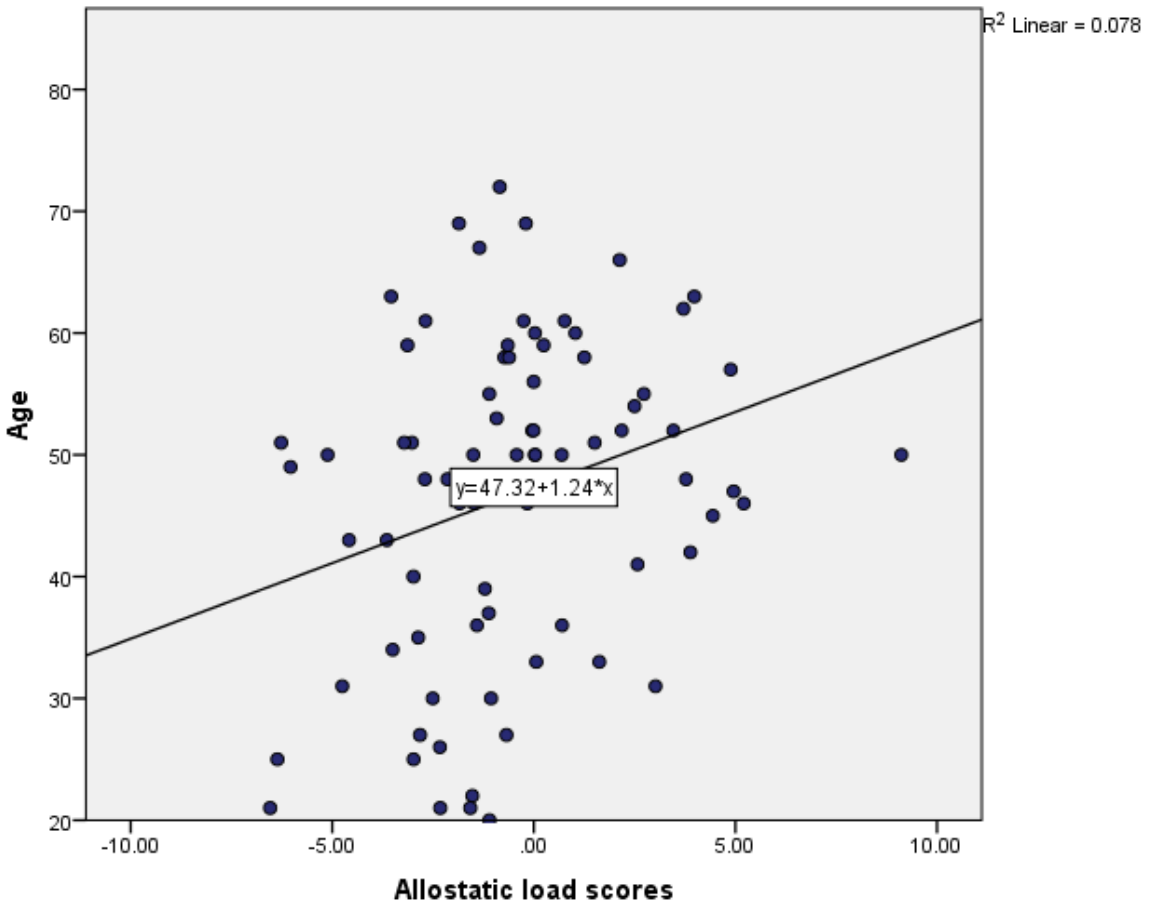

Figure 6 – Scatterplot of AL load scores by age in 77 comparison participants

4.5.4 Hypotheses 2

4.5.4.1 Part I

"High social deprivation is associated with higher allostatic load scores in terms of lower SIMD (2012) datazones"

Figure 7 displays a scatterplot of AL scores plotted against SIMD (2012) datazones, which appears to show a weak positive linear relationship between the two variables. However the Spearman's rank correlation demonstrated no significant relationship (r_s = 0.170, p = 0.139).

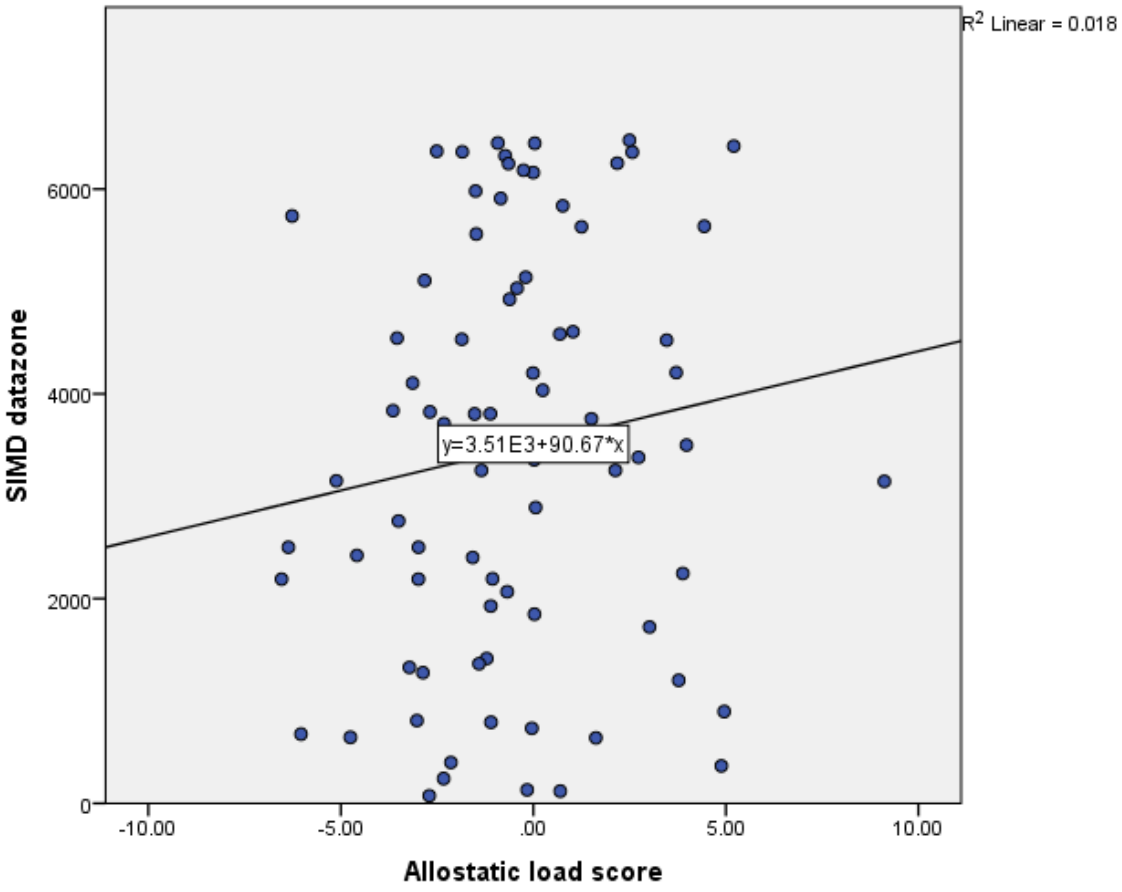

Figure 7 – Scatterplot of AL scores by SIMD (2012) datazone in 77 comparison participants

4.5.4.2 Part II

"High social deprivation is associated with higher allostatic load scores in terms of higher occupation skill category (lower skills)"

The boxplot in figure 8 demonstrates some skewness in the AL scores, particularly in the professional occupations group, which has a number of outliers. The overall

picture suggests an inverse U-shaped relationship between occupational category and AL. A Spearman's rank correlation was used as both variables were not normally distributed and no significant association was found (r_s = 0.076, p = 0.535).

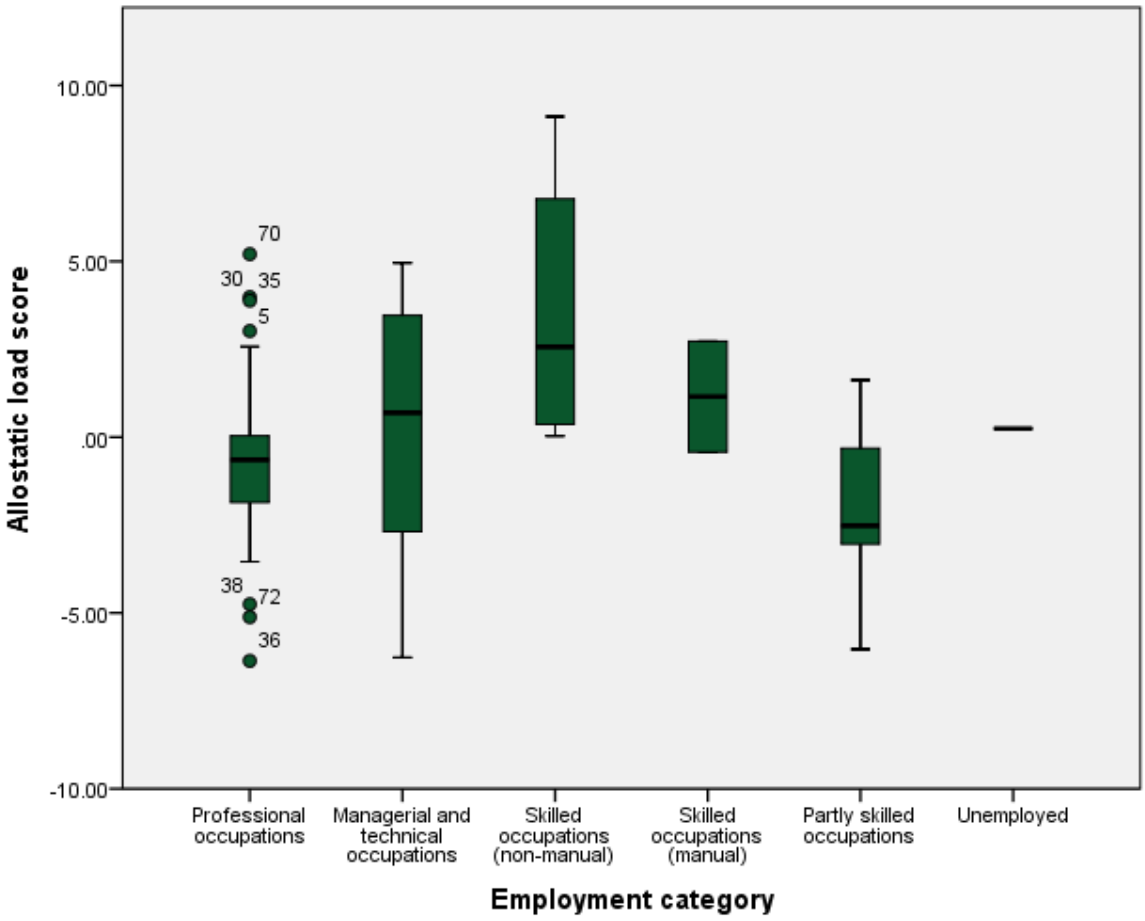

Figure 8 - Boxplots of AL scores by occupation skill category in 69 comparison participants

4.5.5 Hypotheses 3

"High childhood deprivation scores are associated with higher allostatic load scores."

The boxplot in figure 9 suggests a weak, positive linear relationship between childhood deprivation scores and AL scores. A Spearman's rank correlation demonstrated a moderate and statistically significant correlation (r_s = 0.260, p <0.05).

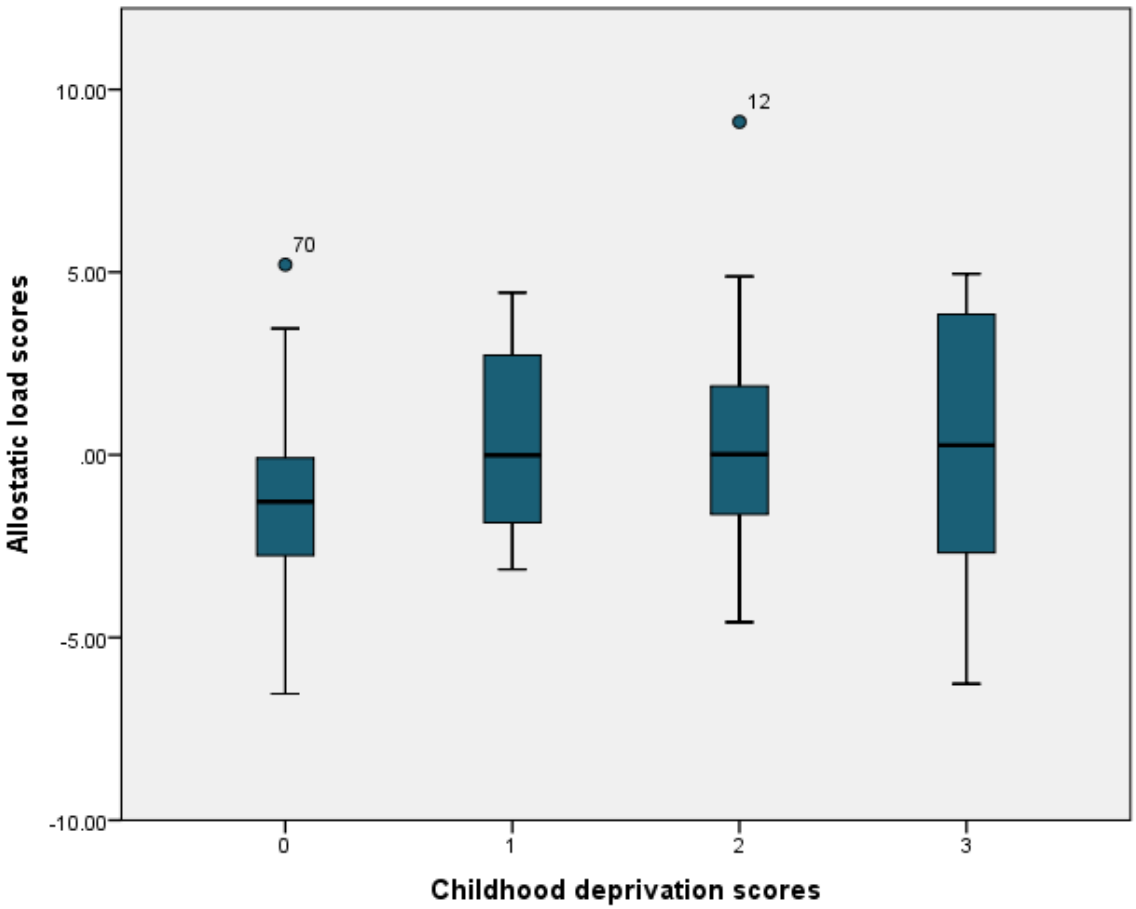

Figure 9 - Boxplots of AL scores by childhood deprivation scores in 77 comparison participants

4.6 Discussion

Age and childhood deprivation had a moderate and statistically significant relationship with the measure of AL in this research supporting its concurrent validity. Contrary to expectation, SIMD (2012) datazones and the measure of current occupation skill did not have a significant relationship with AL scores.

In relation to other studies, AL was demonstrated to increase with age (Crimmins et al., 2003; Dich et al., 2014; Hasson et al., 2009; Yang & Kozloski, 2011). Therefore the same finding in this study demonstrates some validation of the measure of AL. The measure of AL in this study was also moderately associated with childhood deprivation scores, despite only 10% of participants experiencing childhood deprivation on all three questions. Regardless of using different measures of childhood deprivation (parent-child interactions and a combination of parent educational attainment, welfare status, and financial situation) other studies have also shown a relationship between childhood deprivation and AL in

adulthood (Gruenewald et al., 2012; Singer & Ryff, 1999). Therefore again this indicates some validation of the measure of AL in this research.

The lack of association between AL scores and SIMD (2012) datazones and occupational skill category contrasts with previous research that has shown an association between higher AL and greater social deprivation assessed in terms of income, education, occupation, marital status, and residence (Gustafsson et al., 2011; Lipowicz et al., 2014; Upchurch et al., 2015). SIMD is well-established and recommended as an indicator of deprivation in Scotland by the Information Services Division of NHS Scotland and the Scottish Government (Bishop et al., 2004), therefore it is unlikely that the lack of association is due to using SIMD as a measure of social deprivation. The distribution of SIMD (2012) datazones did not differ significantly from normal (table 6) and it appeared to be roughly even across the spectrum of deprivation (figure 7), thus the lack of relationship between SIMD and AL is improbably due to an uneven distribution of SIMD (2012) datazones. Consequently, the findings show that the measure of AL in this research does not map onto social deprivation in terms of SIMD (2012) datazones or skill category in the group of 77 comparison participants.

4.6.1 Strengths and limitations

A weakness of the assessment of childhood deprivation is that it was assessed by recall therefore the answers were vulnerable to errors in memory or reporting.

The results for hypothesis 2 part II should be interpreted with caution given that the professional occupations group had several high and low outliers for AL scores. This skewing may affect the mean AL score for the professional occupations group, altering the relationship between AL and job category. Another issue is the high proportion of participants who were in the professional occupations group (48%), which does not reflect that of the general population (National Records of Scotland, 2011). This is because 38% of participants in this sample were comparison participants from Chapter 8 who were recruited from friends and family of elite level rugby players who in Scotland, tend to belong to middle classes. A consequence of this is the generalisability of these findings is limited when considering the general population.

After the removal of these 7 outliers, there was no significant relationship between AL and occupation category (r_s = 0.097, p = 0.453). The skewed AL scores may indicate that occupation categories are not a valid measure of social deprivation, however further post-hoc analysis showed medium to strong relationships between occupation categories and other measures of deprivation (childhood deprivation scores, r_s = 0.445, p <0.01, and SIMD quintile, r_s = -0.442, p <0.01) adding strength to its use as a measure of social deprivation.

Strength of the AL construct in this research is the range of biomarkers and physical measures of health collected for modelling AL. Whilst not exhaustive, it is much broader than in most other AL research, in particular having at least 2 biomarkers to represent each of the 5 health components as recommended in reviews (Beckie, 2012; Juster et al., 2010). Based on the systematic search in Chapter 2, there is no evidence base of better indicators of health, or methods of constructing AL scores, than those used in this research. Future and larger research studies should use multiple methods of constructing AL scores, to test the concurrent validity of the different methods.

4.7 Conclusion

The hypotheses that age and childhood deprivation would correlate with the measure of AL was supported. The hypotheses that SIMD (2012) datazone and occupation skill category would correlate with AL scores were not supported. Even with a modest sample size however, there was partial validation of the measure of AL used in this research, particularly when compared with age and childhood deprivation scores. In the next chapter this measure of AL is used to investigate the relationship between AL and outcome in hospital, early after HI.

Chapter 5 **Allostatic load and outcome at discharge from hospital following head injury**

Background

Several studies have shown that outcome after head injury (HI) is heterogeneous; severity of the injury and demographic factors only partly explain disability outcome early after injury. Research has shown allostatic load (AL) to be associated with psychosocial functioning, morbidity, and mortality however it has never been compared with outcome after HI. This study was the first to investigate outcome at discharge from hospital after severe HI.

Methods

Thirty-five HI participants were assessed for disability outcome (Glasgow Outcome at Discharge Scale) in hospital. The AL of HI participants was compared to those of a comparison group, matched 1:1 with HI participants on the basis of age (+/- 5 years), gender, and SIMD (2012) quintiles. Potential confounders were adjusted for in the analyses; for AL these included childhood deprivation scores, and taking anti-hypertensive or anti-inflammatory medication, and for disability outcome the potential confounder was age.

Results

Near to discharge from hospital, the HI group had significantly higher AL scores than matched comparison participants (p <0.05), specifically the metabolic and immune components. No significant associations were found between disability outcome and AL scores after HI near to discharge from hospital.

Conclusions

Allostatic load is higher near to discharge from hospital after a HI than in age, SIMD (2012) quintile, and gender matched comparison participants. The findings do not support the view that AL explains the heterogeneity of disability outcome after HI at this time point.

5.1 Introduction

Disability following head injury (HI) is common and the adverse effects can be lifelong (Corkin et al., 1989). This is particularly worrying given the typically young age of HI patients; a median age of 29 was found in a study of 988 patients admitted to one of four British neurosurgical units with a severe HI (Murray et al., 1999). An epidemiological study of the HI population attending UK emergency departments found rates of moderate to severe HI (GCS scores <12) to be highest in men aged 15–19 (approximately 180 per 100,000 men with HI) (Yates et al., 2006).

As described in Chapter 1, research on factors that predict survival early after HI, and which may predispose to enduring disability, has produced inconclusive results. Some evidence indicates that injury-related factors such as lower Glasgow Coma Scores (GCS) at hospital admission, duration of coma, and the presence of CT abnormalities predicted poorer outcomes within a year after injury (Husson et al., 2010). However other studies do not support this (Erlanger et al., 2003; Ponsford et al., 1999; Thornhill et al., 2000).

Studies into whether individual characteristics of participants predict outcome early after injury have also demonstrated conflicting findings. Some evidence indicates that higher social deprivation (in terms of education), older age, and male gender (Silverberg et al., 2015), are associated with poorer outcome, however other studies have not found these demographic variables to be predictors (Husson et al., 2010; Thornhill et al., 2000).

Recent evidence, described in detail in Chapter 1, indicates that disability following HI can be dynamic, improving for some, and becoming worse for others, up to 14 years after injury (Jacobsson et al., 2009; McMillan et al., 2012; Whitnall et al., 2006). In addition to this, evidence shows an increased risk of death following HI, as late as 15 years after injury (Harrison-Felix et al., 2006; McMillan et al., 2011; McMillan et al., 2014; Roberts, 1979; Shavelle et al., 2001). This increased risk of death is not explained by gender, age, social deprivation or the severity of HI, and the causes of death are similar to those occurring in the general population.

Currently, it is difficult to predict which individuals will recover well from a HI and which will remain disabled. What seems clear is that variability in outcome after HI is not explained in simple terms such as severity of injury, social deprivation or rehabilitation inputs, or by existing biological, or psychosocial research, and that for some, outcome is dynamic and can change for better or worse over time. Despite decades of research on outcome after HI, what factors contribute to good or poor recovery are not well understood.

Recent evidence has suggested that lifestyle may be associated with risk of mortality late after HI. The incidence of hospital admission with systemic disease pre- and post-injury was higher among people suffering mild HI than a matched other injury and community control group (McMillan et al., 2014). An increased number of admissions to hospital prior to HI indicate that there may be a measurable difference in health between HI and comparison participants prior to admission to hospital with a HI. A variation in physiological vulnerability at the time of injury, as a result of lifestyle, may also help to understand the heterogeneity of disability outcome early after injury.

As allostatic load (AL) represents an accumulation of physiological damage resulting from the combined effects of genes, early life experiences and lifestyle over time (McEwen, 2000), it may be a factor that explains outcome early after HI. Over the lifetime prior to injury, or resulting from the trauma of injury, the dysregulation of primary outcomes and the resulting modification of secondary outcomes, could lead to variation in AL that may leave some individuals less able to recover and vulnerable to a poor outcome after HI. Exploring AL in HI participants near to hospital discharge will enable investigation of whether this factor explains heterogeneity in outcome early after HI.

In the present study, the AL of HI participants near to hospital discharge was compared to an age, gender, and socioeconomic status matched comparison group to deduce whether any differences in AL may contribute towards the understanding of the observed differences in mortality rates late after injury. The relationship between AL and disability outcome was also investigated using the Glasgow Outcome at Discharge Scale (Appendix C).

5.2 Aims

1. To investigate whether there is a difference in AL between HI participants and a matched comparison group soon after HI.

2. To investigate whether there is a relationship between AL and disability outcome soon after HI.

5.3 Hypotheses

1. Allostatic load scores near to discharge from hospital after a severe head injury are significantly higher than in age, gender, and social position matched comparison participants.

2. High allostatic load scores near to discharge from hospital following severe head injury are associated with lower Glasgow Outcome at Discharge Scale ratings.

5.4 Design

This was a cross-sectional study.

5.5 Methods

5.5.1 Ethics

Ethical approval for this study was obtained from the West of Scotland Research Ethics Committee on 06/01/13. NHS Greater Glasgow and Clyde (GG&C) Research and Development (R&D) approval was received on 05/02/13. This approved the recruitment of NHS participants from any NHS site within GG&C for the purpose of this study (see Appendix A for approval letters).

Due to slow recruitment in GG&C, additional approval was sought from Tayside R&D management (see Appendix A). This granted permission to recruit NHS participants from any NHS Tayside site for the purpose of this study.

5.5.2 Recruitment

Severe HI participants were recruited from NHS hospitals in GG&C (n = 34) and Tayside (n = 1). Participants were recruited as inpatients when the hospital had decided they were well enough to be discharged. The purpose of this was to recruit people as close to injury as possible, but at a time when they were medically stable and had the capacity to give informed consent to take part in the study. It was important that the participant had the capacity to consent in order for them to understand the risks and benefits of taking part, to make a choice, and to understand that consent was voluntary and could be withdrawn at any time.

HI and orthopaedic wards in Glasgow were visited and phoned frequently to check whether any HI patients had been admitted recently. Potential participants were identified by medical staff who gave them the Participant Information Sheet (PIS) to read. If interested in taking part in the study after reading the PIS, potential participant were seen to check that they satisfied inclusion and exclusion criteria and to allow them to ask questions about the study.

5.5.2.1 Inclusion criteria

5.5.2.1.1 Severe head injury

Participants were included if they had been admitted to hospital with a severe HI. Head injuries were classed as severe, if fulfilling one of the following criteria: post traumatic amnesia of more than 24 hours, loss of consciousness for longer than 6 hours, a Glasgow Coma Scale score during hospital admission of less than 9, or an abnormal CT scan (Carroll, Holm, Kraus, & Coronado, 2004).

5.5.2.1.1.1 Glasgow coma scale

The Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974) assesses impaired consciousness from responses of the patient to defined stimuli. It is used to monitor responsiveness and guide decision-making depending on the needs of patients. A score of 3-15 is created by summing scores from three different categories: best motor response (6 = obeying commands, 5 = movement localised to stimulus, 4 = withdraws, 3 = abnormal muscle bending and flexing, 2 = involuntary muscle straightening and extending, 1 = none); best verbal response

(5 = orientated response, 4 = confused conversation, 3 = inappropriate words, 2 = incomprehensible sounds, 1 = none); and eye opening ability (4 = spontaneous, 3 = to speech, 2 = to pain, 1 = none). Severity of HI is categorised as severe (GCS 3-8), moderate (GCS 9-12), or minor (GCS ≥13).

Individuals with a GCS score of less than 9 at any time during hospital admission were identified as having had a severe HI and invited to participate in the study. This did not include participants who were in induced comas. GCS scores and details (natural, induced) are recorded in the medical records of patients who are admitted to hospital. This information was obtained from medical records following participant recruitment to the research study.

5.5.2.1.1.2 Length of loss of consciousness

Length of loss of consciousness is another indicator of severity of HI (Asikainen, Kaste, & Sarna, 1998). A GCS score of less than 9 indicates loss of consciousness, and as described above is one indicator of a severe HI; however because GCS is recorded by a medical professional, GCS scores are only known from when participants have received medical attention (in ambulance notes and from hospital admission, as detailed in the medical records). However HI participants could be unconscious for some time before medical attention is accessed, and by then they may be conscious and orientated. In this example, duration of loss of consciousness is a better indicator of severity of HI than minimum GCS during hospital admission.

Loss of consciousness for more than 6 hours is an indicator of a severe HI (Greenwald, Burnett, & Miller, 2003; Shahin, Gopinath, & Robertson, 2010; Van Den Broek, Schady, & Coyne, 1995) therefore in this research, participants who had a loss of consciousness equal or greater than 6 hours were invited to participate in the study.

Loss of consciousness was estimated from the report of events from the participant, witnesses and ward staff members, and in notes from the ambulance, accident and emergency department, and ward. If there was a lack of agreement between sources, a hierarchy for the best source of information was used, depending on the length of loss of consciousness. If the participant was conscious

on arrival to hospital, ambulance notes and then their own account of events was used to describe length of loss of consciousness. If participants were unconscious on arrival at hospital, the accident and emergency and ward notes were checked, and otherwise staff account of events were used to gain this information. Length of time in induced coma was not counted.

5.5.2.1.1.3 Post traumatic amnesia

Post-traumatic amnesia (PTA) occurs when a HI patient is no longer unconscious following a HI but they are disorientated, confused, or have impaired anterograde memory following head trauma. PTA begins at the point of impact and is no longer present when there is continuous memory for day-to-day events and orientation.

Length of PTA is an indicator of HI severity; length of PTA correlates with disability and global functioning as assessed using the GOS and with return to work at 1 year post HI, and longer durations of PTA are associated with poorer recovery (Asikainen et al., 1998; Brown et al., 2005; Cifu et al., 1997). A HI is classed as severe if the duration of PTA duration is more than 24 hours (Mild Traumatic Brain Injury Committee, 1993; Nakase-Richardson et al., 2011).

In this research, length of PTA was based on an interview with participants about what they remembered following injury and the version of events from members of staff and other witnesses, and notes from the ambulance, accident and emergency department, and ward. HI patients were invited to participate in the study if having PTA for more than 24 hours. It was not feasible to assess PTA using tools such as the Galveston Orientation and Amnesia Test or the Westmead PTA scale because these measures are used to assess current experiences of PTA (Levin, O'Donnell, & Grossman, 1979; Shores, Marosszeky, Sandanam, & Batchelor, 1986); the nature of recruitment in this study meant PTA was required to be assessed retrospectively.

5.5.2.1.1.4 Computerised tomography

Participants were also deemed to have a severe HI if they had an abnormal computerised tomography (CT) scan. CT scans are the primary imaging method for acute assessment of HI and are performed routinely on adults who have sustained

a HI and have any of the following risk factors; GCS less than 13 on initial assessment or GCS less than 15 at 2 hours after assessment, evidence of basal skull fracture, suspected open or depressed skull fracture, focal neurological deficits, or more than one episode of vomiting or post-traumatic seizure (Scottish Intercollegiate Guidelines Network, 2009).

A CT scan is classified as abnormal if there is evidence of skull fracture, contusion, infarction or haemorrhage. All participants in this sample received a CT scan following admission to hospital and the results were obtained from medical records, recorded by the radiologist.

5.5.2.1.2 Age

Inclusion was restricted to participants aged 16-64 years. Sixteen is the lowest age for participants to be able to give consent to take part. The maximum age was set as 64 years as previous AL research suggests that AL scores increase gradually with age and then plateau in the mid-60's (Crimmins et al., 2003).

5.5.2.1.3 Cognitive ability

Participants were only included if conscious, and no longer experiencing PTA so that they had the capacity to provide informed consent to participate.

5.5.2.2 Exclusion criteria

Exclusion criteria included not living locally to the recruitment site (to enable face to face contact at the 6 month follow-up). Individuals were excluded if they had persisting disability as a result of a previous HI. This was because the main aim of the study was to understand the effects of the recent HI and not the cumulative effects of multiple head injuries.

5.5.3 Procedure

5.5.3.1.1 Head injury participants

HI participants were assessed on the ward. They were asked if they had any questions about the study before going through the consent form (see Appendix B). The participant signed and dated the consent form, and I countersigned it. The

consent form for HI participants included permission to access their medical notes. Injury details such as cause, time and date of injury, length of loss of consciousness, minimum GCS during hospital admission and CT scan results were obtained from the medical notes. Information such as time and date of injury could then be used to assess for any PTA by checking for memory loss since the injury with the HI participant. General Practitioners of the HI participants were sent a letter, informing them that their patient was taking part in the study (see Appendix A). A Participant Information Sheet was enclosed with the letter and contact details were provided should they have any questions.

5.5.3.1.2 Comparison participants

A comparison group was matched 1:1 with HI participants on the basis of age (+/- 5 years), gender, and SIMD (2012) quintiles. Comparison participants were recruited from the friends and family of the HI participant, and from adverts placed in community centres and the Big Issue magazine in Glasgow. Interested individuals who made contact were screened by telephone to exclude those with a history of HI. If the participant was suitable, an appointment was made to discuss the assessment. Comparison participants were assessed at the Clinical Research Facility (CRF) at the Glasgow Royal Infirmary, CRF Western Infirmary, or CRF Queen Elizabeth University Hospital.

5.5.4 Measures

5.5.4.1 Descriptors of head injury and comparison group

5.5.4.1.1 General information

Information about age, gender, and contact details for potential follow-up were acquired by interviewer-completed questionnaire. Scottish Index of Multiple Deprivation (SIMD) 2012 quintiles were used to determine the degree of social deprivation (http://www.scotland.gov.uk/Topics/Statistics/SIMD/), ranging from 1 (most deprived) to 5 (most affluent) as detailed in Chapter 3.

5.5.4.1.2 Health information

Participants were asked subjective questions about their health as secondary descriptors. Participants were asked to rate their general health on a Likert scale as 'Very Poor', 'Poor', 'OK', 'Good', or 'Very Good' and this was scored from 1 to 5. HI participants were asked to rate their general health prior to injury. They were asked how many physician diagnosed chronic illnesses they currently had, and how many and what medications they were presently taking. Collecting health information in this way was chosen because access to medical records was not possible for the comparison participants. Collecting health information from different sources could have created a bias.

5.5.4.2 Descriptors of head injury group

5.5.4.2.1 Head injury details

Information regarding cause of HI, minimum GCS score during hospital admission, and if they had been drinking alcohol near to the time of injury was obtained from the medical notes.

5.5.4.3 Main outcomes

5.5.4.3.1 Allostatic load

The method of collecting and constructing AL scores was the same for HI and comparison participants, and is presented in Chapter 3.

5.5.4.3.2 Assessment of disability after head injury

HI participants were given the Glasgow Outcome at Discharge Scale (GODS; McMillan et al. (2013); Appendix C) because they were assessed in hospital. The GODS is described in detail in Appendix D (table 1).

5.5.4.4 Confounders

5.5.4.4.1 Confounders of allostatic load

Childhood deprivation scores (a continuous variable), and whether participants were taking anti-hypertensive or anti-inflammatory medication (binary variables),

were obtained by interviewer-completed questionnaire and included in the analyses as covariates if they were found to be significant predictors of AL scores. A detailed description of how childhood deprivation was assessed can be found in Chapter 3.

5.5.4.4.2 Confounders of disability outcome

As detailed in Chapter 3, older age at injury is a predictor of greater disability following HI (Jacobsson et al., 2009; McMillan et al., 2012; Thornhill et al., 2000), and was included in the analysis as a covariate if it was found to predict GODS ratings in the HI group at discharge from hospital.

5.5.4.4.3 Confounders of disability outcome later after injury

The HI participants were followed up 6 months after their initial assessment in Study 1 (Chapter 5). Previous research has shown that performance on some cognitive tests was associated with poorer outcome later after injury rating of health locus of control as 'Chance', 'Powerful others', and higher perceived stress), and deterioration in disability over time (health locus of control as 'Powerful others') (McMillan et al., 2012). Therefore the HI participants received the Multidimensional Health Locus of Control (Wallston, Wallston, and DeVellis (1978); Appendix C) and the Perceived Stress Scale (Cohen, Kamarck, and Mermelstein (1983); Appendix C) at hospital discharge, for analyses at 6 month follow-up.

5.5.5 Data analysis plan

Data were analysed using SPSS v22. The distributions of the data were determined by conducting Kolmogorov-Smirnov tests on each variable. Demographic information of both groups and HI details were described using summary statistics and differences in secondary health questions investigated using the paired t-test or the Wilcoxon Signed Rank test.

For Hypothesis 1, potential covariates (childhood deprivation scores, anti-inflammatory and anti-hypertensive medication) were investigated using univariate regressions. If the univariate regressions were significant, the data were analysed using hierarchical regressions enabling the adjustment of

covariates. In this instance (even though the groups were matched for age, gender, and SIMD (2012) quintiles), regression models do not compute paired data points, so the matching variables would not be controlled for. The recruitment of participants was not random, particularly comparison participants, who were recruited based on the matching variables. Therefore age, gender, and SIMD (2012) quintiles were also controlled for in the final hierarchical regression model in order to compensate for potential bias in recruitment (Pallant, 2013).

All linear regression output was checked for a number of assumptions; those for the final models are described in the appendix. The model contained outliers if the minimum standardised residual values were equal to or below -3.3 and maximum equal to or above 3.3 (Tabachnick & Fidell, 2007). The assumption of multicollinearity (strong correlations between two or more predictors) was checked using the tolerance and variance inflation factor (VIF) values. If the largest VIF value was greater than 10 and the tolerance value less than 0.1, collinearity could not be assumed (Bowerman & O'Connell, 1990; Field, 2013). Durbin-Watson test statistic values less than 1 and higher than 3 were viewed as not meeting the assumption of independent errors (Field, 2013).

The assumption of homoscedasticity (that residuals and variance of the residuals are close to 0 and are the same through all levels of the predictor, and that the regression model fits the data closely) was checked by examining the scatterplot of residuals (Tabachnick & Fidell, 2007). Residuals are the difference between the observed value of the dependent variable and the value predicted by the regression model. This assumption was met if points on the scatterplot of residuals were distributed about the horizontal line in a rectangular position.

The assumption of normally distributed errors was checked using the histogram and P-P plot of regression standardised residuals. This assumption was met if the histogram followed a bell-curve and the P-P plot showed points that were close to the line, particularly at either end (Field, 2013). Finally, the assumption of non-variance was met by checking that the variance of predictors in the model was above 0.

If the covariates of Hypothesis 1 did not predict the dependent variable, group (HI and comparison participants) differences were investigated using paired t-tests or Wilcoxon signed-rank tests depending on the distribution of the data.

Hypothesis 2 was investigated using ordinal logistic regressions because the GODS is an ordinal scale. The relationship between the confounder variable (age) and GODS ratings was investigated using an ordinal logistic regression and included in the final regression model if a significant association was found. The assumptions of ordinal logistic regression include no multicollinearity of two or more independent variables, and the data should have proportional odds, which is when the odds for each predictor variable are consistent across different levels of the dependent variable (Liao, 1994; O'Connell, 2006). If this assumption was violated, the hypothesis was investigated using a Spearman's correlation.

Cohen's *d* (Cohen, 1988) is reported to indicate the effect size of between group differences (paired t-test or Wilcoxon signed-rank test) and Cohen's f^2 (Cohen, 1988) to indicate the effect size for the proportion of variance accounted for by a variable, over and above covariate variables (hierarchical regression). Pearson's or Spearman's rank correlation coefficients are reported as an indication of effect size for the linear relationship between two continuous variables, and odds ratio are reported for the effect size of the relationship between predictor variables and ordinal or dichotomous outcomes (Field, 2013).

5.6 Results

5.6.1 Recruitment of participants

5.6.1.1 Head injury participants

Figure 10 is a flowchart detailing how 47 potential participants with HI were identified and the 35 participants that were eventually recruited with complete data required for analysis.

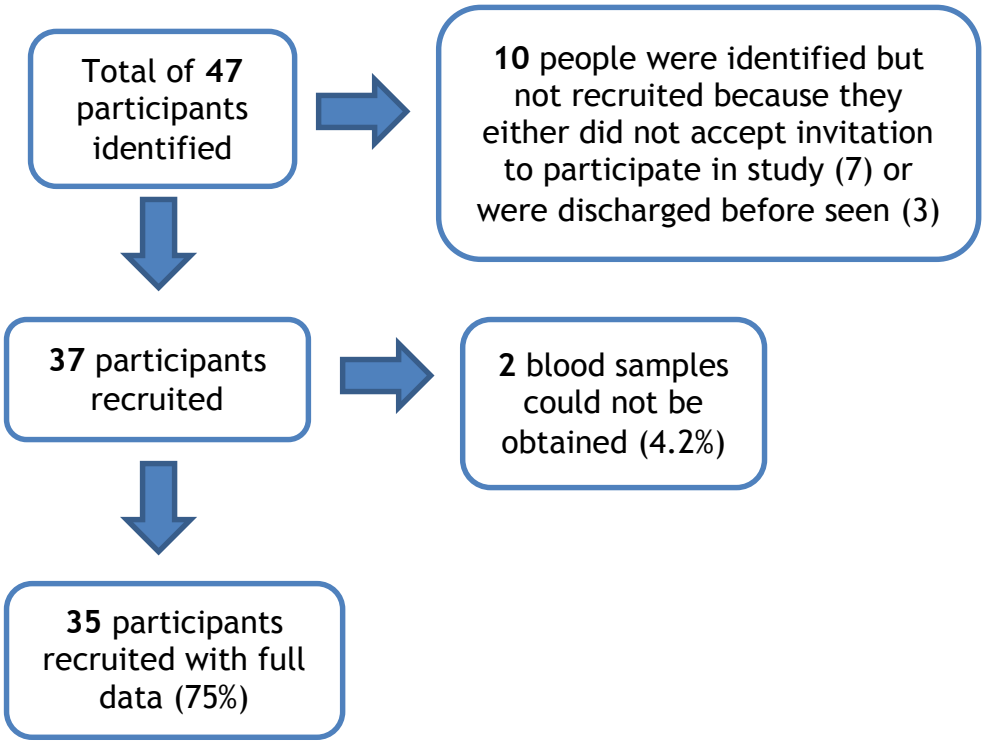

Figure 10 - Recruitment of HI participants in study 1

5.6.1.2 Comparison participants

Figure 11 is a flowchart detailing how 49 potential comparison participants were identified, 47 were screened for suitability, and 35 met the matching criteria to the HI participant to be included in this study.

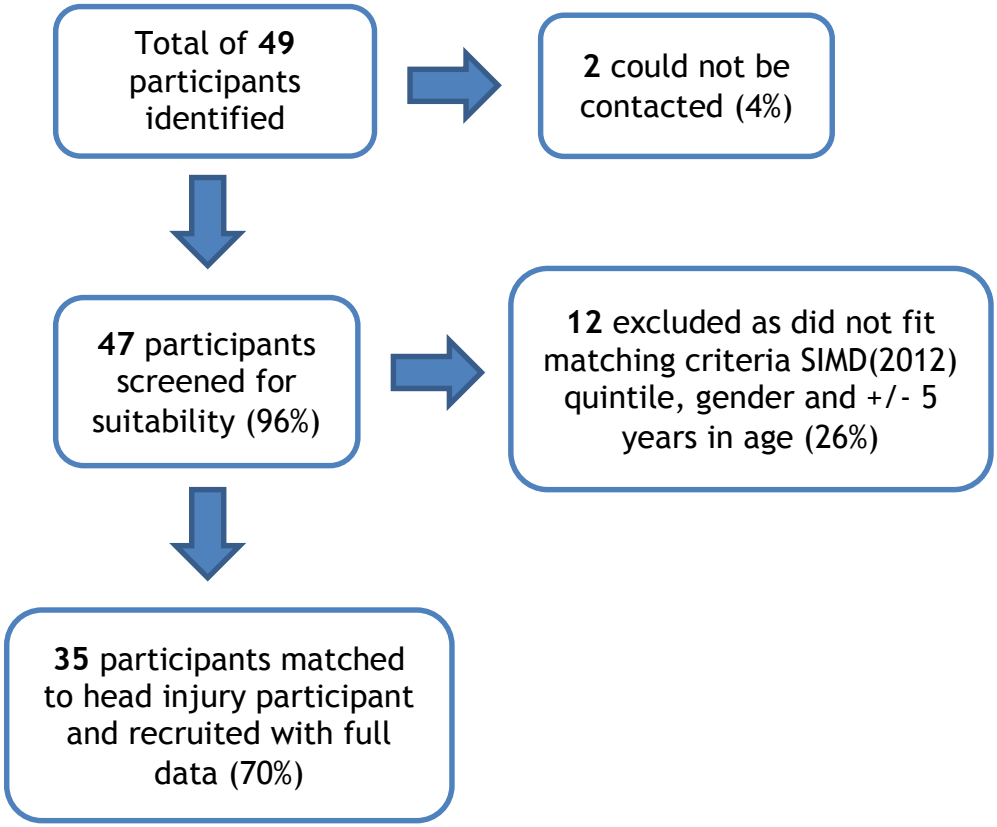

Figure 11 - Recruitment of matched comparison participants in study 1

5.6.2 Demographic information

Complete data were collected for 35 HI participants and 35 comparison participants matched for age (+/- 5 years), gender, and SIMD (2012) quintile.

5.6.2.1 Group matching

The mean age was 41.6 years (SD 14.5, range 16-64) for HI participants and 42.2 years (SD 14.0, range 20-63) for comparison participants. The groups were matched exactly by gender and SIMD (2012) quintile; in each group 27 (77.1%) were male and the majority (65.7%) were from the two most deprived SIMD (2012) quintiles (1 and 2) with 20% from the two most affluent quartiles (4 and 5).

5.6.3 Secondary health information

The descriptive statistics of the secondary health questions are displayed in table 7. There were no significant differences between groups for subjective measure of health (currently in comparison participants and prior to injury in HI participants; p = 0.856, r = 0.02), however HI participants reported a higher number of co-morbidities (p <0.05, r = -0.27) than comparison participants, and were taking significantly more medications (p <0.01, r = -0.59) (see Appendix D, tables 4 and 5 for a list of co-morbidities, and tables 6 and 7 for a list of medication).

	Head injury participants	Comparison participants
	Median (IQR)	Median (IQR)
Subjective measure of health	4 (3, 5) Good (OK, Very good)	4 (4, 4) Good (Good, Good)
Number of co-morbidities	0 (0, 2)	0 (0, 1)
Number of medications	5 (3, 9)	0 (0, 1)

Table 7 - Descriptive statistics of secondary health questions

5.6.4 Head injury group information

5.6.4.1 Length of time between injury and recruitment to study

HI participants were recruited near to discharge from hospital. The time between injury and recruitment ranged from 3 to 279 days (median = 37, IQR: 6, 66).

5.6.4.2 Characteristics of head injury

Table 8 displays the injury characteristics of the HI participants. The most common cause of HI was a fall (57%). Five participants did not lose consciousness and this information was missing for 1 person. This sample is similar in age, gender ratio, cause of injury, and social deprivation to previous Glasgow HI cohorts (McMillan et al., 2012; Thornhill et al., 2000).

Characteristic		n (%)	Median (IQR)	Range
Cause of injury	Fall	20 (57)		
	Assault	7 (20)		
	Road traffic accident	7 (20)		
	Sporting	1 (3)		
Glasgow Coma Scale score		35 (100)	10 (7, 14)	3 - 15
Loss of consciousness		29 (83)	8 hours (0.13, 42.00)	0.1 - 648 hours
Length of post traumatic amnesia		35 (100)	336 hours (24, 696)	0.3 - 1,176 hours
Abnormal CT scan		34 (97)		
Received neurosurgery		13 (37)		
Drinking alcohol at the time of injury		24 (69)		

Table 8 – Characteristics of the injury in the HI group

Table 9 displays the characteristics of severe HI allowing inclusion into the study; participants were included if they had one of these characteristics. All participants had at least one of the required characteristics, 11 (31%) had all four.

	n (%)	GCS <9	PTA >24 hours	Loss of consciousness >6 hours	Abnormal CT scan
	11 (31)	☑	☑	☑	☑
	11 (31)		☑		☑
	8 (23)				☑
	2 (6)	☑	☑		☑
	1 (3)		☑	☑	☑
	1 (3)	☑	☑	☑	
	1 (3)			☑	☑
n (%)	35 (100)	14 (40)	26 (74)	14 (40)	34 (97)

Table 9 – Characteristics of severe HI to be included in study 1

5.6.4.3 Outcome at discharge from hospital on the GODS

The Glasgow Outcome at Discharge Scale (GODS; McMillan et al. (2013); Appendix C) was used as a measure of global outcome after HI near to discharge from hospital. Ratings for the 35 HI participants are given in table 10.

GODS ratings	n	%
Upper Good Recovery (8)	4	11.4
Lower Good Recovery (7)	4	11.4
Upper Moderate Disability (6)	3	8.6
Lower Moderate Disability (5)	4	11.4
Upper Severe Disability (4)	5	14.3
Lower Severe Disability (3)	15	42.9
Total	35	

Table 10 - The frequency and percentage of GODS ratings in the HI group in study 1

When GODS ratings were dichotomised into Good Recovery (≥7) or Disabled (≤6) (Narayan et al., 2002); 8 (23%) participants made a Good Recovery before discharge from hospital and 27 (77%) remained Disabled. Prior to injury, 22 (63%) HI participants were working or in full-time education, 4 (11%) were seeking employment, 1 (3%) was seeking employment, 4 (11%) were receiving disability and sickness benefits, and 4 (11%) were retired.

5.6.5 Hypothesis 1

"Allostatic load scores near to discharge from hospital after a severe head injury are significantly higher than in age, gender, and social position matched comparison participants"

5.6.5.1 Allostatic load score

Tests of normality were conducted initially; the results for the Kolmogorov-Smirnov test indicated that the AL score distribution did not deviate significantly from a normal distribution for HI participants (D = 0.081, p = 0.200) or comparison participants (D = 0.113, p = 0.200). AL scores are shown in table 11.

Participant group	Mean allostatic load score (SD)
Head injury	0.46 (2.22)
Comparison	-0.89 (2.76)

Table 11 – Descriptive statistics for AL scores in study 1

In terms of potential covariates of AL, seventeen (48.6%) HI participants and 8 (22.9%) comparison participants were taking anti-inflammatory medication and 8

(22.9%) HI participants and 2 (5.6%) comparison participants were taking anti-hypertensive medication (see Appendix D, tables 6 and 7 for list). The frequency and percentage of childhood deprivation scores in HI and comparison participants are displayed in table 12. A childhood deprivation score is missing for 1 HI participant as they grew up in care. More comparison participants appeared to experience no childhood deprivation than the HI group; however the groups were more similar higher up the deprivation scale

	Childhood deprivation scores			
Participant group	0 (low)	1	2	3 (high)
	n (%)	n (%)	n (%)	n (%)
Head injury	9 (26)	7 (21)	11 (32)	7 (21)
Comparison	15 (43)	5 (14)	10 (29)	5 (14)

Table 12 - Frequency and percentage of childhood deprivation scores in study 1

Three univariate regressions were used to determine whether the potential confounding variables (childhood deprivation, taking anti-inflammatory, or anti-hypertensive medication) were significantly associated with AL scores. The results are displayed in table 13; childhood deprivation scores significantly predicted AL scores and were therefore included in the analysis as a covariate.

Variable	*b*	*SE B*	*B*	95% CI	*p*
Anti-inflammatory medication	-0.29	0.67	-0.05	-1.63 – 1.04	0.664
Anti-hypertensive medication	-0.41	0.89	-0.06	-2.18 – 1.36	0.643
Childhood deprivation scores	0.60	0.27	0.26	0.05 – 1.14	<0.05

Table 13 - Univariate regression analysis of variables predicting AL scores in study 1

Following this, a two stage hierarchical regression was conducted to determine whether the addition of participant group (HI or comparison group) improved the prediction of AL scores over and above age, gender, SIMD (2012) quintiles, and childhood deprivation scores. The assumptions were checked initially and are reported in the appendix (Appendix E, section 1.1). Table 14 displays the regression statistics for each variable at the step it was entered and the change in R^2. The full model including age, gender, SIMD (2012) quintiles, childhood deprivation scores and participant group was statistically significant (p <0.05). The addition of participant group to the prediction of AL scores (Model 2) led to a statistically significant increase of the predictive capacity of the model by 6%,

with a small-medium effect size (p <0.05, f^2 = 0.07), demonstrating that HI participants had significantly higher AL than comparison participants.

Variable	*b*	*SE B*	*B*	95% CI	*p*	R^2	*Adjusted* R^2	ΔR^2
Step 1						0.14	0.09	-----
Age	0.05	0.03	0.28	0.00 – 0.10	<0.05			
Gender	-0.40	0.75	-0.07	-1.88 – -1.09	0.596			
SIMD (2012) quintile	0.04	0.26	0.02	-0.47 – 0.55	0.867			
Childhood deprivation	0.46	0.31	0.20	-0.17 – 1.08	0.148			
Step 2						0.20	0.14	0.06
Age	0.06	0.02	0.30	0.01 – 0.10	<0.05			
Gender	-0.47	0.72	-0.08	-1.92 – -0.98	0.520			
SIMD (2012) quintile	-0.01	0.25	-0.01	-0.51 – 0.49	0.972			
Childhood deprivation	0.33	0.31	0.15	-0.28 – 0.95	0.283			
Participant group	-1.28	0.59	-0.25	-2.45 – -0.10	<0.05			

Table 14- Hierarchical regression analysis of variables predicting AL scores in study 1

5.6.5.2 Allostatic load components scores

The next section investigated group differences in AL component scores. Scores were checked for normality initially; the Kolmogorov-Smirnov test for normality and the appropriate descriptive statistics are displayed in table 15.

		Kolmogorov-Smirnoff		Descriptive statistics	
Allostatic load component	Participant group	Statistic	*p*	Mean (SD)	Median (IQR)
Cardiovascular	Head injury	0.084	0.200	0.12 (0.92)	
	Comparison	0.077	0.200	0.11 (0.98)	
Neuroendocrine	Head injury	0.082	0.200	-0.44 (1.03)	
	Comparison	0.099	0.200	-0.11 (0.89)	
Anthropometric	Head injury	0.167	<0.05		-0.07 (-0.69, 0.69)
	Comparison	0.186	<0.005		-0.53 (-1.05, 0.69)
Metabolic	Head injury	0.158	<0.05		0.07 (-0.39, 0.54)
	Comparison	0.140	0.080		-0.60 (-0.96, 0.34)
Immune	Head injury	0.120	0.200		0.51 (-0.52, 1.56)
	Comparison	0.177	< 0.01		-0.47 (-0.94, 0.76)

Table 15 – Kolmogorov-Smirnov test and descriptive statistics for AL component scores

Consequently, two univariate regressions demonstrated taking anti-hypertensive medication was not associated with cardiovascular component scores (B = 0.13, 95% CI: -0.29 – 0.99, p = 0.279), and taking anti-inflammatory medication was not associated with immune component scores (B = -0.09, 95% CI: -0.77 – 0.37, p = 0.477), therefore they were not included in the analysis as covariates for their

retrospective component score. Thus paired samples t-tests and Wilcoxon signed-rank tests were used to investigate group differences in AL component scores. Table 16 displays the results; HI participants at discharge from hospital had significantly higher immune and metabolic component scores than comparison participants with medium effect sizes.

	Paired samples t- test				Wilcoxon signed-rank test		
Allostatic load Component	*t*	*df*	*p*	*d*	*T*	*p*	*r*
Cardiovascular	0.03	34	0.974	0.01			
Neuroendocrine	-1.64	34	0.109	0.07			
Anthropometric					259	0.359	-0.11
Metabolic					160	<0.05	0.32
Immune					149	<0.01	0.30

Table 16 – Paired samples t-test and Wilcoxon signed-rank test for differences in AL component scores between groups in study 1

5.6.6 Hypothesis 2

"High allostatic load scores near to discharge from hospital following severe HI are associated with lower Glasgow Outcome near to Discharge Scale ratings"

5.6.6.1.1 Allostatic load scores

The covariate of GODS ratings (age) was checked initially. An ordinal logistic regression demonstrated that age was associated with GODS ratings, with an odds ratio of 0.94, 95% CI of *eB*: 0.90 – 0.99, *B* = -0.06, *S.E B* = 0.02, Wald X^2 = 6.32, *p* <0.05. Although a small effect size, as age increased, GODS ratings decreased (disability increased); therefore it was included in the analysis as a covariate. Following this, 6 ordinal logistic regressions were conducted to investigate whether AL or the component scores predicted GODS ratings at discharge from hospital, controlling for age. Table 17 displays the regression statistics of the final models; higher AL or component scores were not associated with lower GODS ratings. The assumptions were checked and are reported in the appendix (Appendix E, section 1.2).

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for e*β*	*p*
Regression 1						
Age	-0.07	0.03	7.80	0.93	0.89 – 0.98	<0.01
Allostatic load	0.19	0.15	1.63	1.21	0.90 – 1.63	0.202
Regression 2						
Age	-0.07	0.02	7.37	0.94	0.89 – 0.98	<0.01
Cardiovascular	0.35	0.36	1.06	1.42	0.70 – 2.90	0.329
Regression 3						
Age	-0.06	0.02	6.18	0.94	0.90 – 0.99	<0.05
Neuroendocrine	0.04	0.31	0.01	1.04	0.56 – 1.91	0.907
Regression 4						
Age	-0.06	0.02	6.83	0.94	0.90 – 0.99	<0.01
Anthropometric	0.36	0.43	0.69	1.43	0.62 – 3.32	0.407
Regression 5						
Age	-0.06	0.02	5.74	0.95	0.90 – 0.99	<0.05
Metabolic	0.39	0.35	1.24	0.68	0.34 – 1.34	0.265
Regression 6						
Age	-0.06	0.02	6.37	0.94	0.90 – 0.99	<0.05
Immune	0.50	0.29	3.02	1.65	0.94 – 2.91	0.082

Table 17 – Ordinal logistic regression analysis of variables predicting GODS ratings

5.7 Discussion

5.7.1 Principal findings

As expected, near to discharge from hospital, the HI group had significantly higher AL scores than matched comparison participants, and this effect persisted after adjusting for childhood deprivation scores. When the AL component scores were investigated, a significant difference was found between the HI and comparison groups in the metabolic and immune components. Surprisingly, no significant associations were found between disability outcome and AL scores near to discharge from hospital.

5.7.2 Comparison with other studies

There is no previous HI and AL literature with which to directly compare these findings. The higher AL in HI than in comparison participants is consistent with HI participants reporting a significantly higher number of chronic co-morbidities than comparison participants. Higher AL is associated with increased risk of diseases (Juster et al., 2010) thus this secondary finding would support such view. Higher AL at hospital discharge after HI may be relevant to our understanding of the

pathological processes underlying the increased risk of illness and death demonstrated later after HI (McMillan et al., 2011; McMillan et al., 2014).

In particular, the immune and metabolic component scores of HI participants were significantly higher than comparison participants. Thus HI is associated with physiological dysfunction of these two biological symptoms. This may indicate an unhealthier pre-injury lifestyle (McMillan et al., 2014), although evidence for this was not found here. An alternative explanation for this finding is that some in the HI group may have had an acute inflammatory response following the HI, as shown by others (Gentleman et al., 2004; Ikonomovic et al., 2004; Johnson et al., 2013) and this might explain their higher AL. This is supported by the higher immune component score in the HI group.

The higher metabolic component of AL in the HI group could be associated with the immune response as these systems are known to be highly interdependent (Hotamisligil, 2006). For example, insulin resistance is linked to systemic inflammation (Grimble, 2002; Pickup & Crook, 1998). Further, an elevation in cytokine activity can alter metabolism and is associated with organ failure after severe HI (Ott, McClain, Gillespie, & Young, 1994). Evidence from a study of 36 severe HI patients also showed increased plasma insulin and glucagon in the post-resuscitation phase (Chiolero et al., 1989), thus this would be consistent with the observed higher immune and metabolic indicators near to hospital discharge in the participants in this study. However due to the cross-sectional nature of this study, a direct relationship between HI and increased metabolic and immune indicators cannot be determined.

Therefore the higher values for immune and metabolic markers in the HI group may be a result of acute physiological disruption caused by the HI, even though they were recruited near to hospital discharge, after the acute period when some of the physiological systems are more likely to be disrupted. Nevertheless, some may still have had persisting physiological disruption especially given the significantly higher number of medications prescribed in the HI than in the comparison group.

Previous research has linked AL with baseline and follow-up physical (gait, chair stands, hand dexterity, balance, timed measure of foot taps, lower extremity strength and lower extremity dexterity) and cognitive (naming, construction, flexibility, delayed spatial recognition, verbal learning, abstraction, and memory) functioning, however the study populations were healthy Taiwanese and American populations (aged over 54 years) (Goldman et al., 2006; Karlamangla et al., 2002; Seeman et al., 2001; Seeman et al., 1997; Seplaki et al., 2006). This study demonstrated that in a HI population, AL did not help to explain disability outcome, assessed using the GODS.

5.7.3 Strengths and limitations

A limitation of this study is the cross-sectional design, with AL assessed at one time point. It is also not possible to assess AL prior to HI therefore we cannot differentiate between pre-injury differences and acute changes in AL following HI. Another weakness is the use of self-reported secondary health information, for example there may be systemic self-serving bias in over-estimating self-reported ratings of health. Therefore this information may be an unreliable measure of health. The number of medications taken may be a more robust indicator of health as medication use will be mostly prescribed, however this cannot be guaranteed as the data was collected via self-report from participants and not from their medical notes. Despite this caution, the HI participants in this study were taking a significantly higher number than comparison participants. However, this may have been due to managing acute symptoms of the HI rather than being related to systemic diseases.

Another limitation of this study is the difficulty in generalising these findings to other HI populations around the world. For example, an epidemiological study of HI participants admitted to intensive care units in Australia and New Zealand demonstrated that in a sample of 363 severe HI participants, the most common cause of injury was vehicular trauma (59.5%), followed by falls occurring predominantly in elderly patients (24.2%), and then assaults (8.3%) (Myburgh et al., 2008). In this study of Glasgow severe HI participants, the most common cause of injury was falls (57%), followed by assaults and road traffic accidents (20%). Of the 20 participants whose cause of injury was a fall, 80% had been drinking alcohol

at the time of injury. Although the cause of injury in this study is similar to Scotland and Northern Europe (Shivaji, Lee, Dougall, McMillan, & Stark, 2014; Tagliaferri et al., 2006), the different causes of injury in Australia and New Zealand indicate potential differences in lifestyle and demographic factors of HI populations. Further, the environments in which people live are known to have an effect on health and mortality rates. In Glasgow, lower life expectancy is found, linked to poverty and deprivation, than in comparable UK cities such as Manchester and Liverpool (Walsh, McCartney, Collins, Taulbut, & Batty, 2016). This complex, multifactorial phenomenon, known as the 'Glasgow effect', may impact on measures of AL in samples from Glasgow, leading to another limitation in the generalisability of the results from this study to HI populations in other cities or countries.

Strengths of this study include that the HI participants were recruited as soon as medically stable and with capacity to consent after HI. This allows exploration of the relationship between AL and disability outcome at an early time point and prospective investigation of this cohort in future studies. The use of a comparison group also gives this study strength, and the fact that the HI participants were matched very closely to comparison participants; exactly for SIMD (2012) quintile and gender, and very similar in age.

Of note, there was a wide range of time between occurrence of the HI and recruitment to the study. Head injury participants were recruited when they were deemed stable enough to be discharged from hospital and had the capacity to consent. By recruiting participants at this point, GODS ratings were unlikely to be biased by potential covariates such as post traumatic amnesia or medical instability. This enabled a clearer and more comparable picture of functional ability near to discharge from hospital following severe HI. Recovery to this orientated, stable condition varies between HI patients and is not controllable, which explains the wide range of time to recruitment following HI. The analysis was repeated after removing the largest outlier (participant recruited 279 days after injury) and AL was still not associated with GODS ratings, (odds ratio 1.20; 95% CI 0.89, 1.61; β = 0.18, *S.E* β = 0.15, Wald X^2 = 1.36, p = 0.243.

5.7.4 Implications of findings

The group difference in AL scores between HI and comparison participants implies that the HI population may have an unhealthier pre-injury lifestyle than comparison participants. This has large implications in terms of public health and NHS services; how HI participants are treated in hospital and in the community. A HI could be a flag of someone who is at risk of early mortality due to poor lifestyle choices, even those with mild HI. In this case, HI patients should receive education in hospital about lifestyle choices, and community follow-up should be mandatory and standard for all HI participants, as a preventative measure against early mortality.

The other implication from this research is that AL does not explain the heterogeneity of outcome in terms of disability near to discharge from hospital. A ramification of this is that at this time point, how to predict outcome following HI using the GODS remains unclear. However these findings could be explained by persisting physiological disruption caused by the HI. To further explore these findings, AL and disability outcome were reassessed in these HI participants 6 months after injury as describe in Chapter 6.

5.7.5 Conclusion

Head injury participants at discharge from hospital have significantly higher AL than age, SIMD (2012) quintile, and gender matched comparison participants. The findings do not support the view that AL explains the heterogeneity of outcome after HI near to discharge from hospital in terms of disability outcome. To ascertain whether higher AL in the HI group is due to acute physiological dysregulation caused by the HI, the HI participants were followed-up approximately 6 months later as described in Chapter 6.

Chapter 6 **Allostatic load following a severe head injury, 6 months after discharge from hospital**

Background

Chapter 5 demonstrated that HI participants near to discharge from hospital had significantly higher AL scores than comparison participants. It is possible this effect may be due to an acute disruption to physiological systems in response to the HI; thus it is necessary to follow-up the participants from that study to allow any acute effects of the HI to stabilise to ascertain whether they were affecting AL scores in the HI group at discharge from hospital.

Methods

The participants from study 1 were followed-up approximately 6 months after hospital discharge (n = 28). Assessment of AL was repeated and compared to those in the matched comparison participants from study 1 (Chapter 5). AL scores in the HI group were also compared with disability outcome (Glasgow Outcome Scale-Extended) at 6 month follow-up, and this data compared with AL scores and disability outcome near to hospital discharge (study 1, Chapter 5) to investigate change in disability. Any change in disability outcome was explored in terms of AL, and covariates assessed at hospital discharge and at 6 month follow-up.

Results

There was no significant difference in AL scores or component scores between HI participants and comparison participants at 6 month follow-up. AL scores or component scores at hospital discharge or 6 month follow-up did not predict disability outcome at 6 month follow-up, with one exception; high neuroendocrine markers at hospital discharge were associated with lower Glasgow Outcome ratings (greater disability) at 6 month follow-up. Change in disability outcome was observed in 66% of HI participants and did not correlate with AL or the component scores near to hospital discharge or at 6 month follow-up.

Conclusions

The findings of this study do not support the view that brain damage causes higher AL 6 months after discharge from hospital, compared with non-HI participants. Change in AL between hospital discharge and 6 month follow-up does not explain the heterogeneity of disability outcome at 6 months, or change in disability from hospital discharge; with the exception of an inverse relationship between neuroendocrine indicators of health at discharge from hospital and worse disability outcome 6 months later.

6.1 Introduction

In study 1 (Chapter 5) the associations between allostatic load (AL) and early outcomes after head injury (HI) were investigated. The results showed HI participants near to discharge from hospital had significantly higher AL scores than comparison participants. This may indicate that the HI group have an unhealthier pre-injury lifestyle. However these findings may result from an acute disruption to physiological systems in response to the HI. Therefore it is important to investigate AL and disability outcome again later after hospital discharge to allow any acute effects of the HI to stabilise to ascertain whether they were altering AL scores in the HI group at discharge from hospital.

The aim of the present study was to follow-up the participants from study 1 approximately 6 months after hospital discharge. The AL scores in HI participants 6 months after hospital discharge were compared to those in the matched comparison participants described in study 1 (Chapter 5). AL scores in the HI group were also compared with disability outcome on the GOS-E at 6 month follow-up, and this data compared with AL scores and GODS ratings near to hospital discharge (study 1, Chapter 5) to investigate change in disability. Any change in Glasgow Outcome ratings were explored in terms of AL, and covariates assessed at hospital discharge and at 6 month follow-up.

6.2 Aims

1. To investigate whether AL changes between hospital discharge and 6 month follow-up in HI participants compared to a matched comparison group.

2. To investigate whether AL is associated with Glasgow Outcome ratings 6 months after hospital discharge following HI.

3. To investigate whether AL near to discharge from hospital after a HI predicts Glasgow Outcome ratings 6 months later.

4. To investigate whether any change in Glasgow Outcome ratings between hospital discharge and 6 month follow-up is explained by AL.

6.3 Hypotheses

1. The allostatic load score in head injury participants 6 months after hospital discharge is significantly higher than that in age, gender, and social position matched comparison participants.

2. High allostatic load scores, 6 months after hospital discharge following severe head injury, are associated with lower Glasgow Outcome ratings at 6 months.

3. High allostatic load scores near to hospital discharge following severe head injury are associated with lower Glasgow Outcome ratings 6 months later.

4. Low allostatic load scores are associated with an increase in Glasgow Outcome ratings between discharge and 6 month follow-up

6.4 Design

The design was a prospective cohort study.

6.5 Methods

The 35 severe HI participants, who were assessed in study 1, were followed up 6 months later.

6.5.1 Ethics

Ethical approval for this study was obtained at the same time as study 1 from the West of Scotland Research Ethics Service and NHS management approval from NHS Greater Glasgow and Clyde (GG&C) Health Board approval (see Appendix A for approval letters). Tayside R&D management approval was also obtained due to slow recruitment rates (see Appendix A).

6.5.2 Recruitment

6.5.2.1 Head injury participants

Five and a half months following recruitment and first assessment, participants were sent a letter reminding them of the study, thanking them for taking part and

asking them to make contact with the research group for follow-up. If an individual did not respond within 10 days, they were contacted by telephone. Occasionally, participants were not contactable using the address or phone number provided. If so, the GP surgery was contacted to check current contact details.

6.5.2.1.1 Inclusion criteria

HI participants who took part in study 1 were invited for a follow-up assessment. There were no other further inclusion criteria, other than those already detailed for study 1 (Chapter 5).

6.5.2.1.2 Exclusion criteria

There were no further exclusion criteria other than that described previously for study 1 (Chapter 5).

6.5.2.2 Comparison participants

Allostatic load develops slowly over time in the general population (McEwen, 1998b, 2000) therefore the AL scores in the matched comparison participants were not expected to change significantly in 6 months. If a follow-up of comparison participants was attempted, the process could be costly with a high dropout rate anticipated. Therefore the same data from the age, gender, and SIMD (2012) quintile matched comparison participants in Study 1 (Chapter 5) were used for comparison with AL scores in the HI participants 6 months after injury. The comparison group was matched 1:1 to HI participants in study 2 on the basis of age (+/- 5 years), gender, and SIMD (2012) quintile (see Chapter 3 for details).

6.5.3 Procedure

Participants were assessed at the CRF Glasgow Royal Infirmary, CRF Western Infirmary, CRF Southern General Hospital, the rehabilitation centre, or the home of participants.

6.5.4 Measures

6.5.4.1 Main outcomes

6.5.4.1.1 Assessment of disability after head injury

The GOS-E (Wilson et al. (1998); Appendix C) was used to assess disability outcome after HI for participants in the community and the GODS (McMillan et al. (2013); Appendix C) if participants were inpatients in hospital or in a rehabilitation setting. The GODS was developed from the GOS-E; see Appendix D (table 1) and Chapter 3 for a detailed description of both. Therefore for this analysis, a new variable was created that incorporated GOS-E rating for participants living in the community and GODS rating for those in an inpatient setting. Outcome at 6 months after discharge from hospital was disability, independent of whether the individual was in an inpatient in a rehabilitation setting (GODS) or in the community (GOS-E).

6.5.4.1.2 Allostatic load

AL scores were reassessed in HI participants at 6 month follow-up, the procedure is described in Chapter 3.

6.5.4.2 Confounders

6.5.4.2.1 Confounders of disability outcome

6.5.4.2.1.1 The Perceived Stress Scale

Ratings of perceived stress have been shown to predict disability outcome at follow-up (McMillan et al., 2012). Therefore the Perceived Stress Scale (Cohen et al. (1983); Appendix C) was used at hospital discharge (study 1, Chapter 5) to assess self-reported experiences of stress over the last 4 weeks. It is a 14 item self-report questionnaire, rated on a 5-point Likert scale; total scores are obtained by reversing the ratings on the seven positive items, and summing all ratings to create a total out of 56 points. These scores of perceived stress, assessed at hospital discharge (see Chapter 5), were included in analyses if shown to be associated with Glasgow Outcome ratings at 6 month follow-up.

6.5.4.2.1.2 The Multidimensional Health Locus of Control

Health locus of control, particularly as due to Chance or Powerful others is a predictor of disability on the GOS-E at follow-up (McMillan et al., 2012). In study 1 (Chapter 5), HI participants received the Multidimensional Health Locus of Control (MHLC) (Wallston et al. (1978); Appendix C), an 18 item scale administered via a self-completed questionnaire, which assesses beliefs that motivate health-related behaviours as either primarily Internal, due to Chance, or controlled by Powerful others. Scores for Chance and Powerful others using the Multidimensional Health Locus of Control from assessment at hospital discharge (see Chapter 5) were included in analyses as covariates if found to be associated with Glasgow Outcome ratings at 6 month follow-up.

6.5.4.2.1.3 Age

Older age is a predictor of poorer outcome after HI, as described in Chapter 3 (Jacobsson et al., 2009; McMillan et al., 2012; Thornhill et al., 2000); if it was associated with Glasgow Outcome ratings at 6 months, it was included in analyses as a covariate.

6.5.4.2.2 Confounders of change in disability outcome after head injury

6.5.4.2.2.1 The Alcohol Use Disorder Identification Test

As described in Chapter 3, alcohol misuse, assessed retrospectively is associated with poorer outcome after HI, (Whitnall et al., 2006). The Alcohol Use Disorder Identification Test (AUDIT; Saunders et al. (1993); Appendix C) was used at the 6 month follow-up and included in the analysis as a covariate if found to be associated with change in disability. In this study, the AUDIT was phrased to account for patterns of alcohol intake since injury, rather than the standard timeframe of 'in the last year'.

6.5.4.2.2.2 The Multidimensional Health Locus of Control

Perception of health locus of control as 'Powerful others' is associated with increased disability over time (McMillan et al., 2012). Therefore, using the MHLC (Wallston et al. (1978); Appendix C) at hospital discharge, scores of Powerful

others were included in analyses at the 6 month follow-up if shown to be associated with change in disability outcome between these two time points.

6.5.4.2.3 Confounders of allostatic load

Older age, greater social deprivation and childhood deprivation are associated with higher AL and were included in analyses as covariates (Crimmins et al., 2003; Dich et al., 2014; Gruenewald et al., 2012; Hasson et al., 2009; Singer & Ryff, 1999). See Chapter 3 for details of how social deprivation and childhood deprivation were assessed. Anti-hypertensive and anti-inflammatory tablets affect cardiovascular and immune functioning, and were also included as covariates in analyses of their respective components and AL scores if they were found to be significant predictors.

6.5.4.3 Other information

A self-report questionnaire was created to obtain information about access to rehabilitation since hospital discharge. For participants who were inpatients in rehabilitation settings at follow-up, this information was crosschecked with the rehabilitation notes at the centre.

Secondary measures of health from study 1 were repeated including; the current subjective measure of health from 'Very Poor' to 'Very Good', the number of medications participants were taking at follow-up, and the number of new diagnoses in the last 6 months was added to pre-injury co-morbidities.

6.5.5 Data analysis plan

Data were analysed using SPSS v22. The distributions of the data were determined by conducting Kolmogorov-Smirnov tests on each variable. Demographic information for both groups and HI details were initially considered descriptively and differences in secondary health questions investigated using a paired t-test or Wilcoxon Signed- Rank test.

For Hypothesis 1, potential covariates (childhood deprivation scores, anti-inflammatory, and anti-hypertensive medication) were investigated using univariate regressions. If the univariate regressions were significant, the data

were analysed using hierarchical regressions that adjusted for covariates. In this instance, though the groups were matched for age, gender, and SIMD (2012) quintiles, regression models do not compute paired data points. The recruitment of participants was not random, particularly comparison participants, who were recruited based on the matching variables. Therefore age, gender, and SIMD (2012) quintiles were also controlled for in the final hierarchical regression model in order to compensate for potential bias in recruitment (Pallant, 2013). The assumptions of regressions are described in Chapter 5. If the covariates of Hypothesis 1 did not predict the dependent variable, group (HI and comparison participants) differences were investigated using paired t-tests or Wilcoxon signed-rank tests depending on the distribution of the data.

Hypotheses 2, 3, and 4 were investigated using ordinal logistic regression because the Glasgow Outcome Scales are ordinal in nature (assumptions described in Chapter 5). The relationships between confounder variables (age, Perceived Stress Scale scores, and ratings of health locus of control as 'Chance' and 'Powerful others', using the Multidimensional Health Locus of Control) and Glasgow Outcome ratings were investigated using ordinal logistic regressions and included in the final regression model if a significant association was found. If the assumption of proportional odds was violated, these hypotheses were investigated using a Spearman's correlation.

Cohen's *d* (Cohen, 1988) is reported as an indicator of effect size for between group differences (paired t-test or Wilcoxon signed-rank test) and Cohen's f^2 (Cohen, 1988) as an indicator of effect size for the proportion of variance accounted for by a variable, over and above covariate variables (hierarchical regression). Pearson's or Spearman's rank correlation coefficients are reported to indicate the effect size for the linear relationship between two continuous variables, and odds ratios are reported for the effect size of the relationships between predictor variables and ordinal or dichotomous outcomes (Field, 2013).

6.6 Results

6.6.1 Follow-up of head injury participants

Figure 12 details the follow-up of HI participants from study 1.

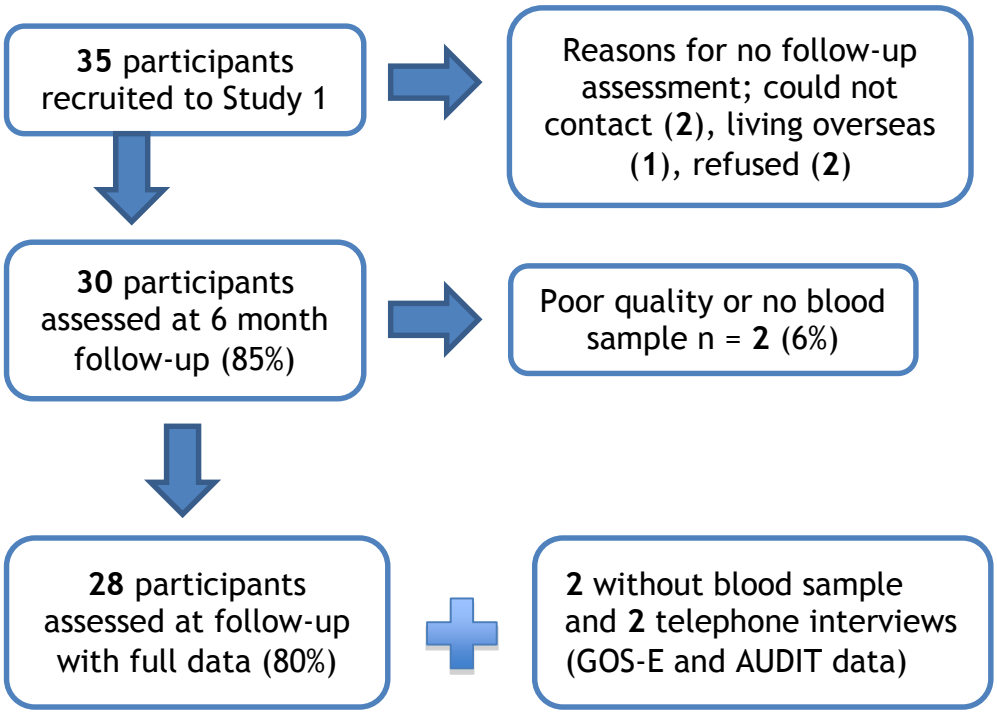

Figure 12 - Follow-up of HI participants 6 months after hospital discharge in study 2

6.6.1.1 Time since recruitment

The median number of days from recruitment to follow-up was 196 (IQR: 182, 221). In terms of time from injury to follow-up assessment, the median number of days was 239 (IQR: 213, 286).

6.6.2 Head injury group information

6.6.2.1 Rehabilitation

Of the 28 HI participants followed-up with full data, 24 (86%) received brain injury rehabilitation. Seven (25%) received inpatient rehabilitation, 10 (36%) received outpatient rehabilitation, and 7 (25%) received both. Four (14%) were inpatients in a neurorehabilitation centre at 6 month follow-up. Four (14%) participants were assessed for rehabilitation but did not require this following discharge from hospital.

6.6.3 Demographic information

Complete data were collected from 28 HI participants and 28 comparison participants matched for age (+/- 5 years), gender and SIMD (2012) quintile.

6.6.3.1 Group matching

The mean age was 44.8 years (SD = 13.5, range 16-64) for HI participants and 45.0 years (SD = 13.5, range 20-63) for comparison participants. Groups were matched exactly for gender and SIMD (2012) quintile, with 20 (71.4%) male in each group and the majority from high deprivation SIMD (2012) quintiles 1 and 2 (64.3%) with 21.4% from 4 and 5 the most affluent quintiles.

6.6.4 Secondary health information

The descriptive statistics for the secondary health questions are displayed in table 18. There were no significant differences between groups for the subjective measure of health (p = 0.951, r = -0.01), or number of chronic co-morbidities (p = 0.653, r = -0.06), however HI participants were taking a significantly higher number of medications than comparison participants (p <0.001, r = -0.60) (see Appendix D, tables 8 and 9 for a list of co-morbidities, and tables 10 and 11 for a list of medication).

	Head injury participants	Comparison participants
	Median (IQR)	Median (IQR)
Subjective measure of health	4 (3, 4) Good (Ok, Good)	4 (4, 4) Good (Good, Good)
Number of co-morbidities	1 (0, 2)	0 (0, 1)
Number of medications	2 (1, 5)	0 (0, 1)

Table 18 - Secondary health questions descriptive statistics in study 2

6.6.5 Disability outcome 6 months after discharge from hospital

Glasgow Outcome ratings for the 28 HI participants at hospital discharge and at 6 month follow-up are displayed in table 19.

Glasgow Outcome Rating	At discharge from hospital Frequency (%)	At 6 month follow-up Frequency (%)
Upper Good Recovery (8)	3 (10.7)	5 (17.9)
Lower Good Recovery (7)	3 (10.7)	4 (14.3)
Upper Moderate Disability (6)	2 (3.6)	3 (10.7)
Lower Moderate Disability (5)	3 (10.7)	4 (14.3)
Upper Severe Disability (4)	4 (14.3)	4 (14.3)
Lower Severe Disability (3)	13 (46.4)	8 (28.6)
Total	28	28

Table 19 - Frequency and percentage of Glasgow Outcome ratings in study 1 and 2

Glasgow Outcome ratings were dichotomised into Good Recovery (a rating of 7 and above) or Disabled (a rating of 6 or below) (Narayan et al., 2002); 32% (n = 9) of participants made a Good Recovery at 6 month follow-up and 69% (n = 19) remained Disabled.

6.6.6 Hypothesis 1

"The allostatic load score of head injury participants 6 months after hospital discharge is significantly higher than that in age, gender, and social position matched comparison participants"

6.6.6.1 Allostatic load scores

Results for the Kolmogorov-Smirnov test for normality indicated that the AL score distribution did not deviate significantly from a normal distribution for HI participants (D = 0.083, p = 0.200) or comparison participants (D = 0.099, p = 0.200). AL scores are shown in table 20.

	Mean allostatic load score (SD)
Head injury participants	-0.64 (2.31)
Comparison participants	-0.97 (2.92)

Table 20 - Descriptive statistics for AL scores in study 2

Three (10.7%) HI participants and 4 (14.3%) comparison participants were taking anti-inflammatory medication and 5 (17.9%) HI participants and 5 (17.9%) comparison participants were taking anti-hypertensive medication (see Appendix D tables 10 and 11 for list). The frequency and percentage of childhood deprivation scores in HI and comparison participants are displayed in table 21. A childhood deprivation score is missing for 1 HI participant as they grew up in care.

Slightly more comparison participants appeared to experience no childhood deprivation than the HI group; however the groups were more similar higher up the deprivation scale.

Childhood deprivation scores	0 (low)	1	2	3 (high)
	n (%)	n (%)	n (%)	n (%)
Head injury group	6 (22)	7 (26)	10 (37)	4 (15)
Comparison group	10 (36)	5 (18)	9 (32)	4 (14)

Table 21 - Frequency and percentage of childhood deprivation scores in study 2

Three univariate regressions were used to determine whether the potential confounding variables (childhood deprivation, taking anti-inflammatory, or anti-hypertensive medication) were significantly associated with AL scores. The results are displayed in table 22; none of the variables predicted AL scores therefore they were not included in the analysis as covariates.

Variable	*b*	*SE B*	*B*	95% CI	*p*
Childhood deprivation scores	-2.36	1.36	-0.32	-5.15 – 0.44	0.095
Anti-hypertensive medication	0.87	1.15	0.15	-1.49 – 3.23	0.454
Anti-inflammatory medication	0.27	0.41	0.13	-0.58 – 1.13	0.514

Table 22 - Univariate regression analysis of variables predicting AL scores

With no covariates to adjust for in the analysis, Hypothesis 1 was investigated using a paired t-test as the groups were matched for age (= /- 5 years), gender, and SIMD (2012) quintile, and were both normally distributed. Results show that the mean score of AL for the HI group was not significantly different from that of the comparison participants ($t(27) = 0.45$, $p = 0.654$).

6.6.6.2 Allostatic load components scores

Results for the Kolmogorov-Smirnov test for normality and the appropriate descriptive statistics are displayed in table 23.

		Kolmogorov-Smirnoff		Descriptive statistics	
Allostatic load Component	Participant group	Statistic	*p*	Mean (*SD*)	Median (IQR)
Cardiovascular	Head injury	0.102	0.200	0.10 (1.06)	
	Comparison	0.099	0.200	0.14 (1.05)	
Neuroendocrine	Head injury	0.108	0.200	-0.02 (1.05)	
	Comparison	0.134	0.200	0.04 (0.92)	
Anthropometric	Head injury	0.178	0.024		-0.27 (-0.72, 0.12)
	Comparison	0.231	<0.005		-0.57 (-1.02, 0.55)
Metabolic	Head injury	0.110	0.200		-0.37 (-0.88, 0.08)
	Comparison	0.182	<0.05		-0.62 (-0.97, 0.23)
Immune	Head injury	0.181	<0.05		-0.14 (-0.89, 0.60)
	Comparison	0.200	<0.01		-0.63 (-1.03, 0.80)

Table 23 - Kolmogorov-Smirnov test and descriptive statistics for AL component scores

Univariate regressions demonstrated that taking anti-hypertensive medication was not associated with cardiovascular component scores (β = -0.10, 95% CI: -1.24 – 0.59, p = 0.479), nor was taking anti-inflammatory medication associated with immune component scores (β = 0.01, 95% CI: -0.77 – 0.84, p = 0.930), therefore they were not included in the analysis as covariates for their retrospective component score. Table 24 shows the results of the paired samples t-tests and Wilcoxon signed-rank tests; there were no significant differences in AL component scores between HI participants 6 months after hospital discharge and comparison participants.

	Paired samples t- test				Wilcoxon signed-rank test		
Allostatic load Component	*t*	*df*	*p*	*d*	*T*	*p*	*r*
Cardiovascular	-0.17	27	0.868	-0.04			
Neuroendocrine	-0.27	27	0.791	-0.08			
Anthropometric					169	0.631	-0.06
Metabolic					181	0.616	-0.07
Immune					211	0.855	0.02

Table 24 - Paired samples t-test and Wilcoxon signed-rank test for group differences in AL component scores.

6.6.7 Hypothesis 2

"High allostatic load scores, 6 months after hospital discharge following severe head injury, are associated with lower Glasgow Outcome ratings at 6 months"

Initially the covariates of Glasgow Outcome ratings (age, ratings of PSS, Health locus of control perceived as 'Powerful others' and 'Chance') were investigated

using four ordinal logistic regressions. Table 25 displays the regression statistics; age predicted Glasgow Outcome ratings (higher age was associated with lower Glasgow Outcome ratings and therefore a poorer outcome), therefore it was included in the analyses as a covariate.

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for e*β*	*p*
Perceived Stress Scale score	0.00	0.03	0.01	1.00	0.95 – 1.06	0.921
'Chance' Locus of Control	-0.03	0.06	0.66	0.17	0.86 – 1.10	0.684
'Powerful others' Locus of Control	-0.01	0.04	0.10	0.99	0.91 – 1.07	0.753
Age	-0.06	0.03	4.44	0.94	0.89 – 1.00	< 0.05

Table 25 - Ordinal logistic regression analysis of variables predicting disability outcome

6.6.7.1 Allostatic load scores

Table 26 displays the regression statistics of the final model; high AL scores were not associated with low ratings on the Glasgow Outcome scales at 6 month follow-up. The assumption of proportional odds was met (X^2 = 5.26, p = 0.729) and tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.97, VIF = 1.03; AL, tolerance = 0.97, VIF = 1.03).

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for e*β*	*p*
Age	-0.06	0.03	4.16	0.94	0.89 – 1.00	<0.05
Allostatic load score	0.03	0.16	0.03	1.03	0.75 – 1.41	0.859

Table 26 - Ordinal logistic regression analysis of variables predicting disability outcome

6.6.7.2 Allostatic load component scores

6.6.7.2.1 Cardiovascular

Table 27 displays the regression statistics; high cardiovascular component scores were not associated with low ratings on the Glasgow Outcome scales at 6 month follow-up. The assumption of proportional odds was met (X^2 = 5.98, p = 0.649) and tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.97, VIF = 1.04; cardiovascular component score, tolerance = 0.97, VIF = 1.04).

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for e*β*	*p*
Age	-0.07	0.03	5.92	0.93	0.87 – 0.99	<0.05
Cardiovascular component score	0.52	0.36	1.06	2.13	0.84 – 3.40	0.145

Table 27 – Ordinal logistic regression analysis of variables predicting disability outcome

6.6.7.2.2 Neuroendocrine

Table 28 displays the regression statistics; high neuroendocrine component scores were not associated with low ratings on the Glasgow Outcome scales at 6 month follow-up. The assumption of proportional odds was met (X^2 = 4.22, p = 0.836) and tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 1.00, VIF = 1.00; neuroendocrine component score, tolerance = 1.00, VIF = 1.00).

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for e*β*	*p*
Age	-0.06	0.03	4.03	0.95	0.90 – 1.00	<0.05
Neuroendocrine component score	-0.40	0.35	1.33	0.67	0.34 – 1.32	0.671

Table 28 – Ordinal logistic regression analysis of variables predicting disability outcome

6.6.7.2.3 Anthropometric

Table 29 displays the regression statistics; high anthropometric component scores were not associated with low ratings on the Glasgow Outcome scales at 6 month follow-up. The assumption of proportional odds was met (X^2 = 3.26, p = 0.515) and tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.97, VIF = 1.03; anthropometric component score, tolerance = 0.97, VIF = 1.03).

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for e*β*	*p*
Age	-0.06	0.03	4.58	0.94	0.89 – 1.00	<0.05
Anthropometric component score	0.18	0.44	0.18	1.20	0.51 – 2.85	0.676

Table 29 – Ordinal logistic regression analysis of variables predicting disability outcome

6.6.7.2.4 Metabolic

Table 30 displays the regression statistics; high metabolic component scores were not associated with low ratings on the Glasgow Outcome scales at 6 month follow-up. The assumption of proportional odds was met (X^2 = 3.59, p = 0.892) and tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.81, VIF = 1.24; metabolic component score, tolerance = 0.81, VIF = 1.24).

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for e*β*	*p*
Age	-0.06	0.03	4.39	0.94	0.90 – 1.00	<0.05
Metabolic component score	0.64	0.41	0.02	1.07	0.48 – 2.39	0.876

Table 30 – Ordinal logistic regression analysis of variables predicting disability outcome

6.6.7.2.5 Immune

Table 31 displays the regression statistics; high immune component scores were not associated with low ratings on the Glasgow Outcome scales at 6 month follow-up. The assumption of proportional odds was met (X^2 = 2.06, p = 0.979) and test to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 1.00, VIF = 1.01; immune component score, tolerance = 1.00, VIF = 1.01).

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for e*β*	*p*
Age	-0.06	0.03	3.90	0.95	0.90 – 1.00	<0.05
Immune component score	-0.15	0.35	0.19	0.66	0.43 – 1.70	0.663

Table 31 – Ordinal logistic regression analysis of variables predicting disability outcome

6.6.8 Hypothesis 3

"High allostatic load scores near to hospital discharge following severe head injury are associated with lower Glasgow Outcome ratings 6 months later"

Allostatic load scores were available for all 35 participants near to hospital discharge. Glasgow Outcome data were available for 32 participants at 6 month follow-up; in addition to the 28 participants successfully follow-up with full data, a further 2 participants attended the follow-up assessment but had poor quality blood samples that could not be included in the analyses for Hypothesis 1 and 2, and 2 participants could not attend follow-up appointments so a telephone interview was conducted to obtain Glasgow Outcome ratings.

It was important to check the relationship between Glasgow Outcome ratings and potential confounders in the 32 participants. Initially the following covariates were investigated using four ordinal logistic regressions: age, ratings of PSS, Health locus of control perceived as 'Powerful others' and 'Chance'. Table 32 displays the regression statistics; age was a significant predictor of Glasgow Outcome ratings at 6 month follow-up (higher age was associated with poorer outcome), therefore it was included in the analyses as a covariate.

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for e*β*	*p*
Perceived Stress Scale score	-0.01	0.03	0.09	0.99	0.94 – 1.05	0.992
'Chance' Locus of Control	-0.04	0.06	0.39	0.96	0.86 – 1.08	0.533
'Powerful others' Locus of Control	-0.03	0.04	0.45	0.97	0.90 – 1.06	0.503
Age	-0.05	0.02	4.35	0.95	0.91 – 1.00	< 0.05

Table 32 – Ordinal logistic regression analysis of variables predicting disability outcome

6.6.8.1 Allostatic load scores

Table 33 displays the regression statistics for the final model; high AL scores at hospital discharge were not associated with low ratings on the Glasgow Outcome Scales at 6 month follow-up. The assumption of proportional odds was met (X^2 = 3.69, p = 0.884) and tests for the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.91, VIF = 1.10; AL score, tolerance = 0.91, VIF = 1.10).

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for e*β*	*p*
Age	-0.05	0.03	3.17	0.96	0.91 – 1.01	<0.05
Allostatic load score	-0.11	0.17	0.43	0.90	0.65 – 1.24	0.896

Table 33 – Ordinal logistic regression analysis of variables predicting disability outcome

6.6.8.2 Allostatic load component scores

6.6.8.2.1 Cardiovascular

Table 34 displays the regression statistics; high cardiovascular component scores at hospital discharge were not associated with low ratings on the Glasgow Outcome Scales at 6 month follow-up. The assumption of proportional odds was met (X^2 = 11.78, p = 0.134) and tests for collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.96, VIF = 1.05; cardiovascular component score, tolerance = 0.96, VIF = 1.05).

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for e*β*	*p*
Age	-0.05	0.03	3.50	0.95	0.91 – 1.00	<0.05
Cardiovascular component score	-0.08	0.39	0.05	0.92	0.43 – 1.99	0.920

Table 34 – Ordinal logistic regression analysis of variables predicting disability outcome

6.6.8.2.2 Neuroendocrine

Table 35 displays the regression statistics; high neuroendocrine component scores at hospital discharge were significantly associated with lower ratings on the Glasgow Outcome Scales (increased disability) at 6 month follow-up with the odds

of 0.49. The assumption of proportional odds was met (X^2 = 1.31, p = 0.995) and for collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.91, VIF = 1.10; neuroendocrine component score, tolerance = 0.91, VIF = 1.10).

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for e*β*	*p*
Age	-0.05	0.03	3.82	0.95	0.91 – 1.00	<0.05
Neuroendocrine component score	-0.71	0.34	4.35	0.49	0.25 – 0.96	<0.05

Table 35 – Ordinal logistic regression analysis of variables predicting disability outcome

6.6.8.2.3 Anthropometric

Table 36 displays the regression statistics; high anthropometric component scores at hospital discharge were not associated with low ratings on the Glasgow Outcome Scales at 6 month follow-up. The assumption of proportional odds was met (X^2 = 1.91, p = 0.984) and tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 1.00, VIF = 1.00; anthropometric component score, tolerance = 1.00, VIF = 1.00).

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for e*β*	*p*
Age	-0.05	0.03	4.10	0.95	0.91 – 1.00	<0.05
Anthropometric component score	-0.41	0.46	0.80	0.66	0.27 – 1.64	0.371

Table 36 – Ordinal logistic regression analysis of variables predicting disability outcome

6.6.8.2.4 Metabolic

Table 37 displays the regression statistics; high metabolic component scores at hospital discharge were not associated with low ratings on the Glasgow Outcome Scales at 6 month follow-up. The assumption of proportional odds was met (X^2 = 11.00, p = 0.202) and tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.91, VIF = 1.00; metabolic component score, tolerance = 0.91, VIF = 1.00).

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for e*β*	*p*
Age	-0.05	0.02	4.34	0.95	0.91 – 1.00	<0.05
Metabolic component score	0.06	0.32	0.03	1.06	0.56 – 1.98	0.863

Table 37 – Ordinal logistic regression analysis of variables predicting disability outcome

6.6.8.2.5 Immune

Table 38 displays the regression statistics; high immune component scores at hospital discharge were not associated lower ratings on the Glasgow Outcome Scales at 6 month follow-up, although it was approaching significance. The

assumption of proportional odds was met (X^2 = 6.51, p = 0.164) and tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.83, VIF = 1.20; immune component score, tolerance = 0.83, VIF = 1.20).

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for e*β*	*p*
Age	-0.05	0.03	4.74	0.95	0.90 – 1.00	<0.05
Immune component score	0.41	0.30	1.77	1.50	0.83 – 2.72	0.082

Table 38 – Ordinal logistic regression analysis of variables predicting disability outcome

6.6.9 Hypothesis 4

"Low allostatic load scores are associated with an increase in Glasgow Outcome ratings between discharge and 6 month follow-up"

Table 39 displays Glasgow Outcome ratings near to hospital discharge and at 6 month follow-up at both time points (n = 32). At hospital discharge, 78% (n = 25) were Disabled and 22% (n = 7) made a Good Recovery. At follow-up 69% (n = 22) were Disabled and 31% (n = 10) made a Good Recovery.

	Time 2: Glasgow Outcome ratings at 6 month follow-up						
Time 1: GODS ratings near to hospital discharge		LSD (3)	USD (4)	LMD (5)	UMD (6)	LGR (7)	UGR (8)
	LSD (3)	6	3	2	2	1	
	USD (4)	3	1	1			
	LMD (5)	1		1	1		1
	UMD (6)					1	1
	LGR (7)		1			1	2
	UGR (8)					1	2

Table 39 - Disability outcome at discharge from hospital after head injury, and at 6 month follow-up
LSD = Lower Severe Disability, USD = Upper Severe Disability, LMD = Lower Moderate Disability, UPM = Upper Moderate Disability, LGR = Lower Good Recovery, UGR = Upper Good Recovery.

Change in Glasgow Outcome ratings between hospital discharge and 6 month follow-up was assessed by subtracting ratings at 6 months from ratings near to discharge from hospital. Disability outcome ratings did not change in 34% (n = 11) of participants, 47% (n = 15) improved (25% (n = 8) by 1 category, 9% (n = 3) by 2 categories, 9% (n = 3) by 3 categories and 3% (n = 1) by 4 categories) and 19% (n = 6) deteriorated (13% (n = 4) by 1 category, 3% (n = 1) by 2 categories and 3% (n = 1) by 3 categories).

6.6.9.1 Hypothesis testing

An ordinal logistic regression was used to investigate whether AUDIT ratings or ratings of Multidimensional Health Locus of Control as 'Powerful others' predicted change in Glasgow Outcome ratings between hospital discharge and 6 month follow-up. Change in Glasgow outcome ratings were not associated with either variable therefore they were not included in the analysis as covariates (table 40).

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for *eβ*	*p*
Alcohol Use Disorder Identification Test scores	-0.06	0.04	2.88	0.94	0.88 – 1.01	0.090
Scores of locus of control as 'Powerful other'	-0.01	0.04	0.05	1.00	0.91 – 1.08	0.816

Table 40 – Ordinal logistic regression analysis of variables predicting change in disability outcome

6.6.9.1.1 Allostatic load scores

Table 41 displays the ordinal logistic regression statistics for the relationship between change in Glasgow Outcome ratings between hospital discharge and 6 month follow-up and AL scores at hospital discharge and at 6 month follow-up. Change in disability was not explained by AL scores at either time point. The assumptions of proportional odds were met and are described in Appendix E (section 1.3).

Allostatic load time point	*b*	*SE b*	Wald X^2	*eβ*	95% CI for e*β*	*p*
Discharge from hospital	-0.14	0.16	0.81	0.87	0.64 – 1.18	0.369
6 month follow-up	0.02	0.15	0.01	1.02	0.76 – 1.36	0.918

Table 41 – Ordinal logistic regression analysis of AL as a predictor of change in disability outcome

6.6.9.1.2 Allostatic load component scores

There was no significant association between change in Glasgow Outcome ratings between hospital discharge and 6 month follow-up and AL component scores at either hospital discharge or 6 month follow-up (table 42). The assumptions of proportional odds were met and are described in Appendix E (section 1.4).

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for eβ	*p*
Component score at hospital discharge						
Cardiovascular	0.13	0.36	0.12	1.13	0.55 – 2.32	0.732
Neuroendocrine	-0.56	0.32	3.09	0.57	0.31 – 1.07	0.079
Immune	-0.05	0.30	0.02	0.96	0.53 – 1.71	0.877
Metabolic	0.35	0.32	1.19	1.42	0.76 – 2.68	0.275
Anthropometric	-0.51	0.46	1.23	0.60	0.25 – 1.48	0.267
Component score at 6 month follow-up						
Cardiovascular	0.04	0.33	0.02	1.05	0.55 – 1.98	0.894
Neuroendocrine	-0.24	0.33	0.54	0.78	0.41 – 1.50	0.463
Immune	-0.14	0.34	0.17	0.87	0.45 – 1.70	0.870
Metabolic	0.39	0.42	0.88	1.48	0.65 – 3.35	0.349
Anthropometric	0.32	0.44	0.53	1.38	0.53 – 3.25	0.465

Table 42 – Ordinal logistic regression analysis of AL component scores as predictors of change in disability outcome

6.7 Discussion

6.7.1 Principal findings

Contrary to expectations, there was no significant difference in AL scores or component scores between HI participants and comparison participants at 6 month follow-up, indicating HI does not contribute to the physiological dysregulation of allostatic biological systems at this time. Similar to the findings at hospital discharge (Chapter 5), AL scores or component scores at hospital discharge or 6 month follow-up did not predict Glasgow Outcome ratings at 6 month follow-up with the exception of the neuroendocrine component at discharge from hospital. Here, high neuroendocrine markers at hospital discharge were associated with low Glasgow Outcome ratings (greater disability) at 6 month follow-up. Although Glasgow Outcome ratings changed in 66% of HI participants between the two time points, change in disability was not explained by AL or the component scores near to hospital discharge or at 6 month follow-up. This suggests that disability outcome and change in disability outcome after HI, is independent to the buildup of stress-related wear- and tear on physiological systems over time.

6.7.2 Relationship to other studies

The findings in this study are novel, as previously the AL of HI participants after hospital discharge, in the community, had not been investigated. The wider implication of the finding that there is no significant difference in AL scores between HI participants 6 months after injury and age, gender, and SIMD (2012) quintile matched comparison participants is that these groups are similar in terms of life-long accumulated physiological damage. This suggests that brain damage, within 6 months post-hospital discharge, does not significantly contribute to multisystem dysfunction that leads to increased AL (McEwen, 1998b). A consequence of this finding is that the previous evidence that HI is associated with an increased risk of mortality late after HI (McMillan et al., 2011; McMillan et al., 2014), is not explained by AL at 6 months after hospital discharge.

The lack of significant difference in AL scores between HI participants and matched comparison participants at 6 month follow-up contrasts with the significant difference near to hospital discharge in study 1 (Chapter 5). Near to hospital discharge, the metabolic and immune component scores were significantly higher in the HI group, contributing to higher AL scores. The matched comparison participant data were the same in study 1 and 2, therefore the lack of difference between groups is a result of the immune and metabolic component scores in the HI group decreasing between near to hospital discharge and 6 month follow-up (change in median metabolic score = -0.44; IQR: +0.49, -0.46, and in immune score = -0.65; IQR: +0.37, -0.96). Therefore the significantly higher AL scores in HI participants near to hospital discharge than comparison participants in study 1 (Chapter 5) appears to result from an acute physiological disruption caused by the HI, with this effect resolving by 6 month follow-up. This is consistent with the view that brain damage does not cause physiological dysfunction associated with AL early after injury (within 6 months of discharge).

The lack of a significant relationship between AL scores or component scores and disability outcome at 6 month follow-up, is consistent with the findings in study 1, indicating that multisystem dysregulation does not drive disability outcome after HI. The exception is the significant association between the neuroendocrine component at hospital discharge and disability at 6 month follow-up. In the AL model, neuroendocrine indicators are primary allostatic mediators, which respond

during the acute stress phase (McEwen & Wingfield, 2003). As figure 3 (Chapter 2) shows, there are a number of conditions that alter the production of primary mediators; however it is a short-term response to an external challenge. For this reason, primary mediators alone do not represent AL, therefore the theory of accumulated physiological damage over time does not explain the association between neuroendocrine component scores and greater disability 6 months later in this study.

The neuroendocrine indicators in this study, DHAS and aldosterone, are released via the HPA axis and adrenal gland, which respond to stress (McEwen, 1998b; McEwen & Wingfield, 2003) including self-report perceived stress (Lambert et al., 2014; Pruessner, Hellhammer, Pruessner, & Lupien, 2003; Watts, 2005). Previous research has shown that improvement in GOS-E rating from 1 to 5-7 years after HI was strongly associated with lower scores for self-rated perception of stress (Whitnall et al., 2006); conversely, higher scores of perceived stress at 5-7 years post-injury, were associated with greater disability at 12-14 year follow-up (McMillan et al., 2012). Therefore potentially greater psychological distress, which may trigger neuroendocrine reaction, hinders the recovery process and has an adverse effect on outcome. Unfortunately, this current study did not find evidence for this hypothesis, as ratings of Perceived Stress at discharge from hospital did not correlate with outcome at 6 month follow-up.

However, this finding is consistent with the hypothesis that well-evidenced acute neuroendocrine dysfunction following brain damage (Agha et al., 2004; Behan, Phillips, Thompson, & Agha, 2008; Cernak, Savic, Lazarov, Joksimovic, & Markovic, 1999; Powner, Boccalandro, Alp, & Vollmer, 2006), potentially compounds the physical and psychological aspects of the injury, interfering with rehabilitation and recovery (Cernak et al., 1999; Eledrisi, Urban, & Lieberman, 2001). It is reasonable to think that abnormalities in hormone functioning have pathophysiological mechanisms following HI. Therefore in this study, greater indicators of neuroendocrine functioning at hospital discharge may cause pathology that inhibit the ability of the brain to recover, or exacerbate impairments during the 6 months after discharge, leading to greater disability. Replication of this finding is required, and future research should also attempt to determine greater specificity of the mechanisms underlying this relationship. For

example, in identifying HI participants with abnormally high and low neuroendocrine functioning early after HI and closely monitoring their recovery, differences in physical and psychological aspects of the recovery may be able to elucidate details about the relationship between neuroendocrine functioning and later disability outcome after HI. If the relationship between neuroendocrine reaction and disability outcome after HI is confirmed, this could create possibilities for intervention of neuroendocrine functioning early after injury to increase the likelihood of better recovery after HI.

The change in disability between near to hospital discharge and 6 month follow-up was similar to previous prospective HI cohort studies where change in disability on the GOS-E was demonstrated at later time points after HI (McMillan et al., 2012; Whitnall et al., 2006). In these studies, roughly half of participants stayed the same, a quarter increased GOS-E ratings and a quarter decreased, between 1 and 5-7 years, then again at 12-14 years (McMillan et al., 2012; Whitnall et al., 2006). In the present study 34% stayed the same in, 47% improved and 19% deteriorated in disability outcome from near to discharge from hospital and 6 month follow-up. The higher rate of improvement in this study is likely to be due to the fact that all participants were in the early stages of recovery, and 86% of participants had received rehabilitation following discharge from hospital. Thus the lack of relationship between AL and change in disability is not due to differences in the sample compared with other studies. This supports the view that in this sample, AL does not explain change in disability after HI within 6 months of hospital discharge.

6.7.3 Strengths and limitations

A limitation of this study is the assumed stability of the AL scores in comparison participants and the resulting repeat use of their data from study 1. Allostatic load scores increase slowly over time and the interval to follow-up was relatively short making this unlikely (McEwen, 1998b, 2000). AL scores in the HI group did not increase over the 6 month follow-up, which supports the view that AL accumulates slowly. Strengths of this study are its prospective cohort design, close matching of the HI and comparison groups and high follow-up rate (80%).

6.8 Conclusions

The findings of this study do not support the view that brain damage causes increased physiological dysregulation 6 months after discharge from hospital. Further, the accumulation of AL does not help to explain the heterogeneity of outcome at this time, or change in disability from hospital discharge; with the exception of an inverse relationship between neuroendocrine indicators at discharge from hospital and worse disability outcome 6 months later. Further research is required to elucidate the mechanisms involved in this relationship and investigate potential interventions. Given the data on heterogeneity and change in disability later after injury (McMillan et al., 2012; McMillan et al., 2014), these outcome were examined in a sample much later after HI, and are described next in Chapter 7.

Chapter 7 **Allostatic load and late outcome following head injury**

Background

Several studies have shown that outcome after head injury (HI) is heterogeneous; in particular late outcome, including disability and increased risk of mortality, are only partly explained by the severity of the injury and demographic factors. Allostatic load (AL) may help to explain outcome after HI, however this was not demonstrated early after HI in Chapters 5 and 6. Poor outcomes in HI populations compared with community controls have been demonstrated much later after HI. It may be that these poor outcomes late after HI are explained by the accumulation of AL over the lifetime. Thus the present study investigated AL, disability and cognitive outcome late after Hi, and is the first study to do so.

Methods

Participants (n = 41) were recruited from two cohorts admitted with a HI to the Institute of Neurological Sciences, Glasgow between 1968 and 1999. Time to follow-up in the present study ranged from 17 to 41 years (median = 27; IQR: 17.5, 34.5). The AL of the HI participants was compared to disability outcome (Glasgow Outcome Scale-Extended), to cognitive functioning using a range of cognitive tests, to change in disability outcome from 6 months after hospital discharge, and to the AL scores of 47 comparison participants from study 1

Results

The HI participants had significantly higher AL scores late after injury than comparison participants, specifically the metabolic and anthropometric component scores. Overall disability outcome (GOS rating) changed between 6 months post-injury and late follow-up in 46% of the HI group, however change in disability, disability outcome, and cognitive functioning late after injury, was not explained by AL scores at late follow-up. There was one exception; there was a significant relationship between a decrease in GOS ratings (worsening disability) and high metabolic component scores at late follow-up (higher triglyceride and creatinine levels and lower levels of albumin and high density lipoprotein).

Conclusions

The findings support the hypothesis that HI is associated with greater physiological dysregulation later after injury; specifically brain damage is associated with higher metabolic and anthropometric indicators of health later in life. The results also indicate that disability following brain damage is unrelated to the accumulation of physiological damage over time. The association between worsening disability over time and higher metabolic indicators of AL may be explained by unhealthier lifestyles of individuals with worsening disability who are less active. An alternative explanation is that change in disability is an effect of higher metabolic components scores; however the direction of this relationship cannot be determined by the cross-sectional assessment of AL in this study.

7.1 Introduction

In Chapters 5 and 6 the associations between allostatic load (AL) and early outcomes after head injury (HI) were investigated. In this chapter the AL model is explored in HI participants several decades after injury. As AL is known to increase throughout life it may be that an association with HI is not evident until late after HI. Over time the chronic stress associated with a HI may cause physiological deregulation, in association with a more limited ability to deal effectively with life stresses as a result of disability, which may contribute to increased AL and the pathological processes underlying the increased risk of illness and death demonstrated later after HI (McMillan et al., 2014). The AL model has not been applied to outcome late after HI, but has the potential to help explain the heterogeneity in outcome.

The present study investigated AL, disability and cognitive outcome late after injury. The study recruited participants from two unique cohorts of HI patients, developed by Professor Graham Teasdale, who were admitted to the Neurosurgical Unit in Glasgow between 1968 and 1999 (Millar et al., 2003; Teasdale, Murray, & Nicoll, 2005). All participants were previously followed-up at 6 months post-injury (and GOS data collected) and a sample were followed up at a mean of 18 years post-injury (Millar et al., 2003; Teasdale et al., 2005). Later follow-up and further study of these cohorts enabled investigation of the time course of recovery. In this chapter, 'late follow-up' or 'late after HI' indicates assessment in the year 2015, which is between 17-41 years after HI for participants.

7.2 Aims

1. To investigate whether there is a difference in AL between HI participants late after injury and comparison participants.

2. To investigate whether there is a relationship between AL and GOS-E ratings late after HI.

3. To investigate whether there is a relationship between AL and cognitive function late after HI.

4. To investigate whether changes in GOS ratings between 6 month after hospital discharge and late follow-up, are explained by AL assessed at late follow-up.

7.3 Hypotheses

1. The allostatic load scores in head injury participants late after injury are significantly higher than in comparison participants.

2. High allostatic load scores late after head injury are associated with low GOS-E ratings.

3. High allostatic load scores late after head injury are associated with poor cognitive functioning.

4. High allostatic load scores late after injury are associated with increased disability on the GOS between 6 months post-injury and late follow-up.

7.4 Design

This was a group comparison observational study.

7.5 Methods

7.5.1 Ethics

Ethical approval for a larger follow-up study, which included this research on AL, was obtained from the West of Scotland Research Ethics Committee on 22/12/14. NHS Greater Glasgow and Clyde (GG&C) Research and Development (R&D) approval was received on 24/02/15. This approved the recruitment of NHS patients from any NHS site within GG&C for the purpose of this study (see Appendix A for approval letters).

7.5.2 Recruitment

7.5.2.1 Head injury participants

Data for this study was collected as part of a larger follow-up study. The HI participants were recruited from two cohorts created by Professor Sir Graham

Teasdale (Millar et al., 2003; Teasdale et al., 2005). Participants in both cohorts were admitted with a HI to the Institute of Neurological Sciences, Glasgow. The Teasdale et al. (2005) cohort comprised 984 participants who were admitted between 1996 and 1999 and followed up 6 months after HI the Glasgow Outcome Scale (GOS). Full data were obtained from 933 participants with a mean age of 35 (SD 21.7; range 1-93). The Millar et al. (2003) cohort comprised 396 people with a HI admitted to the Institute of Neurological Sciences between 1968 and 1985 and who were followed up 6 months after hospital discharge with the GOS. Their average age at injury was 24 (SD 15.3; range 2-70).

General practitioners (GP) of participants from the research cohorts (Millar et al., 2003; Teasdale et al., 2005) were contacted by letter by Professor McMillan to remind them of the previous study, inform them of the new study and ask if there was any reason not to contact their patient (see Appendix A). The Participant Information Sheet (Appendix B) and an example invitation to research study letter were enclosed. If approved by the GP, Professor Teasdale wrote to patients to introduce Professor McMillan and seek their agreement to meet with the present research team (Appendix A). Contact details for the current research team were given, allowing interested participants to telephone to ask questions or to arrange a time and place for the assessment to take place.

7.5.2.1.1 Inclusion criteria

Participants were included if they had previously participated in the Millar et al. (2003) or Teasdale et al. (2005) studies. Participants were only included if able to complete the assessment, and having the capacity to provide informed consent.

7.5.2.1.2 Exclusion criteria

Exclusion criteria included not living local to the recruitment site (to enable face to face assessment).

7.5.2.2 Comparison participants

Health and AL data were available for 47 comparison participants from study 1 (Chapter 5). They had signed a consent form agreeing that their data could be used in other studies by the Head Injury Research Group (see Appendix B). The

details of the recruitment and assessment of these participants is given in Chapter 5. Participants were from the general Scottish population, comprising 33 men and 14 women, aged between 18 and 64, from a range of Scottish Index of Multiple Deprivation (SIMD) 2012 quintiles (SES). Any differences between HI participants in this study and the comparison group in age, gender, or SIMD (2012) quintiles were adjusted for in the analysis if shown to have a significant relationship with the dependent variable.

7.5.3 Procedures

HI participants were assessed at the Clinical Research Facility (CRF) at the Glasgow Royal Infirmary, the Western Infirmary, or the Queen Elizabeth University Hospital. Participants were asked if they had any questions about the study before going through the consent form (Appendix B). The participant signed and dated the consent form, and it was counter signed and dated by a member of the Head Injury Research Group.

7.5.4 Measures

7.5.4.1 General information

A general information checklist was used to check age and determine current postcode. Postcode data were collected in order to determine the SIMD (2012) quintile for each participant, to determine the degree of socioeconomic deprivation of the neighbourhoods in which participants lived, ranging from 1 (most deprived) to 5 (most affluent). Chapter 3 describes how SIMD (2012) quintiles are derived.

7.5.4.2 Secondary Health information

In order to gain a broader picture of the health of participants, they were asked subjective questions about their health as secondary descriptors. Participants were asked to rate their general health on a Likert scale from ‘Very Poor, ‘Poor’, ‘OK’, ‘Good’, or ‘Very Good’, scored from 1 to 5. They were asked how many physician-diagnosed chronic co-morbidities they currently have, and how many medications they were presently taking.

7.5.4.3 Assessment of disability after head injury

Disability late after HI was assessed using the Glasgow Outcome Scale-Extended (Wilson et al. (1998); Appendix C). Glasgow Outcome Scale (GOS) ratings were derived from the GOS-E, to explore change in GOS ratings from the 6 month follow-up. The GOS-E is an extension of the GOS; table 43 shows how GOS and GOS-E rating categories compare, and how GOS ratings were derived from GOS-E ratings in this study. A description of how the GOS-E was assessed is found in Chapter 3.

Glasgow Outcome Scale- Extended (rating)	Glasgow Outcome Scale (rating)
Upper Good Recovery (8)	Good Recovery (5)
Lower Good Recovery (7)	
Upper Moderate Disability (6)	Moderate Disability (4)
Lower Moderate Disability (5)	
Upper Severe Disability (4)	Severe Disability (3)
Lower Severe Disability (3)	

Table 43 – GOS and GOS-E rating categories

7.5.4.4 Tests of cognitive function

This study was part of a larger study that followed-up HI participants from the Millar et al. (2003) study; this included repeating a broad range of cognitive tests to allow comparison over time. Therefore the cognitive tests in this study were selected on the basis of having been given in the Millar et al. (2003) study, and because they cover the common range of impairments after HI. The cognitive functioning of HI participants was assessed using the following tests:

1. The Symbol Digit Modalities Test was used to assess information processing speed (Smith, 2002) ; Appendix C); correct answers were summed to create a total score of 110.

2. The Wechsler Memory Scale-Revised test was used to assess immediate and long-term narrative memory (Wechsler (1987); Appendix C), with a total score of 50 for each.

3. The Wechsler Memory Scale-Revised test was used to assess immediate and long-term verbal memory for associated word pairs (Wechsler (1987); Appendix C). A maximum score of 24 was possible for immediate recall and 8 for long-term recall.

4. The Stroop test assessed executive skills; impulsivity and attention (Trenerry, Crosson, DeBoe, and Leber (1989); Appendix C). Participants were given 2 minutes to complete Form B, and the total score out of 112 recorded. However some people completed the task within the time limit, so their full ability to perform the task was inhibited by this time cut-off. Therefore for analysis, Stroop scores were also dichotomised into 'impaired' or 'not impaired' categories based on the age norms provided in the instruction manual (Trenerry et al., 1989).

7.5.4.5 Allostatic load

Details of how AL was assessed are described in Chapter 3.

7.5.4.6 Confounders

7.5.4.6.1 Confounders of disability outcome

Older age is a predictor of poorer outcome after HI, as described in Chapter 3 (Jacobsson et al., 2009; McMillan et al., 2012; Thornhill et al., 2000); if it was associated with GOS-E ratings late after injury, it was included in analyses as a covariate.

7.5.4.6.2 Confounders of change in disability outcome after head injury

As described in Chapter 3, alcohol misuse is associated with poorer outcome after HI (Whitnall et al., 2006). Thus, the Alcohol Use Disorder Identification Test (AUDIT) (Saunders et al., 1993); Appendix C) was given at follow-up and included in the analysis as a covariate. Chapter 3 details how the AUDIT was scored.

7.5.4.6.3 Confounders of allostatic load

Increased age, and high levels of social deprivation, and ratings of childhood deprivation are associated with higher AL therefore they were included in the

analysis as covariates if they were found to predict AL scores (Crimmins et al., 2003; Dich et al., 2014; Gruenewald et al., 2012; Hasson et al., 2009; Singer & Ryff, 1999). Chapter 3 describes how childhood deprivation scores were assessed and how social deprivation was derived from postcodes using SIMD (2012) quintiles. Anti-hypertensive and anti-inflammatory medication also affect measures of cardiovascular and immune functioning, so they were also included in the analysis as covariates of their respective components and AL scores (see Chapter 3 for further details). These data were obtained from a general information checklist.

7.5.4.6.4 Confounders of cognitive function

Age and years of education were obtained from a general information checklist and adjusted for in the final models if they were found to predict cognitive function.

7.5.5 Data analysis plan

Data were analysed using SPSS v22. The distributions of the data were determined by conducting Kolmogorov-Smirnov tests on each variable. Demographic information of the HI and comparison groups were described using summary statistics and differences in secondary health questions investigated using independent t-tests or Mann-Whitney U tests.

Linear regression was used to investigate hypotheses 1 and 3 where dependent variables were continuous (AL scores and cognitive function scores). The relationship between confounder variables, non-matched characteristics (age, gender, and SIMD quintiles) of the groups and dependent variables were investigated using univariate linear regression. If the univariate regressions were significant, the data were analysed using hierarchical regressions that adjusted for covariates (Pallant, 2013). Confounding variables of AL scores include: age, social deprivation (SIMD 2012 quintiles), childhood deprivation scores, anti-inflammatory and anti-hypertensive medication, and confounders of cognitive function include age and number of years in education. The assumptions of the final model, which are described in Chapter 5, were checked and reported in the appendix.

If the assumptions of the linear regression were violated, but the continuous dependent variable could be dichotomised into 2 groups with a minimum of 10 participants in each group per independent variable, a logistic regression was used (Hosmer & Lemeshow, 2000; Peduzzi, Concato, Kemper, Holford, & Feinstein, 1996). Logistic regression was also used if the dependent variable was already categorical (impaired/ not impaired Stroop test scores). The goodness-of-fit of the model was checked using the Hosmer-Lemeshow statistic, which indicates that the model fits well if $p < 0.05$ (Hosmer & Lemeshow, 2000). When there was more than one independent variable, multicollinearity was checked using tolerance and VIF values.

Hypothesis 2 and 4 were investigated using ordinal logistic regressions because the GOS-E is an ordinal scale. For hypothesis 2, the relationship between the confounder variable (age) and GOS-E ratings was investigated using an ordinal logistic regression and included in the final regression model if a significant association was found. The assumptions of an ordinal logistic regression are described in Chapter 5.

If the assumptions of the ordinal logistic regression were violated, if it was not possible to dichotomise the dependent variable, or if the covariates were not found to be significant predictors of the dependent variable, then between group differences were explored using independent t-tests or Mann Whitney U tests, and within group associations using Pearson's or Spearman's rank correlations.

Cohen's *d* (Cohen, 1988) is reported as an indication of effect size of between group differences (independent t-test or Mann-Whitney test), and Cohen's f^2 (Cohen, 1988) as an indication of effect size for the proportion of variance accounted for by a variable, over and above covariate variables (hierarchical regression). Pearson's or Spearman's rank correlation coefficients are reported as an indication of effect size for the linear relationship between two continuous variables, and odds ratio are reported for the effect size of the relationship between predictor variables and ordinal or dichotomous outcomes (Field, 2013).

7.6 Results

7.6.1 Recruitment of participants

This study was part of a larger study investigating heterogeneity of outcome after HI, which will continue until late 2017 (n = 1,329 potential participants). For the present study, data were obtained from the first 41 participants followed-up. The time between injury and follow-up in 2015 ranged from 17 to 41 years (median = 27; IQR: 17.5, 34.5). The comparison participants in this study (n = 47) were recruited for study 1; the details of how they were recruited are described in Chapter 5.

7.6.2 Demographic information

The mean age was 48.6 years (SD 11.8, range 21-68) for HI participants and 41.5 years (SD 13.0, range 20-63) for comparison participants; HI participants were significantly older than comparison participants, although the effect size was small (U = 679.50, p <0.05, r = 0.02). The majority of participants in each group were male; (HI group 28 (68.3%) and comparison group 33 (70.2%); X^2 = 0.04, p = 0.846). There was no significant difference between groups by SIMD (2012) quintile (U = 814.00, p = 0.199, r = -0.14; see table 44).

SIMD (2012) quintile	Head injury group (%)	Comparison participant group (%)
1 higher deprivation	29.3	34.0
2	14.6	27.7
3	17.1	14.9
4	22.0	10.6
5 lower deprivation	17.1	12.8

Table 44- Percentage of SIMD (2012) quintiles in study 3

7.6.2.1 Secondary health information

There were no significant differences between groups on a subjective measure of health (U = 988.50, p = 0.221, r = 0.02), or for the number of co-morbidities (U = 1,051.00, p = 0.356, r = 0.10), see table 45 for descriptive statistics. HI participants were taking significantly more medications than comparison participants (U = 709.50, p <0.05 r = -0.24) (see Appendix D, tables 12 and 14 for a list of co-morbidities, and tables 13 and 15 for a list of medication).

	Head injury participants	Comparison participants
	Median (IQR)	Median (IQR)
Subjective measure of health	4 (3, 5) Good, (Ok, Very good)	4 (4, 4) Good (Good, Good)
Number of co-morbidities	0.0 (0.0, 0.5)	0.0 (0.0, 1.0)
Number of medications	1 (0, 2)	0 (0, 1)

Table 45 - Descriptive statistics of the secondary health questions in study 3

7.6.3 Head injury group information

7.6.3.1 GCS at accident and emergency

The GCS score on arrival at accident and emergency was available for 17 (36.5%) participants from the Teasdale et al. (2005) cohort. GCS scores ranged from 3 to 15, median = 15, IQR: 8.5, 15. Four people were unconscious on arrival at accident and emergency (GCS< 9).

7.6.3.2 Disability outcome late after head injury

GOS-E ratings for the 41 HI participants are displayed in table 46.

Glasgow Outcome Rating	n	Percentage
Upper Good Recovery (8)	8	19.5
Lower Good Recovery (7)	16	39.0
Upper Moderate Disability (6)	5	12.2
Lower Moderate Disability (5)	9	22.0
Upper Severe Disability (4)	1	2.4
Lower Severe Disability (3)	2	4.9

Table 46 - The frequency and percentage of GOS-E ratings late after HI

GOS-E ratings were dichotomised into Good Recovery (≥7) or Disabled (≤6) (Narayan et al., 2002); 24 (58.5%) participants had made a Good Recovery late after injury and 17 (41.5%) remained Disabled.

7.6.3.3 Other information

The median rating for the AUDIT was 5 (IQR: 2, 10). Fourteen (34%) of the HI participants had an AUDIT rating of 8 or above, which indicates hazardous drinking over the last year (Babor et al. (2001).

7.6.4 Hypothesis 1

"The allostatic load scores of head injury participants late after injury are significantly higher than that in comparison participants"

7.6.4.1 Allostatic load scores

Initially the data were checked for normality; table 47 shows the results of the Kolmogorov-Smirnov test for normality and descriptive statistics for AL scores of HI and comparison participants; the AL score of comparison participants was not normally distributed.

		Kolmogorov-Smirnoff		Descriptive statistics
	Participant group	Statistic	*p*	Median (IQR)
Allostatic load score	Head injury	0.063	0.200	1.01 (-0.79, 2.89)
	Comparison	0.141	<0.05	-1.10 (-2.87, 0.37)

Table 47 - Kolmogorov-Smirnov test and descriptive statistics for AL scores

With regards to the potential confounders of AL, eight (19.5%) HI participants and 9 (19.1%) comparison participants were taking anti-inflammatory medication and 6 (14.6%) HI participants and 3 (6.4%) comparison participants were taking anti-hypertensive medication (see Appendix D, tables 13 and 15 for list). The frequency and percentage of childhood deprivation scores in HI and comparison participants are displayed in table 48. More comparison participants appeared to experience no childhood deprivation than the HI group; however the groups were more similar higher up the deprivation scale.

	Childhood deprivation scores			
Participant group	0 (low)	1	2	3 (high)
	n (%)	n (%)	n (%)	n (%)
Head injury	7 (17)	10 (24)	16 (39)	8 (20)
Comparison	19 (40)	8 (17)	14 (30)	6 (13)

Table 48 – Frequency and percentage of childhood deprivation scores in study 3

Next, 6 univariate regressions were used to check whether potential confounding variables (childhood deprivation, taking anti-inflammatory, or anti-hypertensive medication) and differences between groups (age, gender, SIMD (2012) quintile) were associated with AL scores. The results are displayed in table 49; age and childhood deprivation scores were significantly associated with AL scores, therefore they were included in the analysis as covariates.

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	0.08	0.02	0.36	0.04 – 0.13	<0.005
Gender	-0.30	0.69	-0.04	-1.64 – 1.12	0.710
SIMD (2012) quintile	0.03	0.22	0.02	-0.41 – 0.48	0.878
Anti-inflammatory medication	-0.74	0.81	-0.10	-2.35 – 0.86	0.359
Anti-hypertensive medication	-0.77	1.05	-0.08	-2.87 – 1.32	0.466
Childhood deprivation scores	1.12	0.27	0.42	0.64 – 1.72	<0.001

Table 49 – Univariate regression analysis of variables predicting AL scores

Following this, a two stage hierarchical regression was conducted to determine whether the addition of participant group (HI or comparison group) improved the prediction of AL scores over and above age and childhood deprivation scores. The assumptions were checked initially and are reported in Appendix E (section 1.4). Table 50 displays the regression statistics for each variable at the step it was entered and the change in R^2. The full model of age, childhood deprivation scores and participant group was statistically significant (p <0.001); the addition of participant group to the prediction of AL scores (Model 2) led to a significant increase of the predictive capacity of the model of 4%, with a small-moderate effect size (p <0.05, f^2 = 0.07); demonstrating that HI participants had significantly higher AL than comparison participants.

Variable	*b*	*SE B*	*B*	95% CI	*P*	R^2	*Adjusted* R^2	ΔR^2
Model 1						0.21	0.21	-----
Age	0.05	0.02	0.23	0.01 – 0.10	<0.05			
Childhood deprivation	0.93	0.29	0.34	0.36 – 1.51	<0.005			
Model 2						0.26	0.24	0.04
Age	0.04	0.02	0.18	-0.01 – 0.09	0.090			
Childhood deprivation	0.86	0.29	0.31	0.29 – 1.43	<0.005			
Participant group	-1.24	0.59	-0.21	-2.40 – -0.08	<0.05			

Table 50- Hierarchical regression analysis of variables predicting AL scores

7.6.4.2 Allostatic load component scores

7.6.4.2.1 Cardiovascular

Next, group differences in AL component scores were investigated. Firstly, the Kolmogorov-Smirnov test for normality showed the cardiovascular component scores of both groups were normally distributed (table 51 displays the descriptive statistics)

		Kolmogorov-Smirnoff		Descriptive statistics
Allostatic load component	Participant group	Statistic	*p*	Mean (SD)
Cardiovascular	Head injury	0.127	0.096	0.33 (1.06)
	Comparison	0.060	0.200	0.05 (0.94)

Table 51 - Kolmogorov-Smirnov test and descriptive statistics for cardiovascular component scores

Next, 4 univariate regressions were used to investigate whether the unmatched group criteria and potential confounder (taking anti-hypertensive medication) were associated with cardiovascular component scores. Table 52 shows the regression outputs; age and gender were significantly associated with cardiovascular component scores therefore they were adjusted for in the analysis.

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	0.02	0.01	0.23	0.00 – 0.03	<0.05
Gender	0.60	0.22	0.28	0.15 – 1.04	<0.01
SIMD (2012) quintiles	0.04	0.08	0.05	-0.11 – 0.19	0.614
Anti-hypertensive medication	0.05	0.35	0.01	-0.66 – 0.75	0.896

Table 52 – Univariate regression analysis of variables predicting cardiovascular component scores

Thus, a two stage hierarchical regression (table 53) demonstrated the full model of age, gender and participant group was statistically significant (p <0.01); however the addition of participant group to the prediction of cardiovascular component scores (Model 2) did not lead to a statistically significant increase in R^2 (p = 0.458, f^2 = 0.01). The assumptions were checked initially and are reported in the appendix (Appendix E, section 1.5).

Variable	*b*	*SE B*	*B*	95% CI	*P*	R^2	*Adjusted* R^2	ΔR^2
Model 1						0.12	0.10	-----
Age	0.02	0.01	0.22	0.00 – 0.03	<0.05			
Gender	0.57	0.22	0.27	0.14 – 1.01	<0.05			
Model 2						0.13	0.10	0.01
Age	0.02	0.01	0.20	0.00 – 0.03	0.069			
Gender	0.57	0.22	0.27	0.13 – 1.01	<0.05			
Participant group	-0.16	0.21	-0.08	-0.58 – 0.26	0.458			

Table 53- Hierarchical regression analysis of variables predicting cardiovascular component scores

7.6.4.2.2 Neuroendocrine

Table 54 shows the results of the Kolmogorov-Smirnov test for normality and descriptive statistics for neuroendocrine component scores of HI and comparison participants; the neuroendocrine component scores of both groups were normally distributed.

		Kolmogorov-Smirnoff		Descriptive statistics
Allostatic load component	Participant group	Statistic	*p*	Mean (SD)
Neuroendocrine	Head injury	0.092	0.200	0.37 (1.01)
	Comparison	0.066	0.200	-0.06 (0.91)

Table 54 - Kolmogorov-Smirnov test and descriptive statistics for neuroendocrine component scores

The unmatched group characteristics were then investigates age was significantly associated with neuroendocrine component scores therefore it was adjusted for in the analysis (table 55).

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	0.04	0.01	0.49	0.02 – 0.05	<0.001
Gender	0.39	0.22	0.19	-0.05 – 0.84	0.080
SIMD (2012)quintiles	0.13	0.07	0.20	-0.01 – 0.27	0.067

Table 55 – Univariate regression analysis of variables predicting neuroendocrine component scores

Therefore adjusting for age, table 56 displays a two stage hierarchical regression showed the full model of age and participant group was statistically significant (p <0.001), however the addition of participant group to the prediction of neuroendocrine component scores (Model 2) did not lead to a statistically significant increase in R^2 (p = 0.340, f^2 = 0.01). The assumptions were checked initially and are reported in the appendix (Appendix E, section 1.6).

Variable	*b*	*SE B*	*B*	95% CI	*P*	R^2	*Adjusted* R^2	ΔR^2
Model 1						0.24	0.23	-----
Age	0.04	0.01	0.49	0.02 – 0.05	<0.001			
Model 2						0.25	0.23	0.01
Age	0.04	0.01	0.18	0.02 – 0.05	<0.001			
Participant group	-0.18	0.19	-0.21	-0.56 – 0.20	0.340			

Table 56- Hierarchical regression analysis of variables predicting neuroendocrine component scores

7.6.4.2.3 Anthropometric

Table 57 shows the results of the Kolmogorov-Smirnov test for normality and descriptive statistics for anthropometric component scores of HI and comparison participants; the anthropometric component scores of comparison participant deviated significantly from normal.

		Kolmogorov-Smirnoff		Descriptive statistics
Allostatic load component	Participant group	Statistic	*p*	Median (IQR)
Anthropometric	Head injury	0.107	0.200	0.46 (-0.28, 1.08)
	Comparison	0.167	<0.005	-0.74 (-1.29, 0.76)

Table 57 - Kolmogorov-Smirnov test and descriptive statistics for anthropometric component scores

Following this, the unmatched group characteristic were investigated and age was shown to be significantly associated with anthropometric component scores (table 58).

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	0.02	0.01	0.21	0.00 – 0.04	<0.05
Gender	-0.30	0.28	-0.11	-0.85 – 0.26	0.290
SIMD (2012) quintiles	-0.12	0.09	-0.14	-0.29 – 0.06	0.195

Table 58 – Univariate regression analysis of variables predicting anthropometric component scores

Therefore adjusting for age, a two stage hierarchical regression demonstrated the full model of age and participant group was statistically significant (p <0.05); the addition of participant group to the prediction of anthropometric component scores (Model 2) led to a statistically significant increase in the predictive capacity of the model by 5%, with a small- moderate effect size (p <0.05, f^2 = 0.06), demonstrating that HI participants had significantly higher anthropometric component scores than comparison participants (table 59). The assumptions were checked initially and are reported in the appendix (Appendix E, section 1.7).

Variable	*b*	*SE B*	*B*	95% CI	*p*	R^2	*Adjusted* R^2	ΔR^2
Model 1						0.05	0.04	-----
Age	0.02	0.01	0.21	0.00 – 0.04	<0.05			
Model 2						0.10	0.07	0.05
Age	0.02	0.01	0.15	-0.01 – 0.03	0.164			
Participant group	-0.55	0.26	-0.23	-1.06 – -0.04	<0.05			

Table 59- Hierarchical regression analysis of variables predicting anthropometric component scores

7.6.4.2.4 Metabolic

Table 60 shows the results of the Kolmogorov-Smirnov test for normality and the descriptive statistics of metabolic component scores; scores of both groups were not normally distributed.

		Kolmogorov-Smirnoff		Descriptive statistics
Allostatic load component	Participant group	Statistic	*p*	Median (IQR)
Metabolic	Head injury	0.145	<0.05	-0.23 (-0.57, 0.77)
	Comparison	0.146	<0.05	-0.60 (-0.97, 0.34)

Table 60 - Kolmogorov-Smirnov test and descriptive statistics for metabolic component scores

Next the unmatched group characteristics were checked as potential confounders and gender was significantly associated with metabolic component scores (table 61).

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	0.01	0.01	0.10	-0.01 – 0.03	0.350
Gender	-0.77	0.23	-0.35	-1.21 – -0.32	<0.005
SIMD (2012) quintiles	0.05	0.08	0.07	-0.10 – 0.20	0.516

Table 61 - Univariate regression analysis of variables predicting metabolic component scores

Thus, adjusting for gender, a two stage hierarchical regression (table 62) showed the full model of gender and participant group was statistically significant (p <0.001); the addition of participant group to the prediction of metabolic component scores (Model 2) led to a statistically significant increase of the predictive capacity of the model by 6%, with a small- moderate effect size (p <0.05, f^2 = 0.07), demonstrating that HI participants had significantly higher metabolic component scores than comparison participants. The assumptions were checked initially and are reported in the appendix (Appendix E, section 1.8).

Variable	*b*	*SE B*	*B*	95% CI	*p*	R^2	*Adjusted* R^2	ΔR^2
Model 1						0.12	0.11	-----
Gender	-0.77	0.23	-0.35	-1.21 – -0.32	<0.005			
Model 2						0.18	0.16	0.06
Gender	-0.78	0.22	-0.35	-1.21 – -0.34	<0.005			
Participant group	-0.50	0.20	-0.24	-0.90 – -0.10	<0.05			

Table 62- Hierarchical regression analysis of variables predicting metabolic component scores

7.6.4.2.5 Immune

Table 63 shows the results of the Kolmogorov-Smirnov test for normality and descriptive statistics of the immune component score; the immune component scores of comparison participants deviated significantly from normal.

		Kolmogorov-Smirnoff		Descriptive statistics
Allostatic load component	Participant group	Statistic	*p*	Median (IQR)
Immune	Head injury	0.132	0.070	-0.18 (-0.82, 0.86)
	Comparison	0.146	<0.005	-0.42 (-0.88, 0.69)

Table 63 - Kolmogorov-Smirnov test and descriptive statistics for immune component scores

Next the unmatched group characteristics and the potential covariate (anti-inflammatory medication) were checked; none of the variables were significantly associated with immune component scores (table 64). This the difference between groups in immune component score was investigated using a Mann-Whitney U test. There was no significant difference in immune component scores between HI and comparison participant groups (U = 915, p = 0.685, r = -0.04).

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	0.00	0.01	0.00	-0.02 – 0.02	0.980
Gender	-0.19	0.21	-0.09	-0.61 – 0.24	0.386
SIMD (2012) quintiles	-0.07	0.07	-0.11	-0.21 – 0.07	0.312
Anti-inflammatory medication	0.20	0.25	0.09	-0.29 – 0.70	0.420

Table 64 - Univariate regression analysis of variables predicting immune component scores

7.6.5 Hypothesis 2

"High allostatic load scores late after head injury are associated with low GOS-E ratings"

An ordinal logistic regression demonstrated age was not associated with GOS-E ratings, therefore it was not included in the analysis as a covariate (β = -0.01, *S.E* β = 0.02, Wald X^2 = 0.23, $e\beta$ = 0.99, 95% CI of $e\beta$: 0.94 – 1.04, p = 0.632).

7.6.5.1 Allostatic load score

The assumption of proportional odds was violated ($p < 0.01$), and the distribution of GOS-E ratings was significantly different from normal ($D = 0.265$, $p < 0.001$), therefore the association between AL scores and GOS-E ratings was investigated using a Spearman's rank correlation. There was no significant association between AL and GOS-E ratings late after HI (r_s (41) = 0.097, $p = 0.547$).

7.6.5.2 Allostatic load component score

The assumption of proportional odds was violated for cardiovascular, neuroendocrine, metabolic, and anthropometric component scores ($p < 0.05$), therefore their relationship with GOS-E ratings late after injury was investigated using Spearman's correlation. Table 65 shows the results of the Spearman's rank correlation, there were no significant relationship between anthropometric, cardiovascular, neuroendocrine, metabolic component scores and GOS-E ratings late after HI. The assumption of proportional odds was met for immune component scores ($X^2 = 1.43$, $p = 0.839$). An ordinal logistic regression showed there was no relationship between immune component scores and GOS-E ratings late after HI ($\beta = 0.25$, $S.E\ \beta = 0.30$, Wald $X^2 = 0.68$, $e\beta = 1.29$, 95% CI of $e\beta$: 0.71 – 2.33, $p = 0.410$).

Allostatic load component score	*r*	*p*
Cardiovascular	-0.110	0.495
Neuroendocrine	-0.101	0.528
Metabolic	0.096	0.549
Anthropometric	0.189	0.237

Table 65 – Spearman's correlation between AL component scores and Glasgow Outcome ratings

7.6.6 Hypothesis 3

"High allostatic load scores late after head injury are associated with poor cognitive functioning"

7.6.6.1 Symbol Digits Modalities Test

The data were checked for normality initially, Symbol Digit Modalities Test (SDMT) scores did not deviate significantly from a normal distribution ($D = 0.067$, $p = 0.200$); the mean score was 41.32 (SD 13.72). Next, the potential confounders

were checked using two univariate regressions; age was significantly associated with SDMT scores (table 66).

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	-0.37	0.18	-0.32	-0.73 – -0.01	<0.05
Number of years in education	0.49	0.66	0.12	-0.85 – 1.82	0.466

Table 66 – Univariate regression analysis of variables predicting SDMT scores

Adjusting for age, a two stage hierarchical regression (table 67) showed the full model of age and AL scores was not statistically significant (p = 0.120); the addition of AL scores to the prediction of SDMT scores (Model 2) did not lead to a statistically significant increase in R^2 (p = 0.648, f^2 = 0.00). The assumptions were checked initially and are reported in the appendix (Appendix E, section 1.9).

Variable	*b*	*SE B*	*B*	95% CI	*p*	R^2	*Adjusted* R^2	ΔR^2
Model 1						0.10	0.08	-----
Age	-0.37	0.18	-0.32	-0.73– -0.01	<0.05			
Model 2						0.10	0.05	0.00
Age	-0.37	0.18	-0.32	-0.73 – 0.00	<0.05			
Allostatic load score	-0.40	0.87	-0.07	-2.17 – 1.36	0.648			

Table 67- Hierarchical regression analysis of variables predicting SDMT test scores

7.6.6.2 Immediate recall of narrative memory

Scores of immediate recall of narrative memory did not deviate significantly from a normal distribution (D = 0.087, p = 0.200); the mean score was 18.29 (SD 6.81). Subsequently, the potential confounders were investigated; neither age nor numbers of years in education were significantly associated with immediate recall of narrative memory scores (table 68),

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	-0.07	0.09	-0.12	-0.25 – 0.12	0.460
Number of years in education	0.47	0.32	0.23	-0.18 – 1.12	0.154

Table 68 – Univariate regression analysis of variables predicting immediate recall of narrative memory scores

The Kolmogorov-Smirnov test showed the distribution of AL scores (D = 0.061, p = 0.200) also did not differ significantly from normal, therefore a Pearson correlation was used to investigate the relationship with immediate recall of narrative memory scores; there was no significant relationship between the two variables late after HI (p = 0.542, r = 0.098).

7.6.6.3 Delayed recall of narrative memory

The data were checked for normality initially; delayed recall of narrative memory did not deviate significantly from a normal distribution (D = 0.096, p = 0.200); the mean score was 13.88 (SD 7.53). Following this, the potential confounders were investigated; neither age nor numbers of years in education were significantly associated with delayed recall of narrative memory scores (table 69). A Pearson correlation demonstrated there was no significant relationship between AL scores and long-term narrative memory scores late after HI (p = 0.853, r = -0.030).

Variable	*b*	*SE B*	*β*	95% CI	*p*
Age	-0.08	0.10	-0.13	-0.29 – 0.12	0.414
Number of years in education	0.30	0.36	0.13	-0.44 – 1.03	0.416

Table 69 – Univariate regression analysis of variables predicting delayed recall of narrative memory scores

7.6.6.4 Immediate verbal recall of paired associates

Scores of immediate verbal recall of paired associates did not deviate significantly from a normal distribution (D = 0.106, p = 0.200); the mean score was 15.80 (SD 4.26). Next, the potential confounders were checked; age was significantly associated with immediate verbal recall for paired associates scores (table 70).

Variable	*b*	*SE B*	*β*	95% CI	*p*
Age	-0.11	0.06	-0.31	-0.22 – -0.00	<0.05
Number of years in education	0.30	0.20	0.24	-0.10 – 0.71	0.139

Table 70 – Univariate regression analysis of variables predicting immediate verbal recall for paired associates scores

Subsequently, a two stage hierarchical regression adjusting for age (table 71) showed the full model of age and AL scores was not statistically significant (p = 0.112); the addition of AL scores to the prediction of immediate verbal recall of paired associates scores (Model 2) did not lead to a statistically significant increase in R^2 (p = 0.498, f^2 = 0.00). The assumptions were checked initially and are reported in the appendix (Appendix E, section 1.10).

Variable	*b*	*SE B*	*B*	95% CI	*p*	R^2	*Adjusted* R^2	ΔR^2
Model 1						0.10	0.08	-----
Age	-0.10	0.05	-0.31	-0.21 – -0.00	<0.05			
Model 2						0.10	0.06	0.01
Age	-0.11	0.05	-0.33	-0.21 – -0.00	<0.05			
Allostatic load score	0.14	0.27	0.08	-0.40 – 0.68	0.605			

Table 71- Hierarchical regression analysis of variables predicting immediate verbal recall for paired associates scores

7.6.6.5 Delayed verbal recall of paired associates

Scores of delayed verbal recall of paired associates deviated significantly from the normal distribution (D = 0.169, p <0.01); the median score was 6 (IQR: 4, 7). Next, the potential confounders were investigated (table 72); neither age nor numbers of years in education were significantly associated with delayed verbal recall for paired associates scores. Thus a Spearman's correlation was used to investigate the relationship between AL scores and delayed verbal recall for paired associates scores and no significant association was demonstrated (p = 0.993, r_s = 0.002).

Variable	*b*	*SE B*	*β*	95% CI	*p*
Age	-0.04	0.02	-0.28	-0.78 – 0.01	0.080
Number of years in education	0.07	0.08	0.14	-0.09 – 0.24	0.389

Table 72 – Univariate regression analysis of variables predicting delayed verbal recall for paired associates scores

7.6.6.6 Stroop colour-word test (continuous score)

Scores of Stroop colour-word test deviated significantly from a normal distribution (D = 0.152, p <0.05); the median score was 94 (IQR: 78, 110). Subsequently, the potential confounders were checked neither age nor numbers of years in education were significantly associated with stroop colour-word test scores (table 73). Therefore a Spearman's rank correlation was used and showed there was no significant relationship between AL scores and stroop colour-word test scores (p = 0.075, r_s = -0.281).

Variable	*b*	*S.E B*	*β*	95% CI	*p*
Age	-0.30	0.30	-0.16	-0.89 – 0.30	0.321
Number of years in education	0.22	1.07	0.03	-1.93 – 2.38	0.835

Table 73 – Univariate regression analysis of variables predicting Stroop colour-word test scores

7.6.6.7 Stroop colour-word test (dichotomised)

When the stroop colour-word test scores were dichotomised, 13 participants had an impaired score and 27 had a non-impaired score. Subsequently logistic regressions were used to check the potential confounders (table 74); age and numbers of years in education were not significantly associated with impaired/ not impaired colour-word test scores therefore they were not included in the analysis as covariates. Thus the final logistic regression revealed that AL scores were not significantly associated with stroop colour- word test impaired/not impaired categories (B = 0.13, $S.E\ B$ = 0.14, Wald X^2 = 0.81, p = 0.369, eB = 1.13). The Hosmer-Lemeshow statistic indicated the model fitted the data well (p = 0.575).

Variable	B	$S.E\ B$	Wald X^2	p	eB
Age	-0.04	0.03	1.53	0.217	0.96
Years in education	-0.03	0.11	0.06	0.805	0.97

Table 74- Logistic regression analysis of variables predicting impaired/ not impaired scores on the Stroop colour-word test

7.6.7 Hypothesis 4

"High allostatic load scores late after injury are associated with increased disability on the GOS between 6 months post-injury and late follow-up"

Table 75 displays the change in GOS ratings; change occurred in 46% (n = 19) of participants; ratings decreased in 22% (n = 9), improved in 24% (n = 10) and stayed the same in 54% (n = 22).

	Time 2: GOS at late follow-up (2015)			
Time 1: GOS at 6 months post discharge		SD (3)	MD (4)	GR (5)
	SD (3)	2	5	1
	MD (4)	1	3	4
	GR (5)	2	6	17

Table 75 – Change in GOS rating between 6 months post discharge and late follow-up

7.6.7.1 Hypothesis testing

The relationship between change in GOS ratings between 6 months post-injury and late after HI and the potential confounder (AUDIT ratings late after injury) was investigated first. Using an ordinal logistic regression, the assumption of proportional odds was violated (p <0.01). Next checking the distribution of the data, the distribution of change in GOS ratings deviated significantly from a normal distribution (D = 0.269, p <0.001), therefore a Spearman's correlation was used to investigate the relationship between change in GOS ratings and AUDIT ratings; there was no significant association therefore AUDIT ratings were not included in the analysis as a covariate of change in GOS rating (p = 0.959, r_s = -0.008).

7.6.7.2 Allostatic load score

Using an ordinal logistic regression, the assumption of proportional odds was violated (p < 0.01); therefore a Spearman's correlation was used to investigate the relationship between AL scores late after HI and change in GOS ratings; there was no significant association between the two variables (p = 0.454, r_s = -0.120).

7.6.7.2.1 Allostatic load component scores

Next, using ordinal logistic regression to investigate the relationship between AL component scores and change in GOS rating from 6 months post- HI and late after HI, the assumption of proportional odds was violated for immune and metabolic component scores (p <0.01). Therefore Spearman's correlations were used to investigate the relationship between these component scores and change in GOS ratings. There were no significant associations between change in GOS ratings and immune component scores (p = 0.130, r_s = 0.240). However, there was a significant, inverse, moderate association between change in GOS ratings and metabolic component scores at late follow-up (p <0.05, r_s = -0.324). As GOS ratings decreased (disability worsened), metabolic component scores increased (figure 13).

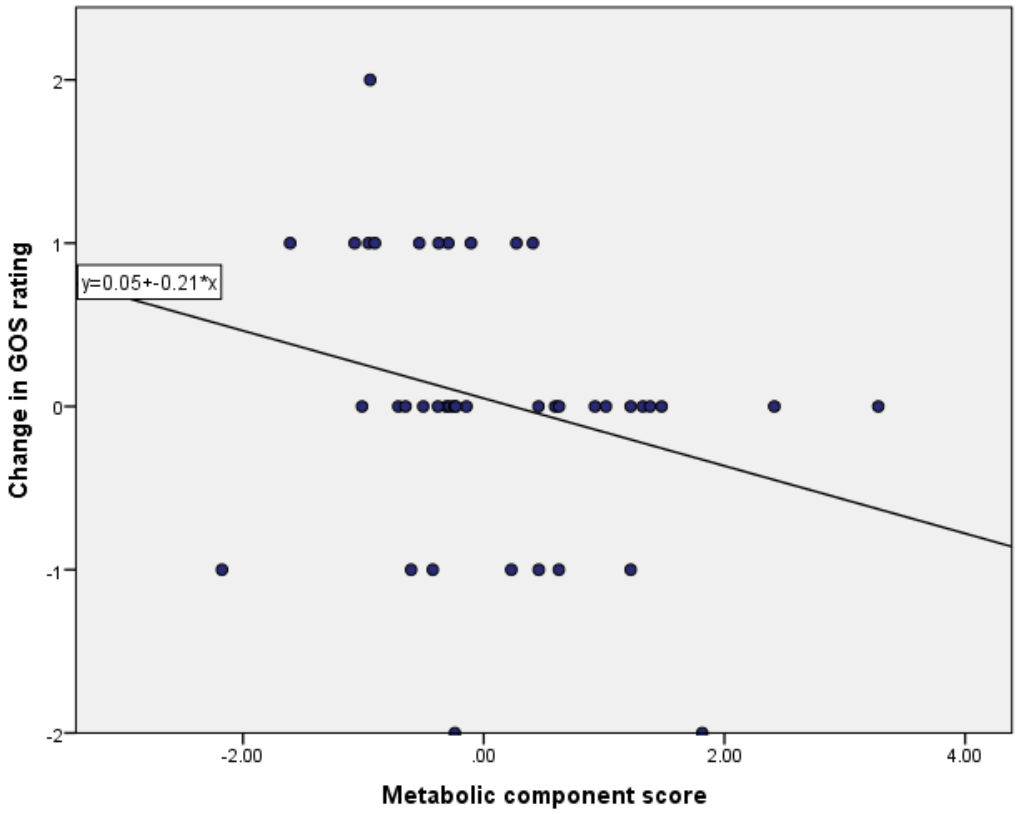

Figure 13 - Scatterplot of metabolic component scores and change in GOS rating

Subsequently, 3 ordinal logistic regressions were used to investigate the remaining AL component scores. No significant associations between change in GOS ratings and neuroendocrine, cardiovascular, or anthropometric component scores were found, although the relationship with anthropometric component scores approached significance (table 76), with high anthropometric scores associated with worsening GOS-E ratings and increasing disability. The assumptions of proportional odds were met and are described in Appendix E (section 1.11).

Allostatic load component score	*b*	*SE b*	Wald X^2	*Eβ*	95% CI for e*β*	*p*
Cardiovascular	-0.11	0.28	0.16	0.89	0.52 – 1.55	0.687
Neuroendocrine	-0.12	0.30	0.17	0.89	0.50 – 1.58	0.681
Anthropometric	-0.60	0.32	3.43	0.55	0.29 – 1.04	0.064

Table 76 - Ordinal logistic regression analysis of the relationship between AL component scores late after HI and change in GOS rating

7.7 Discussion

7.7.1 Principal findings

As expected, HI participants had significantly higher AL scores late after injury (median 27 years) than comparison participants after adjustment for age and

childhood deprivation scores; although having a HI only improved the predictive capacity of the model by 4%. Despite this, this finding provides support for the hypothesis that HI is associated with increased physiological dysregulation over time. When the AL component scores were investigated, HI participants had significantly higher metabolic and anthropometric component scores; implying brain damage causes higher metabolic and anthropometric indicators of health later in life.

Overall disability outcome (GOS rating) changed between 6 months post-injury and late follow-up in 46% of the HI group with 22% improving and 24% deteriorating. However contrary to expectation, change in disability (GOS) and disability outcome (GOS-E), was not explained by AL scores at late follow-up. Consistent with this, AL was not associated with cognitive function late after HI. This suggests the process of global recovery from brain damage, and the development of sequelae, is unrelated to the accumulation of physiological damage over time. There was one exception; a significant relationship between a decrease in GOS ratings and high metabolic component scores at late follow-up (higher triglyceride and creatinine levels and lower levels of albumin and high density lipoprotein). This implies that worsening disability over time results in increased secondary outcomes of the AL model, in this case specifically metabolic indicators. An explanation for this may lie in the likelihood that the lifestyles of individuals with worsening disability are less active and healthy. An alternative explanation is that change in disability is an effect of higher metabolic components scores. However due to the cross-sectional assessment of AL, this direction of the relationship cannot be determined.

7.7.2 Comparison with other studies

This is the first study investigating AL in HI participants late after injury. It is known that AL increases steadily over the life course (Crimmins et al., 2003); however the findings in this study show that AL, specifically metabolic and anthropometric component scores, were higher in the HI group than the comparison participants. Metabolic and anthropometric indicators of health are secondary outcomes of the AL model, which are modified over time by the typical production of primary allostatic mediators (neuroendocrine stress hormones) during the acute stress response (McEwen, 2002). There are a number of

conditions (figure 3, Chapter 2) that alter the production of primary mediators, which over time modify the normal regulation boundary of biological systems such as metabolic and anthropometric. The result of this more long-term stress response and adjustment of secondary outcomes is an increased risk of poor health, diseases, and mortality (McEwen & Stellar, 1993; Seeman et al., 2001). This indicates that the higher metabolic and anthropometric component scores in the HI participants is a consequence of ineffective or overactive management of the primary allostatic mediators, than the non-head injured comparison participants.

This finding contrasts with those at 6 months post discharge (study 2, Chapter 5), where there was no significant difference between HI and matched comparison participants (mean -0.64, SD 2.31; -0.97, 2.92). This suggests that brain damage does not affect AL in the acute stages, however over time it causes over or underactivity of allostatic systems, which lead to the accumulation of physiological dysregulation. There could be a number of explanations for this.

The AL model might indicate that the HI participants have experienced more stressors over time than the comparison participants, and this would result in higher metabolic and anthropometric component scores. Practical and emotional adjustment to living with a disability following a HI, and stress due to reduced ability, could cause physical or psychological stress that would contribute to increased accumulative physiological damage. Common physical sequelae following HI may cause AL to increase; such as sleep disorders, which are associated with increased AL and impairment in brain function (Castriotta et al., 2007; McEwen, 2006b; Orff, Ayalon, & Drummond, 2009; Ponsford et al., 2012). HI is linked with subjective mental fatigue years after injury and slower performance and more errors on measures of attention (Johansson, Berglund, & Rönnbäck, 2009; Ziino & Ponsford, 2006). An explanation for this is survivors of HI may require increased cognitive effort to perform tasks. This has been supported by evidence from an fMRI study in which HI participants demonstrated increased brain activity performing a cognitive task than age-matched comparison participants (Kohl, Wylie, Genova, Hillary, & Deluca, 2009). Increased levels of mental effort are associated with general arousal and autonomic changes, such as heart rate elevation, heart rate variability, glucose administration, and pupil

dilation (Kennedy & Scholey, 2000; Mulder, 1986; Segerstrom & Nes, 2007; Zekveld, Kramer, & Festen, 2010). Increased mental effort after HI and potential additional physiological responses, may lead to ineffective management of the primary allostatic mediators that is associated with accumulative AL (McEwen, 1998b).

Another explanation for the increased AL in the HI group could be maladaptive coping styles or changes in lifestyle after injury, which are unhealthier than comparison participants. For example, the higher metabolic biomarkers (or decreased metabolic 'healthy' biomarkers such as HDL) and anthropometric physical measures of health found in the HI group, are associated with conditions such as obesity, insulin resistance and metabolic syndrome (Eckel, Grundy, & Zimmet, 2005). The etiology of these conditions is multifactorial, ranging from the influence of genes, excess energy consumption and insufficient energy expenditure, to side effects of medication (Aronne, Nelinson, & Lillo, 2009; Park et al., 2003). Thus, albeit beyond the data in this study, the higher metabolic indicators may be caused by the HI participants being less healthy (potentially less active, or by having a poorer diet) than the comparison participants, as suggested by evidence that they take more medication. Inadequate sleep is also a risk factor for obesity and higher metabolic indicators, and sleep disorders are common after HI (Castriotta et al., 2007; Gangwisch, Malaspina, Boden-Albala, & Heymsfield, 2005; Orff et al., 2009; Ponsford et al., 2012). Therefore the AL of the HI participants could be a result of factors such as smoking, diet, sleep quality, medication and physical activity. Unfortunately in this study, further information about lifestyle such as these were not assessed. Therefore it is difficult to elucidate the cause of higher metabolic and anthropometric component scores in the HI group. Future research should aim to replicate this finding and collect further information about lifestyle, even though it might be retrospective and vulnerable to bias, further detail such as this may help to explain the differences in metabolic and anthropometric component scores between HI and comparison participants observed in this study.

However it is not simply lifestyle behaviours that cause AL to accumulate, it is a combination of genetic predisposition, early life events, social relationships, stressful life events with health-related choice and lifestyle behaviours (McEwen,

1998b). These factors would be difficult to assess retrospectively and combine into a model of risk of AL. Further, the appeal and ease of measuring AL is that it is the end-point physiological result of all of these factors on health. However it remains difficult to make recommendations about how to delay the faster increase of AL following HI based on the data collected in this study.

An implication of higher AL late after HI is that it is associated with increased risk of tertiary outcome of AL; disease and mortality (Gruenewald et al., 2006; Seeman, Crimmins, et al., 2004; Seeman et al., 2001). Consistent with this, abnormalities in metabolic and anthropometric systems are associated with increased risk of cardiovascular disease and type 2 diabetes (Lakka et al., 2002; Wilson, D'Agostino, Sullivan, Parise, & Kannel, 2002). Therefore the findings of this study could in part contribute to our understanding of recent evidence that HI participants have a significant increased risk of mortality late after injury, when compared with age, gender, and SES matched comparison participants (McMillan et al., 2011; McMillan et al., 2014). Also general admission to hospital rises following HI, which indicates that the injury has a fundamental effect on the increased risk of systemic and chronic disease (Masel & DeWitt, 2010; McMillan et al., 2014). The accumulation of AL may explain the pathological processes underlying the increased risk of illness and death late after HI.

The finding of no relationships between AL scores, component scores and disability outcome, on the GOS-E late after injury, is comparable with the findings in study 1 (Chapter 5: at hospital discharge) and study 2 (Chapter 6: 6 months post-discharge). Therefore the findings in this thesis consistently do not support the view that accumulated physiological dysregulation across multiple biological systems explains impairment or disability in these HI samples. Another novel finding in this study is that AL was not associated with change in disability between 6 months post discharge from hospital and late after HI. This indicates that multisystem dysregulation also does not drive disability outcome even late after HI. The change in disability over time observed in this study is consistent with the findings of study 2 (Chapter 6) where disability changed in 66% between near to hospital discharge and at 6 month follow-up. It is also similar to other previous prospective HI cohort studies based in Glasgow (McMillan et al., 2012;

Whitnall et al., 2006). Therefore the lack of finding is unlikely to be due to the sample and the rates of change in disability.

The lack of finding is consistent to that in study 2 (Chapter 6), which demonstrated AL was not associated with change in disability between discharge from hospital and approximately 6 months later. This is also similar to the finding that AL did not correlate with disability outcome assessed using the GODS at hospital discharge, both the GODS and GOS-E at 6 months post discharge, and the GOS-E late after injury. Therefore there is no evidence in these HI samples that disability or change in disability, early or late after injury is associated with accumulated physiological dysregulation.

However a novel finding in this study was a significant inverse relationship between change in GOS ratings between 6 months post-discharge and late follow-up 27 years later and metabolic component scores measured at late follow-up; higher metabolic indicators (higher levels of triglycerides and creatinine and lower levels of high density lipoprotein and albumin) were associated with worsening disability. As described above, metabolic indicators of health are secondary outcomes of the AL model and part of the long-term stress response (McEwen, 2002). Therefore a possible explanation of this finding may be that worsening disability over time modifies the typical production of primary allostatic mediators, causing metabolic indicators to adjust their normal operating ranges, in this case increasing. This interpretation is supported by the results of hypothesis 1, which demonstrated the metabolic component scores in the HI group were significantly higher than comparison participants. Therefore brain damage and/or the experience of increasing disability over a number of years may cause an increase in metabolic component scores.

Due to the cross-sectional assessment of AL in this study, the interpretation of the temporal relationship between change in disability and metabolic component scores is limited to this conclusion, and the causes of change in disability remain unknown. However studies that have prospectively assessed indicators of metabolic functioning (including serum creatinine and albumin like in this study, and other measures such as glucose and low-density lipoprotein) at hospital admission following HI demonstrated an association with Glasgow Outcome Scale GOS ratings at 6 month follow-up (Chen, Bao, Lu, & Xu, 2014; Husson et al., 2010;

Murray et al., 2007; Nelson et al., 2012). This indicates that metabolic components scores may play a role in predicting poor outcome after HI. Unfortunately such conclusions cannot be drawn from the findings in this study.

There are implications of increasing disability potentially triggering a long-term stress response resulting in higher metabolic indicators later after injury. Metabolic indicators are secondary outcomes in the AL model, which if continue to be produced at an increase level, deregulation becomes a chronic condition and this predisposes individuals to serious pathophysiology, morbidity and mortality (Juster et al., 2010; McEwen & Stellar, 1993). Evidence shows high metabolic indicators are associated with co-morbidities such as diabetes and obesity (Eckel et al., 2005). Therefore it is important that this finding is replicated to investigate and confirm the temporal relationship between change in disability and metabolic components scores, in order to consider possible interventions in the development of high metabolic indicators.

In this study, AL was not associated with cognitive functioning; the absence of association contrast with previous research that has demonstrated higher AL is associated with impaired performance on cognitive tasks. The participants in these previous studies were mostly older than the participants in this study: Goldman et al. (2006) age 54-91 years; Seplaki et al. (2006), age 54- 90 years; Karlamangla et al. (2002), age 70-79 years; Seeman et al. (2001), age 70-79 years; Booth et al. (2015), mean age of 72.5 (SD = 0.7) years), the mean age of participants in the current study was 49 years. However Karlamangla et al. (2014) also demonstrated AL predicted episodic memory scores and executive function in middle aged to slightly older adults (age 49-66; mean age 57); therefore the difference in finding is unlikely to be due to the age of participants in this study.

The specific tests of cognitive function used in previous research that demonstrated an association with AL were different to those used in this research although they are validated and assess the same cognitive functions; processing speed, memory, and executive function (Booth et al., 2015; Goldman et al., 2006; Karlamangla et al., 2002; Seeman et al., 2001; Seplaki et al, 2006). Thus the difference in finding is unlikely to be caused by the sensitivity of the cognitive tests used.

The evidence that AL is associated with cognitive impairment or decline is based on healthy populations in the United States (Karlamangla et al., 2002; Seeman et al., 2001), Taiwan (Goldman et al., 2006; Seplaki et al., 2006), and Scotland (Booth et al., 2015). Therefore the difference in findings implies that the accumulation of AL following brain damage is different to that observed in healthy aging populations, and which has previously demonstrated correlations with cognitive function. This might be supported by the finding of hypothesis 1 that HI participants late after injury had significantly higher AL scores than healthy comparison participants. The elevated metabolic and anthropometric component scores may confound the typical relationship between AL and cognitive function observed in the previous studies.

7.7.3 Strengths and limitations

Due to the cross-sectional assessment of AL late after HI, it is difficult to consider the relationship of AL, disability and cognitive outcome over time. Also, little further information was collected regarding life-long health behaviours. Thus the causes and consequences of higher AL in the HI group, and the temporal relationship between metabolic component scores and deterioration in GOS rating over time remain unknown unless they are followed-up at a later date. It is also important to remember that although having a HI was associated with a significantly higher AL scores, it only increased the predictive capacity of the model by 4%.

Another limitation of this study is a potential survival bias in the recruitment of participants from the original HI cohorts. No comparison can be made between the AL and health of participants in this study and the individuals in the cohort who died previously. It is possible that individuals who died prior to the beginning of this study potentially had AL scores that were associated with disability. Those that remain in the cohort may have factors in their life that act as a buffer against stress and the accumulation of AL, such as social support and a healthy diet (McEwen & Gianaros, 2011). To fully explore AL in a HI cohort, a longitudinal study is required with multiple follow-ups to enable the observation of how and why AL accumulates over time, and what consequence this has on disability and health outcomes.

Strength of this study include the use of a prospective cohort that has enabled the investigation of change in GOS ratings at two time points and of late outcome after HI. The use of a comparison group also enabled the investigation of the effects of having a HI on AL. The present study is also the first to consider AL late after HI and compare it with disability outcome and change in outcome over time.

7.7.4 Implications of findings

Allostatic load, specifically metabolic and anthropometric component scores were higher late after severe HI than in comparison participants. This finding supports the view that HI is a chronic condition associated with physiological deregulation late after injury. Other research has shown that higher AL is associated with increased risk of disease and mortality, however a longitudinal study is required to investigate the causes and consequences of high AL in the HI population, and which can consider those who die late after HI.

AL does not explain the heterogeneity of outcome in terms of disability or cognitive function late after injury, or change in disability over time; a consequence of this is that predicting outcome late after HI remains impractical. The relationship between metabolic component scores and deterioration in GOS rating over time requires further investigation to understand the temporal relationship between these factors.

The finding that disability changes late after HI is consistent with other research (McMillan et al., 2012; Whitnall et al., 2006) and has implications in terms of expectations of recovery for HI patients and their families. However further research is required to understand the factors associated with change in disability.

7.8 Conclusion

The findings do not support the view that accumulated physiological dysregulation across multiple biological systems explains cognitive impairment or disability late after injury. However brain damage is associated with higher AL late after HI in particular the metabolic and anthropometric component scores, and increase in disability over time is also associated with higher metabolic component scores at late follow-up. This may be due to a long-term stress response to adjusting to life

with a disability, or potentially maladaptive coping styles or changes in lifestyle after injury. The implications of higher anthropometric and metabolic component scores is an increased risk of morbidities, therefore future research should try replicating these findings, collecting more information about health and lifestyle choice, in order to understand the causes of these higher component scores and work towards possible interventions.

This study, and studies 1 and 2 (Chapter 5 and 6) were conducted with participants from a Glasgow HI population, which is largely socially deprived (McMillan et al., 2011; McMillan et al., 2014; Thornhill et al., 2000). In studies 1, 2 and 3, SIMD (2012) scores indicated the majority of participants were living in areas of high social deprivation. Social deprivation is a known confounder of AL, and therefore the results of these studies may be affected by the health of the population recruited. These participants were also recruited after having a moderate or severe HI. Thus, to check whether the severity of HI or the high levels of deprivation were inhibiting the investigation of AL and outcome after HI, the next study examines any accumulating effects of repeat concussion on AL, in a sample of retired international rugby players.

Chapter 8 **Allostatic load and repeat concussion in retired international rugby players**

Background

The studies in Chapter 5-7 explored the extent to which allostatic load (AL) is associated with cognitive and disability outcome, and change in disability over time after moderate to severe head injury (HI). To investigate the potential relationship between AL and HI outcome in a healthier and milder HI group, this study examined allostatic load and outcome late after repeat concussion in retired international rugby players.

Methods

Retired international rugby players were recruited from a database of former Scottish international rugby players held by the Scottish Rugby Union (n = 48). A measure of AL was compared to the number of self-reported concussions, depression scores, disability outcome (Glasgow Outcome Scale-Extended), cognitive function (using a range of cognitive tests) and to the AL scores of demographically similar non-head injured comparison participants. Potential confounders were adjusted for in the analyses.

Results

The retired international rugby players reported a high number of concussions; however AL was not associated with number of concussions. Following this, no difference was found in AL scores between retired international rugby players, and comparison participants, and AL was not associated with disability outcome late after repeat concussion. Similarly, no relationship was found between self-ratings of depression and AL, except for a significant, moderate relationship between higher self-ratings of depression and higher metabolic component scores (higher triglyceride and creatinine levels and lower levels of albumin and high density lipoprotein). In terms of cognitive functioning, a significant relationship was found between high AL scores and faster time to complete a fine motor task with the dominant and non-dominant hands.

Conclusions

The findings demonstrate that concussion does not contribute to wear-and-tear on allostatic systems over time and therefore does not support the view that repeat concussion is associated with increased AL in retired international rugby players. As a result of this, AL is not a helpful predictor of outcomes in this group of elite athletes, including global disability and specific cognitive tests, except for an inverse relationship with fine motor control using the dominant and non-dominant hand. There was no evidence for a group difference in AL, and therefore no suggestion of pathological processes increasing the risk of illness and death, between retired international rugby players and comparison participants. Future research should explore the consequences of AL in elite athletes.

8.1 Introduction

The results of the study 1 and 2 (Chapter 5 and 6) demonstrated that allostatic load (AL) was not associated with disability outcome early after head injury (HI), but there was evidence in study 3 (Chapter 7) that brain damage causes higher metabolic and anthropometric indicators of health later in life. As an extension of these previous empirical studies, and to inspect whether the high levels of deprivation and more moderate to severe HI experienced by participants in these groups affected the measure of AL, this next study investigated whether AL explained outcome after HI using a healthy and repeat mild HI group.

There is growing concern in the scientific community, in the media, and in sports governing bodies about the health consequences of concussion (Meehan, Mannix, Zafonte, & Pascual-Leone, 2015; Sanderson, Weathers, Snedaker, & Gramlich, 2016; Utecht, 2014). In particular exposure to repetitive concussion has been linked to neuropathology and long-term health consequences such as Alzheimer's disease (McCrory, 2011; McCrory, Meeuwisse, Kutcher, Jordan, & Gardner, 2013).

Rugby Union is acknowledged as having a concussion incidence amongst the highest for contact sports, estimated between 4 and 11 concussions per 1,000 player hours (Hollis et al., 2009; Kemp, Hudson, Brooks, & Fuller, 2008), with the most recent Rugby Football Union injury audit listing concussion as the most common match injury in 2012 (5.1 concussions/ 1,000 player hours) (England Professional Rugby Injury Surveillance Project Steering Group, 2013); however there are few studies that have investigated the outcome of repeat concussion.

A recent cross-sectional study by Decq et al. (2016), into the long-term consequences of recurrent sports concussion in 239 French retired rugby players and a comparison group of 138 other retired sportsmen (sailing, skiing, horse riding, athletics, rock climbing, weightlifting, canoeing, gliding, squash, badminton, swimming, triathlon, pelota, archery, table tennis, fencing, paragliding, golf), investigated the prevalence of major depressive disorder (The Patient Health Questionnaire-9; PHQ-9), mild cognitive disorder (The French Telephone Interview for Cognitive Status Modified), fluency disorder (Isaacs Set Test) and headache frequency (Headache Impact Test-6). The retired rugby players reported a higher number of repeat concussions than the other retired

sportsmen (p <0.001). A higher rate of major depressive disorder was reported in the retired rugby player group (9% versus 6%, p <0.05), and the PHQ-9 score was associated with number of repeat concussion regardless of sport played. The retired rugby player group also reported higher rates of mild cognitive disorders (57% versus 40%, p <0.01), but this was not associated with number of repeat concussions. Headache severity did not differ between groups but was associated with the number of repeat concussions (p <0.05).

There is evidence of continued neuroinflammation associated with white matter degeneration in survivors for many years after severe head injury (HI) (Gentleman et al., 2004) including after a single traumatic brain injury (Johnson et al., 2013). Alzheimer's disease- like pathologies (tau, amyloid-beta deposits) have also been detected as early as two hours after severe HI (Ikonomovic et al., 2004) and in long-term survivors (Johnson et al., 2012). This evidence from severe HI studies may help to explain the link between mild HI and late emotional and cognitive effects.

Neuropathologies in the form of p-tau immunoreactive neurofibrillary tangles and astrocytic tangles have also been found in individuals with a history of repeat mild HI (McKee et al., 2013). The participants (n = 68, mean age 59.5 years) in this study included professional footballers (n = 34), a semi-professional footballer (n = 1), amateur footballers (n = 15), professional boxers (n = 7), an amateur boxer (n = 1), a professional wrestler (n = 1), professional hockey players (n = 4), an amateur hockey player (n = 1) and individuals with no history of contact sport but history of repeated mild HI (n = 4). Post-mortem family interviews and medical records described clinical symptoms ranging from a cluster of non-specific complaints such as depression, irritability, poorer concentration, and memory impairments to more widespread and severe cognitive complaints and personality change that are consistent with dementia.

These research findings suggest there may be ongoing biological processes that begins almost immediately after injury and continues throughout the life-span. It is not yet understood whether or how this long-term neuroinflammation affects disability outcome or the progression of neurodegenerative disease in HI survivors. Further to this, as described in Chapter 1, there is evidence that mild HI is associated with an increased risk of death later after injury (McMillan et al., 2014).

As detailed in Chapter 2, allostatic load (AL) has been shown to be associated with various health outcome including physical functioning as well as all-cause mortality (Gruenewald et al., 2009; Seeman et al., 2001). With regards to cognitive functioning in an older, healthy population, high AL is associated with poorer performance on a number of valid and reliable tests (Goldman et al., 2006; Hampson et al., 2005; Karlamangla et al., 2002; Seeman et al., 1997; Seplaki et al., 2006). Potentially repeat mild trauma to the brain may cause dysregulation of the primary mediators of AL, given the evidence of chronic inflammation after HI (Johnson et al., 2013). Over time, this might create atypical functioning in the secondary outcomes of AL that eventually lead to tertiary outcomes observed in groups following repeat concussion such as depression or cognitive impairments (Decq et al., 2016).

Despite the link between repetitive concussion and an enhanced risk of the late development of cognitive and mental health consequences, and the high levels of participation in rugby in Britain, there have been no formal studies directed at investigating the long-term neuropsychological outcomes in British rugby players. Investigating AL in a group of participants with a history of repeat mild HI may help explain the varying degree of outcome in terms of cognitive impairment, neuropathology, and increased risk of death after mild HI.

This study aimed to investigate AL and the long-term cognitive health outcomes in retired Scottish international rugby players with self-reports of concussion history. The retired international rugby player data were compared to age and demographically similar comparison participants with no known exposure to repeat concussion, to enable the investigation of late outcome after repeat concussion. This investigation was part of a larger study that intends to follow-up a cohort of retired international rugby players, monitoring cognitive health over time.

8.2 Aims

1. To compare the AL of retired international rugby players to that of comparison participants.

2. To determine whether a higher frequency of reported concussion is associated with higher AL.

3. To investigate whether AL is associated with disability outcome (GOS-E ratings), depression or incidence of cognitive impairment later in life in retired international rugby players.

8.3 Hypotheses

1. Allostatic load scores of retired international rugby players are significantly higher than comparison participants.

2. A higher frequency of reported concussion in retired international rugby players is associated with higher allostatic load scores.

3. Higher allostatic load scores are associated with lower GOS-E ratings later in life in retired international rugby players.

4. Higher allostatic load scores are associated with higher rates of depression later in life in retired international rugby players.

5. Higher allostatic load scores are associated with increased cognitive impairment in later life in retired international rugby players.

8.4 Design

This was a cross-sectional study.

8.5 Methods

8.5.1 Ethics

Ethical permission was obtained from the College of Medical, Veterinary & Life Sciences Ethics Committee for Non-Clinical Research Involving Human Subjects at the University of Glasgow on 22nd January 2014 (See appendix A for approval letter).

8.5.2 Recruitment

8.5.2.1 Retired international rugby players

Potential participants were contacted by means of a database of approximately 350 former Scottish international rugby players held by the Scottish Rugby Union (SRU). Those comprising the database had agreed that the SRU could contact them. The SRU contacted potential participants by e-mail, inviting them to participate and providing them with a Participant Information Sheet (Appendix B). Potential participants were given contact information for the Head Injury Research Group, if they required further information or wanted to take part.

8.5.2.1.1 Inclusion criteria

Participants were included in the research if they were a retired international rugby player, aged over 18, capable of giving consent to take part and available and capable of assessment. Participants were also required to be fluent in English because some of the assessments were standardised for English speakers.

8.5.2.2 Comparison participants

Comparison participants were recruited from friends, colleagues or relatives of the retired international rugby players because they were likely to be of similar age, and social economic status to the retired international rugby players. Recruited retired international rugby players were given Comparison Participant Information Sheets (Appendix B) at the end of their assessment, and asked to distribute to male friends, colleagues, or relatives. These Information Sheets contained contact information for the Head Injury Research Group, so potential comparison participants could phone or email to enquire about taking part. All potential comparison participants were screened on the telephone for the inclusion and exclusion criteria before a date and place of assessment was made.

8.5.2.2.1 Inclusion criteria:

Comparison participants were included if they were male, as the retired international rugby player group were all male. Participants had to be capable of giving consent to take part and be fluent in English (the assessments are standardised for English speakers).

8.5.2.2.2 Exclusion criteria

Comparison participants were excluded if they reported a concussion on more than one occasion (either with loss of consciousness and/or associated symptoms of confusion or disorientation, nausea, dizziness, poor balance, blurred vision or severe headache) or had any previous severe HI (reporting loss of consciousness (LoC) for 30 minutes or more or post-traumatic amnesia for more than 1 day) or a mild HI on more than 1 occasion (HI with reported LoC <30 minutes or post traumatic amnesia <24hr).

8.5.3 Procedure

Assessments took place at the Clinical Research Facilities at The Glasgow Royal Infirmary and the Western Infirmary in Glasgow, at the Murrayfield stadium in Edinburgh, or at the Imperial College London. Participants were asked if they had any questions about the study before signing the consent form. The consent form was counter-signed and dated by a member of the Head Injury Research Group. The interview and assessment lasted approximately 60-90 minutes. I collected all the blood samples and the remaining data in half of the sample, Dr. Lin McLean collected the remaining data for the other half of the sample, and Ms. Jennifer Hay prepared the blood samples for analysis (spinning and pipetting serum).

8.5.4 Measures

8.5.4.1 Descriptors

8.5.4.1.1 General information

Information about age, number of years spent in education, and postcode were obtained by interviewer-completed questionnaire. Scottish Index of Multiple Deprivation (SIMD) 2012 quintiles were used to assess socioeconomic deprivation, ranging from 1 (most deprived) to 5 (most affluent). Chapter 3 describes how SIMD (2012) quintiles are calculated based on the postcodes of participants.

8.5.4.1.2 Health information

As secondary descriptors of health, participants were asked how many physician diagnosed chronic illnesses they had (listed in Appendix D, section 16 and 17), how

many medications they took (listed in Appendix D, section 18 and 19), and to subjectively rate their health on a Likert scale as ‘Very Good’, ‘Good’, ‘OK’, ‘Poor’, or ‘Very Poor’ scored from 1 to 5.

8.5.4.1.3 History of concussion

A brief self-report inventory was used to assess history of concussion, including concussion in and outside of playing rugby (see Appendix C). Repeat concussions were included in the analysis both as a continuous scale and, because there was likely to be high variability in responses, they were also grouped into 3 levels: no repeat concussions (0-1), moderate repeat concussion (2-9) and high frequency of repeats (10 or more).

8.5.4.2 Main outcomes

8.5.4.2.1 Allostatic Load

A description of how AL was assessed is presented in Chapter 3.

8.5.4.2.2 Assessment of disability after head injury

The GOS-E (Wilson et al. (1998); Appendix C) was used to assess any gross changes in global functioning as a result of repeat concussions in the retired international rugby player group.

8.5.4.2.3 Cognitive assessments

At this assessment, it was expected that cognition and depression in some of the retired rugby cohort would range from normal to mild impairment due to the invited retired rugby player participants ranging in age and history of concussion. Therefore it was necessary to use tests that were sensitive to mild cognitive impairment; that assessed cognitive functions that are vulnerable to impairment following repeat concussion (executive function and delayed recall; Belanger et al. (2010)) and more generally a broad range of assessments of cognitive and psychological function in order to detect change at future follow-up. These included:

1. **The Montreal Cognitive Assessment**: A brief screening test of general cognitive function (Nasreddine et al. (2005); Appendix C). With a maximum score of 30 points possible; a score of 26 and above was viewed as normal (Nasreddine et al., 2005).

2. **Symbol Digit Modalities Test**: A test of information processing speed (Smith (2002); Appendix C); the maximum score is 110.

3. **Trail Making Test**: A test of executive function (Reitan (1958); Appendix C); the outcome was time taken (in seconds) to complete part B.

4. **Auditory Verbal Learning Test**: A test of memory and learning (Schmidt (1996); Appendix C), with a maximum score for immediate recall of 75 and of 15 for delayed recall.

5. **Judgment of Line Orientation Test**: a test of visuospatial skills (Benton, Hamsher, Varney, & Spreen, 1983), with a total possible score of 30 points.

6. **Lafayette Grooved pegboard:** A sensitive assessment of fine motor co-ordination (Klove, 1963; Matthews & Klove, 1964). The test was conducted twice, first with the dominant hand then with the non-dominant hand and time taken to complete the task was recorded in seconds.

8.5.4.2.4 Mental health information

The Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith (1983); Appendix C) was used to assess depression in the retired international rugby player group. The HADS is a 14 item questionnaire about the experience of symptoms of anxiety and depression in the past week; 7 items relate to symptoms of anxiety and 7 to depression (maximum of 3 points each depending on symptom severity). Scores of anxiety and depression range from 0 to 21 grouped into the following categories; 0-7 representing ‘normal’, 8-10 ‘mild’, 11-14 ‘moderate’ and 15-21 ‘severe’ levels.

8.5.4.3 Confounders

8.5.4.3.1 Confounders of allostatic load

Higher age, social deprivation, and ratings of childhood deprivation are associated with higher AL and were included in the analysis as covariates (Crimmins et al., 2003; Dich et al., 2014; Gruenewald et al., 2012; Hasson et al., 2009; Singer & Ryff, 1999). Anti-hypertensive and anti-inflammatory medications affect measures of cardiovascular and immune functioning, and were included in the analysis as covariates of their respective components and AL scores.

8.5.4.3.2 Confounders of disability outcome

Older age is a predictor of poorer outcome after HI, as described in Chapter 3 (Jacobsson et al., 2009; McMillan et al., 2012; Thornhill et al., 2000); if it was associated with GOS-E ratings, it was included in analyses as a covariate.

8.5.4.3.3 Confounders of cognitive function

Age, years of education, number of concussions, and concussion category (3 levels: no repeat concussions = 0-1, moderate repeat concussion = 2-9, and high frequency = 10 or more) were adjusted for in statistical regression models of cognitive function. Number of concussions assessed as a continuous scale has more statistical power, but categorised number of concussions reduces variability, therefore they were both included in the analysis to investigate if either method were better at correlating with cognitive function. In the event that both the continuous and categorical variables of number of concussion were associated with cognitive function, only the continuous variable was kept in the final model as it has more statistical power due to containing more information (Royston, Altman, & Sauerbrei, 2006).

8.5.4.3.4 Confounders of scores of depression

As described in the introduction, previous research has demonstrated higher number of repeat concussion is associated with higher rates of depression (Decq et al., 2016; McKee et al., 2013). Therefore if number of concussions was associated with HADS ratings of depression, they were included in the analysis as a covariate.

8.5.5 Data analysis plan

Data were analysed using SPSS v22. The distributions of the data were examined using Kolmogorov-Smirnov tests on each variable. Demographic information of the retired international rugby players and comparison participants was described using summary statistics and differences in secondary health questions investigated using independent t-tests or Mann-Whitney U tests.

Multiple univariate regressions were used to investigate whether differences in group characteristics or confounders predicted the continuous dependent variables in hypotheses 1, 2, 4 and 5. Significant covariates were kept in the final model and adjusted for using hierarchical regressions (Pallant, 2013). The assumptions of the final model (described in Chapter 5) were checked and detailed in the Appendix.

Hypothesis 3 was investigated using ordinal logistic regressions because the GOS-E is an ordinal scale. The relationship between the confounder variable (age) and GOS-E ratings was investigated using an ordinal logistic regression and included in the final regression model if a significant association was found. The assumptions of an ordinal logistic regression are described in Chapter 5.

If any of the assumptions of a hierarchical regression were violated or the confounders were found to not significantly predict the dependent variable, then between group differences were explored using independent t-tests or Mann Whitney U tests, and within group associations investigated using Pearson's or Spearman's rank correlations depending on the distribution of the data.

Cohen's *d* (Cohen, 1988) is reported as an indication of effect size for between group differences (independent t-test or Mann-Whitney U test), Cohen's f^2 (Cohen, 1988) as an indication of effect size for the proportion of variance accounted for by a variable, over and above covariate variables (hierarchical regression), and either Pearson's or Spearman's rank correlation coefficients as an indication of effect size for linear relationship between two variables.

8.6 Results

8.6.1 Recruitment of participants

8.6.1.1 Retired international rugby players

Figure 14 details the recruitment of retired international rugby players for study 4.

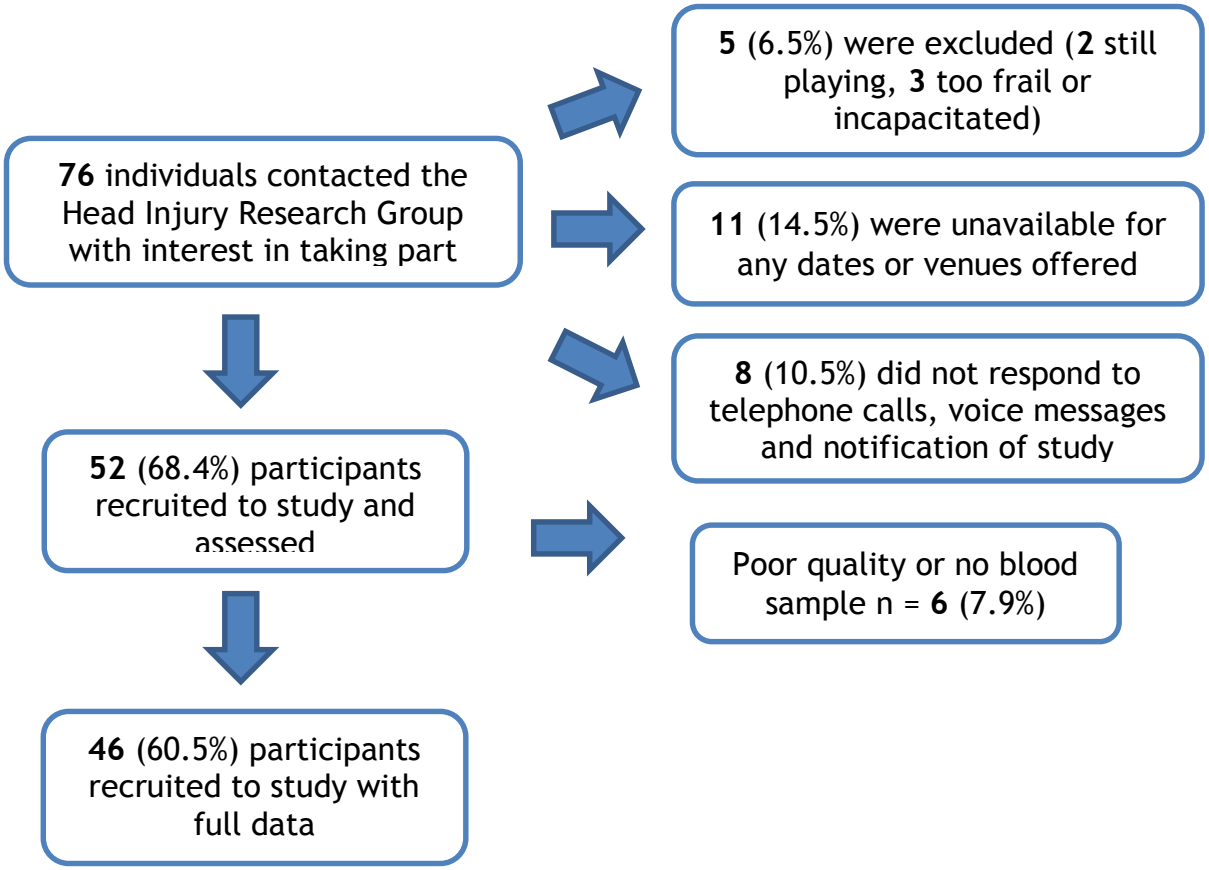

Figure 14 – Recruitment of retired international rugby players in study 4 Adapted from McMillan et al. (2015).

8.6.1.2 Comparison participants

Figure 15 details the recruitment of comparison participants for study 4.

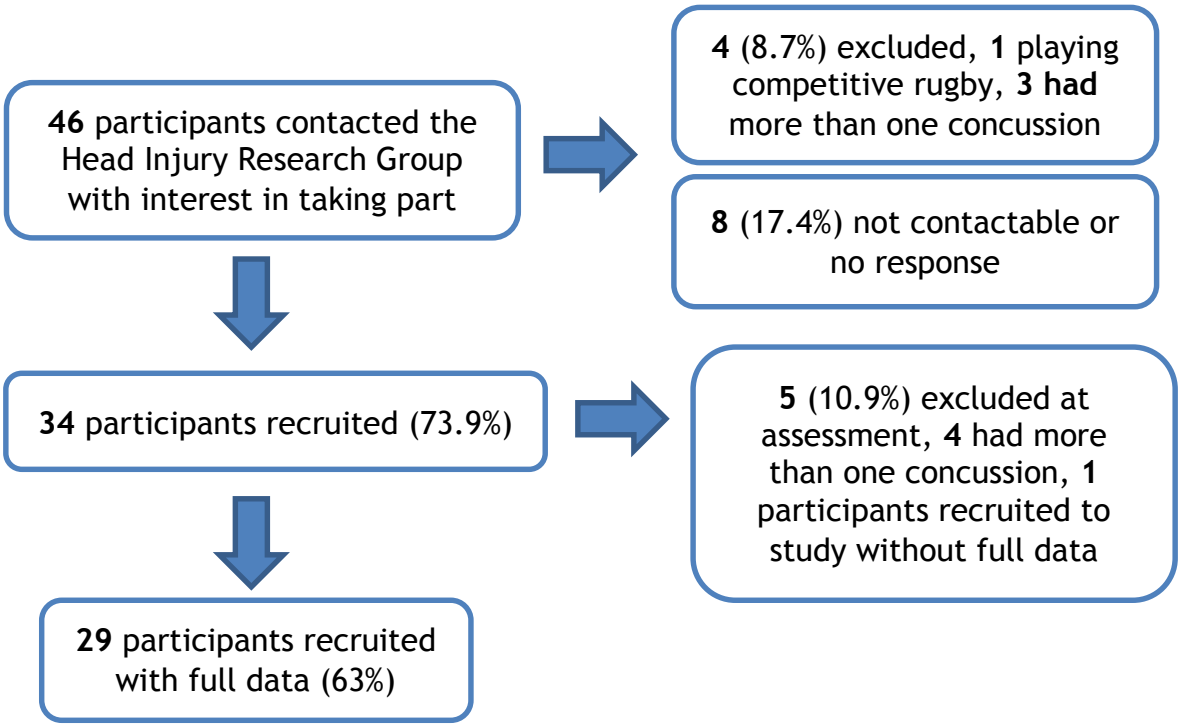

Figure 15 – Recruitment of comparison participants in study 4
Adapted from McMillan et al. (2015).

8.6.2 Demographic information

The mean age of the retired international rugby players was 54.1 years (SD 12.8, range 26-79) and 55.1 years (SD 9.1, range 36-72) for comparison participants. All the participants were male. Table 77 shows the groups were similar in SIMD (2012) quintiles (lower values indicate higher deprivation).

SIMD (2012) quintile	Retired international rugby players (%)	Comparison participants (%)
2	2.3	3.4
3	16.3	20.7
4	18.6	27.6
5	62.8	48.3

Table 77- Percentages of SIMD (2012) quintiles in study 4

8.6.2.1 Group matching

There was no significant difference in SIMD (2012) quintiles (U = 536.50, p = 0.264, r = -0.13) or age (t = -0.34, p = 0.733) between groups.

8.6.2.2 Secondary health information

The descriptive statistics for the secondary health questions are displayed in table 78. There were no significant differences between groups for number of co-morbidities (U = 574.00, p = 0.237, r = -0.14), subjective measure of health (U = 668.50, p = 0.986, r = 0.01), or in the number of medications presently taken (U = 744.00, p = 0.366, r = 0.10) (see Appendix D, tables 16 and 17 for a list of co-morbidities, and tables 18 and 19 for a list of medication).

	Retired international rugby players	Comparison participants
	Median (IQR)	Median (IQR)
Subjective measure of health	2 (1, 2) Good (Very Good, Good)	2 (1, 2) Good (Very Good, Good)
Number of co-morbidities	1 (0, 1)	0 (0, 1)
Number of medications	0.00 (0.00, 1.25)	1.00 (0.00, 2.00)

Table 78 - Descriptive statistics for the secondary health questions in study 4

8.6.3 International rugby player group information

8.6.3.1 Rugby playing history

Table 79 displays details of the rugby playing history of the 46 retired international rugby players and for the 19 comparison participants who had ever played rugby. As was expected, retired international rugby players had played rugby for longer, were older when they stopped playing and had played more recently than comparison participants who had played rugby. In the retired international rugby players group, the average number of international matches played was 25 (SD = 25). Twenty-six (56.5%) of the retired international rugby players stopped playing before the sport turned professional in 1995 (Ryan, 2009).

	Retired International Rugby Players	Comparison participants
Ever played rugby	46 (100%)	19 (63%)
Number of years playing rugby Median (IQR)	23.0 (19.8, 25.0)	5.0 (3.0, 16.0)
Age when stopped playing Median (IQR)	33.0 (30.8, 35.0)	17.0 (16.0, 27.0)
Years since stopped playing Mean (SD; Min, Max)	21.2 (12.6; 1, 48)	33.7 (10.5; 10, 53)

Table 79 - Descriptive statistics for history of rugby playing in study 4
Adapted from McMillan et al. (2015)

8.6.3.2 History of head injury

Table 80 shows the history of HI in the retired international rugby player and comparison groups. No participant reported a HI with loss of consciousness for more than 30 minutes indicating the head injuries were all 'mild' (Cassidy et al., 2004). Ten controls (34%) reported history of a single concussion (one with loss of consciousness of 3 seconds and one of 17.5 minutes). In the retired international rugby player group the longest loss of consciousness reported ranged between 3 seconds and 15 minutes (median 1 minute; IQR: 13.5 seconds, 4.8 minutes).

	Retired International Rugby Players	Comparison participants
Experienced concussion Rugby Related Non-rugby Related	43 (93%) 43 (93%) 14 (30%)	10 (34%) 3 (10%) 7 (24%)
Number of concussions Median (IQR)	6.5 (3.0, 17.0)	0.0 (0.0, 1.0)
Number of concussion with symptoms lasting +1 hour Median (IQR)	1.0 (0.0, 2.3)	0.0 (0.0, 0.0)
Estimated cumulative loss of consciousness (minutes) Median (IQR)	0.5 (0.0, 3.3)	0.0 (0.0, 0.0)

Table 80 - Descriptive statistics for concussions from rugby or other causes Adapted from McMillan, McConnachie, Wainman-Lefley, Maclean, McSkimming, Hay, & Stewart (2016).

8.6.3.3 Disability outcome late after repeat concussion

GOS-E ratings of the 46 retired international rugby players are displayed in table 81.

Glasgow Outcome Rating	n	%
Upper Good Recovery (8)	34	73.9
Lower Good Recovery (7)	10	21.8
Upper Moderate Disability (6)	2	4.3
Lower Moderate Disability (5)	0	
Upper Severe Disability (4)	0	
Lower Severe Disability (3)	0	

Table 81 - The frequency and percentage of GOS-E ratings in study 4

When GOS-E ratings were dichotomised, 44 (95.7%) retired international rugby players had made a Good Recovery (≥7) and 2 (4.3%) were Disabled (≤6) (Narayan et al., 2002).

8.6.3.4 Symptoms of depression late after repeat concussion

The median rating of depression on the HADS was 2 (IQR: 1, 4). The maximum score was 7; therefore all retired international rugby players scored within the 'normal' category for depression scores (Zigmond & Snaith, 1983).

8.6.4 Hypothesis 1

"Allostatic load scores of retired international rugby players are significantly higher than comparison participants"

8.6.4.1 Allostatic load scores

Table 82 shows the results of the Kolmogorov-Smirnov test for normality and descriptive statistics for AL scores of retired international rugby players and comparison participants; the AL scores of both groups were normally distributed.

		Kolmogorov-Smirnoff		Descriptive statistics
	Participant group	Statistic	*p*	Mean (SD)
Allostatic load scores	Retired international rugby players	0.069	0.200	-0.23 (2.69)
	Comparison	0.099	0.200	-0.29 (2.58)

Table 82 - Kolmogorov-Smirnov test and descriptive statistics for AL scores

Fifteen (32.6%) retired international rugby players and 5 (17.2%) comparison participants were taking anti-inflammatory medication and 8 (17.4%) retired international rugby players and 10 (34.5%) comparison participants were taking anti-hypertensive medication (see Appendix D, tables 18 and 19 for list). The frequency and percentage of childhood deprivation scores in retired international rugby player and comparison participants are displayed in table 83. A childhood deprivation score is missing for 1 retired international rugby player as they grew up in care. The groups were roughly similar with the highest frequency of retired international rugby players and comparison participants not experiencing any childhood deprivation.

	Childhood deprivation scores			
Participant group	0 (low)	1	2	3 (high)
	n (%)	n (%)	n (%)	n (%)
Retired international rugby player	26 (58)	13 (29)	5 (11)	1 (2)
Comparison	20 (69)	5 (17)	2 (7)	2 (7)

Table 83 - Percentage of childhood deprivation scores in study 4

Five univariate regressions were used to check whether potential confounding variables (childhood deprivation, taking anti-inflammatory, and anti-hypertensive medication) and differences between groups (age and SIMD (2012) quintile) were associated with AL scores. The results are displayed in table 84; none of the potential confounders were significantly associated with AL scores, therefore they were not included in the analysis as covariates and an independent t-test was used to explore group differences in AL scores. There was no significant difference in AL scores between retired international rugby players and comparison participants (t = 0.11, p = 0.772, d = 0.02).

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	0.03	0.03	0.12	-0.03 – 0.08	0.322
SIMD (2012) quintile	0.20	0.36	0.07	-0.52 – 0.92	0.582
Anti-inflammatory medication	-0.63	0.69	-0.11	-2.00 – 0.74	0.362
Anti-hypertensive medication	-0.98	0.71	-0.16	-2.39 – 0.43	0.168
Childhood deprivation scores	0.26	0.37	0.08	-0.48 – 1.01	0.480

Table 84 – Univariate regression analysis of variables predicting AL scores

As detailed in Table 80, 3 (7%) retired international rugby players reported no history of concussion, therefore sensitivity analysis was conducted by repeating the above analysis, after removing the data of these 3 participants, to investigate whether this affects group differences in allostatic load scores.

Five univariate regressions were used to check whether potential confounding variables (childhood deprivation, taking anti-inflammatory, and anti-hypertensive medication) and differences between groups (age and SIMD (2012) quintile) were associated with AL scores of the 43 retired international rugby players and 29 comparison participants. The results are displayed in table 85; none of the potential confounders were significantly associated with AL scores, therefore they were not included in the analysis as covariates and an independent t-test was used to explore group differences in AL scores. There was no significant difference in

AL scores between retired international rugby players and comparison participants (t = -0.15, p = 0.812, d = 0.04).

Variable	*b*	*SE B*	*B*	95% CI	*P*
Age	0.02	0.03	0.09	-0.04 – 0.07	0.478
SIMD (2012) quintile	0.22	0.38	0.07	-0.54 – 0.98	0.573
Anti-inflammatory medication	-0.65	0.70	-0.11	-2.05 – 0.75	0.358
Anti-hypertensive medication	-1.13	0.71	-0.19	-2.54 – 0.28	0.114
Childhood deprivation scores	0.26	0.38	0.08	-0.50 – 1.02	0.501

Table 85 – Univariate regression analysis of variables predicting AL scores

This sensitivity analysis shows that removing the 3 retired international rugby players who reported no history of concussion, did not change the result; there remained no group difference in AL. These 3 retired international rugby players were kept in the remaining analysis as even though they reported no memory of a history of concussion, playing international rugby would certainly expose them to risk of concussion, even if they were not aware of it.

8.6.4.2 Allostatic load component scores

8.6.4.2.1 Cardiovascular

Table 86 shows the results of the Kolmogorov-Smirnov test for normality and descriptive statistics for cardiovascular component scores of retired international rugby players and comparison participants; scores for comparison participants deviated significantly from normal.

		Kolmogorov-Smirnoff		Descriptive statistics
Allostatic load component	Participant group	Statistic	*p*	Median (IQR)
Cardiovascular	Retired international rugby player	0.100	0.200	-0.27 (-1.04, 0.30)
	Comparison	0.166	<0.05	-0.48 (-0.87, 0.48)

Table 86- Kolmogorov-Smirnov test and descriptive statistics for cardiovascular component scores

Retired international rugby players and comparison participants were not matched for age or SIMD (2012) quintile; therefore univariate regressions were used to investigate whether these variables were associated with cardiovascular component scores, in addition to the potential covariate of anti-hypertensive medication. Table 87 shows the regression outputs; age was significantly

associated with cardiovascular component scores therefore it was adjusted for in the analysis.

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	0.03	0.01	0.33	0.01 – 0.05	<0.005
SIMD (2012) quintiles	0.07	0.13	0.07	-0.18 – 0.33	0.565
Anti-hypertensive medication	-0.36	0.25	-0.17	-0.86 – 0.14	0.158

Table 87 – Univariate regression analysis of variables predicting cardiovascular component scores

A two stage hierarchical regression was conducted to determine whether the addition of participant group (rugby player or comparison group) improved the prediction of cardiovascular component scores over and above age. The assumptions were checked initially and are reported in the appendix (Appendix E, section 1.12). Table 88 displays the regression statistics for each variable at the step it was entered and the change in R^2. The full model of age and participant group was statistically significant (p <0.01), however the addition of participant group to the prediction of cardiovascular component scores (Model 2) did not lead to a statistically significant increase in R^2 (p = 0.325, f^2 = 0.01). Therefore exposure to repeat concussion was not associated with higher AL scores.

Variable	*b*	*SE B*	*B*	95% CI	*p*	R^2	*Adjusted* R^2	ΔR^2
Model 1						0.11	0.10	-----
Age	0.03	0.01	0.33	0.01 – 0.05	<0.005			
Model 2						0.12	0.10	0.01
Age	0.03	0.01	0.33	0.01 – 0.05	<0.005			
Participant group	0.21	0.21	0.11	-0.21 – 0.63	0.325			

Table 88- Hierarchical regression analysis of variables predicting cardiovascular component scores

8.6.4.2.2 Neuroendocrine

Table 89 shows the results of the Kolmogorov-Smirnov test for normality and descriptive statistics for neuroendocrine component scores of retired international rugby players and comparison participants; both groups were normally distributed.

		Kolmogorov-Smirnoff		Descriptive statistics
Allostatic load component	Participant group	Statistic	*p*	Mean (SD)
Neuroendocrine	Retired international rugby player	0.098	0.200	-0.06 (0.96)
	Comparison	0.115	0.200	0.04 (0.78)

Table 89- Kolmogorov-Smirnov test and descriptive statistics for neuroendocrine component scores

Two univariate regressions were used to investigate whether age and SIMD (2012) quintiles were associated with neuroendocrine component scores of participants; age was significantly associated with neuroendocrine component scores therefore it was adjusted for in the analysis (table 90).

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	0.03	0.01	0.37	0.01 – 0.05	<0.005
SIMD (2012) quintiles	0.07	0.12	0.07	-0.18 – 0.31	0.594

Table 90 – Univariate regression analysis of variables predicting neuroendocrine component scores

A two stage hierarchical regression was conducted to determine whether the addition of participant group (rugby player or comparison group) improved the prediction of neuroendocrine component scores over and above age. The assumptions were checked initially and are reported in the appendix (Appendix E, section 1.13). Table 91 displays the regression statistics for each variable at the step it was entered and the change in R^2. The full model of age and participant group was statistically significant (p <0.01), however the addition of participant group to the prediction of neuroendocrine component scores (Model 2) did not lead to a statistically significant increase in R^2 (p = 0.719, f^2 = 0.00).

Variable	*b*	*SE B*	*B*	95% CI	*p*	R^2	*Adjusted* R^2	ΔR^2
Model 1						0.14	0.13	-----
Age	0.03	0.01	0.37	0.01 – 0.05	<0.005			
Model 2						0.14	0.12	0.00
Age	0.03	0.01	0.37	0.01 – 0.05	<0.005			
Participant group	0.07	0.20	0.04	-0.32 – 0.47	0.719			

Table 91- Hierarchical regression analysis of variables predicting neuroendocrine component scores

8.6.4.2.3 Anthropometric

Table 92 shows the results of the Kolmogorov-Smirnov test for normality and descriptive statistics for anthropometric component scores of retired

international rugby players and comparison participants; both groups were normally distributed.

		Kolmogorov-Smirnoff		Descriptive statistics
Allostatic load component	Participant group	Statistic	*p*	Mean (SD)
Anthropometric	Retired international rugby player	0.063	0.200	0.17 (0.99)
	Comparison	0.118	0.200	-0.23 (0.91)

Table 92- Kolmogorov-Smirnov test and descriptive statistics for anthropometric component scores

Two univariate regressions were used to investigate whether age and SIMD (2012) quintiles were associated with anthropometric component scores of participants; neither age or SIMD (2012) quintiles were significantly associated (table 93) therefore they were not adjusted for in the analysis and an independent t-test was used to explore group differences in anthropometric component scores. The analysis showed there was no significant difference in anthropometric component scores between retired international rugby players and comparison participants, although it was approaching a trend with a medium effect size (t = 1.77, p = 0.087, d = 0.42).

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	0.00	0.01	0.04	-0.02 – 0.02	0.712
SIMD (2012) quintiles	-0.11	0.13	-0.10	-0.37 – 0.16	0.412

Table 93 – Univariate regression analysis of variables predicting anthropometric component scores

8.6.4.2.4 Metabolic

Table 94 shows the results of the Kolmogorov-Smirnov test for normality and descriptive statistics for metabolic component scores of retired international rugby players and comparison participants; both groups were normally distributed.

		Kolmogorov-Smirnoff		Descriptive statistics
Allostatic load component	Participant group	Statistic	*p*	Mean (SD)
Metabolic	Retired international rugby player	0.092	0.200	0.06 (0.94)
	Comparison	0.100	0.200	0.10 (0.91)

Table 94- Kolmogorov-Smirnov test and descriptive statistics for metabolic component score

Two univariate regressions were used to investigate whether age and SIMD (2012) quintiles were associated with metabolic component scores; age was significantly associated with metabolic component scores therefore it was adjusted for in the analysis (table 95).

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	-0.03	0.01	-0.33	-0.04 – -0.01	<0.005
SIMD (2012) quintiles	0.07	0.13	0.06	-0.19 – 0.32	0.597

Table 95 – Univariate regression analysis of variables predicting metabolic component scores

A two stage hierarchical regression was conducted to determine whether the addition of participant group (rugby player or comparison group) improved the prediction of metabolic component scores over and above age. The assumptions were checked initially and are reported in the appendix (Appendix E, section 1.14). Table 96 displays the regression statistics for each variable at the step it was entered and the change in R^2. The full model of age and participant group was statistically significant (p <0.05), however the addition of participant group to the prediction of metabolic component scores (Model 2) did not lead to a statistically significant increase in R^2 (p = 0.733, f^2 = 0.00).

Variable	*b*	*SE B*	*B*	95% CI	*p*	R^2	*Adjusted* R^2	ΔR^2
Model 1						0.11	0.09	-----
Age	-0.03	0.01	-0.33	-0.04 – -0.01	<0.005			
Model 2						0.11	0.08	0.00
Age	-0.03	0.01	-0.33	-0.04 – -0.01	<0.005			
Participant group	0.07	0.21	0.04	-0.35 – 0.49	0.733			

Table 96- Hierarchical regression analysis of variables predicting metabolic component scores

8.6.4.2.5 Immune

Table 97 shows the results of the Kolmogorov-Smirnov test for normality and descriptive statistics for immune component scores of retired international rugby players and comparison participants; both groups were normally distributed.

		Kolmogorov-Smirnoff		Descriptive statistics
Allostatic load component	Participant group	Statistic	*p*	Mean (SD)
Immune	Retired international rugby player	0.125	0.068	0.05 (0.96)
	Comparison	0.120	0.200	-0.10 (0.93)

Table 97- Kolmogorov-Smirnov test and descriptive statistics for immune component scores

Univariate regressions were used to investigate whether age, SIMD (2012) quintiles and anti-inflammatory medication use were associated with immune component scores of retired international rugby players and comparison participants; none of the variables were significantly associated with immune component scores (table 98) therefore differences between groups was investigated using an independent t-test. The analysis showed there was no significant difference in immune component scores between retired international rugby players and comparison participants (t = 0.24, p = 0.813, d = 0.16).

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	-0.01	0.01	-0.08	-0.03 – 0.01	0.486
SIMD (2012) quintiles	0.10	0.13	0.09	-0.16 – 0.36	0.445
Anti-inflammatory medication	-0.10	0.25	-0.05	-0.59 – 0.39	0.687

Table 98 – Univariate regression analysis of variables predicting immune component scores

8.6.5 Hypothesis 2

"A higher frequency of reported concussion in retired international rugby players is associated with higher allostatic load scores"

Results for the Kolmogorov-Smirnov test for normality indicated that number of concussion incidents deviated significantly from normal for retired international rugby players (D = 0.283, p <0.001). The median number of concussions experienced by the retired international rugby players was 6.5 (IQR: 3, 17).

8.6.5.1 Allostatic load score

Previously, univariate regressions demonstrated the potential confounding variables (childhood deprivation, taking anti-inflammatory and anti-hypertensive medication) were not associated with AL scores (table 84). A Spearman's correlation demonstrated that the number of concussion incidents were not associated with AL scores (r_s = -0.181, p = 0.229).

8.6.5.2 Allostatic load component scores

There were no significant associations between number of concussion incidents and the AL component scores in the retired international rugby players (see table 99).

Variable	r_s	*p*
Cardiovascular	-0.247	0.098
Neuroendocrine	-0.107	0.478
Immune	-0.179	0.234
Metabolic	0.149	0.323
Anthropometric	-0.069	0.647

Table 99 – Spearman's correlations between AL component scores and number of concussion incidents

8.6.6 Hypothesis 3

"Higher allostatic load scores are associated with lower GOS-E ratings later in life in retired international rugby players"

8.6.6.1 Allostatic load scores

Initially the relationship between GOS-E ratings and the potential covariate (age) was investigated using an ordinal logistic regression. There was no significant association therefore age was not included in the analysis as a covariate (*B* = 0.04, *S.E B* = 0.03, Wald X^2 = 2.59, *eB* = 1.05, 95% CI of *eB*: 0.99 – 1.10, *p* = 0.108). A further ordinal logistic regression demonstrated no significant relationship between AL scores and GOS-E ratings in the retired international rugby player group (*B* = 0.15, *S.E B* = 0.13, Wald X^2 = 1.32, *eB* = 1.17, 95% CI of *eB*: 0.90 – 1.51, *p* = 0.250). The assumption of proportional odds was met (*p* = 0.778).

8.6.6.2 Allostatic load component scores

There were no significant associations between the AL component scores and GOS-E ratings (table 100). The assumptions of proportional odds were met and are described in Appendix E, section 1.15.

Variable	*b*	*SE b*	Wald X^2	*eβ*	95% CI for e*β*	*p*
Cardiovascular	0.62	0.40	2.42	1.86	0.85 – 4.06	0.120
Neuroendocrine	0.34	0.39	0.73	1.40	0.65 – 3.37	0.393
Immune	0.37	0.39	0.92	1.45	0.68 – 3.09	0.337
Metabolic	0.07	0.36	0.03	1.07	0.53 – 2.17	0.854
Anthropometric	-0.05	0.34	0.02	0.95	0.49 – 1.85	0.881

Table 100 – Ordinal logistic regression analysis of the relationship between AL component scores and GOS-E ratings

8.6.7 Hypothesis 4

"Higher allostatic load scores are associated with higher rates of depression later in life in retired international rugby players"

A univariate regression showed there were no significant association between number of concussions and HADS ratings of depression (β = 0.22, 95% CI: -0.01 – 0.07, p = 0.147), therefore it was not included in the analysis as a covariate. Results for the Kolmogorov-Smirnov test for normality indicated that depression ratings on the HADS for retired international rugby players deviated significantly from normal (D = 0.168, p <0.005), therefore a Spearman's correlation was used to investigate the relationship between AL scores and ratings of depression.

8.6.7.1 Allostatic load scores

There was no significant association between AL scores and ratings of depression using the HADS (r_s = 0.153, p = 0.310).

8.6.7.2 Allostatic load component scores

There were no significant associations between ratings of depression and the AL component scores (see table 101), except for metabolic component score, which showed a positive relationship with scores of depression with a medium effect size.

Variable	r_s	*p*
Cardiovascular	-0.042	0.782
Neuroendocrine	-0.050	0.742
Immune	0.070	0.643
Metabolic	0.294	<0.05
Anthropometric	-0.012	0.142

Table 101 - Spearman's correlations between AL component scores and scores of depression

8.6.8 Hypothesis 5

"Higher allostatic load scores are associated with increased cognitive impairment in later life in retired international rugby players"

8.6.8.1 The Montreal Cognitive Assessment

Results for the Kolmogorov-Smirnov test for normality indicated that test scores for the Montreal Cognitive Assessment (MOCA) of retired international rugby players deviated significantly from normal (D = 0.191, p <0.001). The median MOCA score was 28/30 (IQR: 26, 29). Six participants (13%) scored less than 26 points (cut-off for 'normal'), but higher than 21, so categorised as 'mild cognitive impairment' (Folstein, Folstein, McHugh, & Fanjiang, 2001).

Four univariate regressions were used to check whether age, number of years in education, number of concussions as a continuous scale, and number of concussion categories in an ordinal scale, were associated with MOCA scores. The results are displayed in table 102; none of the potential confounders were significantly associated with MOCA scores, therefore they were not included in the analysis as covariates, and the relationship between AL scores and MOCA scores was investigated using a Spearman's correlation. AL scores were not significantly associated with MOCA scores (r_s = 0.081, p = 0.590).

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	-0.04	0.02	-0.26	-0.09 – 0.01	0.085
Number of years in education	0.19	0.12	0.23	-0.06 – 0.44	0.129
Concussions (continuous)	0.30	0.02	-0.01	-0.07 – 0.94	0.943
Concussions (categorical)	-0.40	0.47	-0.13	-1.34 – 0.55	0.403

Table 102 - Univariate regression analysis of variables predicting MOCA scores

8.6.8.2 Symbol Digit Modalities Test

The Kolmogorov-Smirnov test for normality indicated that test scores for the Symbol Digit Modalities Test (SDMT) of retired international rugby players did not deviate significantly from normal (D = 0.096, p = 0.200); the mean score was 50.9 (SD = 10.8). The output of the 4 covariate univariate regressions is displayed in table 103; age and number of years education were significantly associated with SDMT scores, therefore they were included in the analysis as covariates.

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	-0.45	0.11	-0.53	-0.67 – -0.23	<0.001
Number of years in education	1.38	0.61	0.32	0.16 – 2.61	<0.05
Concussions (continuous)	0.15	0.12	0.19	-0.09 – 0.39	0.208
Concussions (categorical)	3.23	2.37	-0.20	-1.54 – 8.00	0.179

Table 103 – Univariate regression analysis of variables predicting SDMT scores

A two stage hierarchical regression was conducted to determine whether AL scores improved the prediction of SDMT scores over and above age and number of years in education. The assumptions were checked initially and are reported in the appendix (Appendix E, section 1.16). Table 104 displays the regression statistics for each variable at the step it was entered and the change in R^2. The full model of age, number of years education, and AL scores was statistically significant (p <0.001), however the addition of AL scores to the prediction of SDMT scores (Model 2) did not lead to a statistically significant increase in R^2 (p = 0.421, f^2 = 0.02).

Variable	*B*	*SE B*	*B*	95% CI	*p*	R^2	*Adjusted* R^2	ΔR^2
Model 1						0.39	0.36	-----
Age	-0.40	0.09	-0.53	-0.58 – -0.22	<0.001			
Years of education	1.22	0.46	0.32	0.31 – 2.14	<0.05			
Model 2						0.40	0.35	0.01
Age	-0.41	0.09	-0.55	-0.60 – -0.23	<0.001			
Years of education	1.20	0.46	0.32	0.28 – 2.13	<0.05			
Allostatic load score	0.36	0.44	0.10	-0.53 – 1.24	0.421			

Table 104- Hierarchical regression analysis of variables predicting SDMT scores

8.6.8.3 Trail Making Test

Results for the Kolmogorov-Smirnov test for normality indicated that test scores for time (seconds) to complete part B of the Trail Making Test (TMTB) deviated significantly from normal in retired international rugby players (D = 0.134, p <0.05); the median time was 53 seconds (IQR: 44.6, 64.7).

The output of the 4 covariate univariate regressions is displayed in table 105; all of the variables were significantly associated with TMTB therefore they were included in the analysis as covariates. However because number of concussions as a continuous scale and categorical scale measure the same variable, only the continuous measure of number of concussions was included as it contains more information and therefore more statistical power than the categorised version (Royston et al., 2006).

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	0.63	0.19	0.45	0.26 – 1.01	<0.005
Number of years in education	2.63	0.99	-0.37	-4.62 – 0.64	<0.05
Concussions (continuous)	-0.41	0.19	-0.31	-0.79 – -0.03	<0.05
Concussions (categorical)	-8.97	3.76	-0.34	-16.54 – 1.40	<0.05

Table 105 – Univariate regression analysis of variables predicting time to complete the Trail Making Test

A two stage hierarchical regression was conducted to determine whether AL scores improved the prediction of time (seconds) to complete TMTB over and above age, number of years in education, and number of concussions. The assumptions were checked initially and are reported in the appendix (Appendix E, section 1.17). Table 106 displays the regression statistics for each variable at the step it was entered and the change in R^2. The full model of age, number of years in education, number of concussions, and AL scores was statistically significant (p <0.005), however the addition of AL scores to the prediction of time to complete TMTB over and above age (Model 2) did not lead to a statistically significant increase in R^2 (p = 0.535, f^2 = 0.02).

Variable	*b*	*SE B*	*B*	95% CI	*p*	R^2	*Adjusted* R^2	ΔR^2
Model 1						0.36	0.32	-----
Age	0.52	0.20	0.37	0.13– 0.92	<0.05			
Years Education	-2.70	0.87	-0.38	-4.46 – -0.94	<0.005			
Number of concussions	-0.21	0.19	-0.16	-0.59 – 0.16	0.260			
Model 2						0.37	0.31	0.01
Age	0.53	0.20	0.38	0.13 – 0.93	<0.05			
Years Education	-2.67	0.88	-0.38	-4.46 – -0.90	<0.005			
Number of concussions	-0.23	0.19	-0.18	-0.62 – 0.15	0.228			
Allostatic load score	-0.55	0.87	-0.08	-2.31 – 1.22	0.535			

Table 106- Hierarchical regression analysis of variables predicting time to complete the Trail Making Test

8.6.8.4 Immediate recall of the Auditory Verbal Learning Test

Results for the Kolmogorov-Smirnov test for normality indicated that scores of immediate recall for auditory verbal learning in retired international rugby players did not deviate significantly from normal (D = 0.084, p = 0.200); the mean score was 50 (SD = 11). The output of the 4 covariate univariate regressions is displayed in table 107; age and number of concussions (continuous scale) were significantly associated with scores of immediate recall for auditory verbal learning, therefore they were included in the analysis as covariates.

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	-0.48	0.11	-0.56	-0.70 – -0.27	<0.001
Number of years in education	0.54	0.65	0.12	-0.77 – 1.84	0.413
Concussions (continuous)	0.24	0.12	0.29	0.00 – 0.47	<0.05
Concussions (categorical)	3.23	2.40	0.20	-1.61 – 8.06	0.186

Table 107 - Univariate regression analysis of variables predicting scores of immediate recall for auditory verbal learning

A two stage hierarchical regression was conducted to determine whether AL scores improved the prediction of immediate recall scores for auditory verbal learning over and above age and number of concussions. The assumptions were checked initially and are reported in the appendix (Appendix E, section 1.18). Table 108 displays the regression statistics for each variable at the step it was entered and the change in R^2. The full model of age, number of concussions, and AL scores was statistically significant (p <0.001), however the addition of AL scores to the prediction of immediate recall scores for auditory verbal learning (Model 2) did not lead to a statistically significant increase in R^2 (p = 0.121, f^2 = 0.06).

Variable	*b*	*SE B*	*B*	95% CI	*p*	R^2	*Adjusted* R^2	ΔR^2
Model 1						0.32	0.29	-----
Number of concussions	0.02	0.12	0.03	-0.21 – 0.24	0.889			
Age	-0.47	0.12	-0.55	-0.72– -0.23	<0.001			
Model 2						0.36	0.31	0.04
Number of concussions	0.05	0.11	0.06	-0.18 – 0.28	0.668			
Age	-0.48	0.12	-0.57	-0.73 – -0.24	<0.001			
Allostatic load score	0.84	0.53	0.20	-0.23 – 1.92	0.121			

Table 108- Hierarchical regression analysis of variables predicting scores of immediate recall for auditory verbal learning

8.6.8.5 Delayed recall of the Auditory Verbal Learning Test

Results for the Kolmogorov-Smirnov test for normality indicated that scores of delayed recall for auditory verbal learning of retired international rugby players did not deviate significantly from normal (D = 0.125, p = 0.068); the mean score was 10.5 (SD = 3.4). The output of the 4 covariate univariate regressions is displayed in table 109; age was significantly associated with delayed recall scores of auditory verbal learning, therefore it was included in the analysis as a covariate.

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	-0.15	0.03	-0.55	-0.22 – -0.08	<0.001
Number of years in education	0.03	0.20	0.02	-0.38 – 0.44	0.883
Concussions (continuous)	0.06	0.04	0.25	-0.01 – 0.14	0.093
Concussions (categorical)	1.17	0.75	0.23	-0.34 – 2.67	0.125

Table 109 - Univariate regression analysis of variables predicting delayed recall scores of auditory verbal learning

A two stage hierarchical regression was conducted to determine whether AL scores improved the prediction of delayed recall scores for auditory verbal learning over and above age. The assumptions were checked initially and are reported in Appendix E, section 1.19. Table 110 displays the regression statistics for each variable at the step it was entered and the change in R^2. The full model of age and AL scores was statistically significant (p <0.001), however the addition of AL scores to the prediction of delayed recall scores for auditory verbal learning (Model 2) did not lead to a statistically significant increase in R^2 (p = 0.482, f^2 = 0.01).

Variable	*B*	*SE B*	*B*	95% CI	*p*	R^2	*Adjusted* R^2	ΔR^2
Model 1						0.31	0.29	-----
Age	-0.15	0.03	-0.55	-0.22– -0.08	<0.001			
Model 2						0.32	0.28	0.01
Age	-0.15	0.03	-0.57	-0.22 – -0.08	<0.001			
Allostatic load score	-0.12	0.17	0.09	-0.22 – 0.46	0.482			

Table 110- Hierarchical regression analysis of variables predicting delayed recall scores of auditory verbal learning

8.6.8.6 Judgment of Line Orientation Test

Results for the Kolmogorov-Smirnov test for normality indicated that test scores for the Judgement of Line Orientation Test scores of retired international rugby players deviated significantly from normal (D = 0.246, p <0.001); the median was 29 (IQR: 27, 30). The output of the 4 covariate univariate regressions is displayed in table 111; none of the confounders were associated with scores for the Judgement of Line Orientation Test, therefore they were not included in the analysis as a covariate, and the relationship between AL scores and Judgement of Line Orientation Test scores was investigated using a Spearman's correlation. AL scores were not associated with Judgement of Line Orientation Test scores (r_s = -0.029, p = 0.846).

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	-0.01	0.02	-0.07	-0.05 – 0.03	0.642
Number of years in education	0.21	0.11	0.28	-0.01 – 0.42	0.059
Concussions (continuous)	0.00	0.02	-0.03	-0.05 – 0.04	0.850
Concussions (categorical)	-0.29	0.41	-0.11	-1.11 – 0.54	0.488

Table 111 - Univariate regression analysis of variables predicting Judgement of Line Orientation Test scores

8.6.8.7 Grooved pegboard (dominant hand)

Results for the Kolmogorov-Smirnov test for normality indicated that time (seconds) to complete the Grooved Pegboard with the dominant hand did not deviate significantly from normal (D = 0.106, p = 0.200) for retired international rugby players; the mean time was 75 seconds (SD = 12.4). The output of the 4 covariate univariate regressions is displayed in table 112; age was significantly associated with time to complete the Grooved Pegboard with the dominant hand, therefore it was included in the analysis as a covariate.

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	0.55	0.12	0.57	0.31 – 0.80	<0.001
Number of years in education	-0.67	0.73	-0.14	-2.14 – 0.80	0.365
Concussions (continuous)	-0.10	0.14	-0.11	-0.38 – 0.17	0.453
Concussions (categorical)	-3.32	2.72	-0.18	-8.80 – 2.17	0.230

Table 112 – Univariate regression analysis of variables predicting time to complete the Grooved Pegboard with the dominant hand

A two stage hierarchical regression was conducted to determine whether AL scores improved the prediction of time to complete the Grooved Pegboard with the dominant hand over and above age. The assumptions were checked initially and are reported in Appendix E, section 1.20. Table 113 displays the regression statistics for each variable at the step it was entered and the change in R^2. The full model of age and AL scores was statistically significant (p <0.001); the addition of AL scores to the prediction of time to complete the Grooved Pegboard with the dominant hand (Model 2) significantly increasing the predictive capacity of the model by 8% (p <0.05, f^2 = 0.14). As AL scores increased, time (seconds) to complete the Grooved Pegboard with the dominant hand decreased.

Variable	*B*	*SE B*	*B*	95% CI	*p*	R^2	*Adjusted* R^2	ΔR^2
Model 1						0.33	0.31	-----
Age	0.55	0.12	0.57	0.31– 0.80	<0.001			
Model 2						0.41	0.38	0.08
Age	0.60	0.12	0.62	0.37 – 0.83	<0.001			
Allostatic load score	-1.35	0.55	-0.29	-2.45 – -0.24	<0.05			

Table 113- Hierarchical regression analysis of variables predicting time to complete the Grooved Pegboard with the dominant hand

8.6.8.8 Grooved Pegboard (non-dominant hand)

Results for the Kolmogorov-Smirnov test for normality indicated that time to complete the Grooved Pegboard with the non-dominant hand did deviate significantly from normal for retired international rugby players (D = 0.145, p <0.05); the median time was 84 seconds (IQR: 73.94, 99.83). The output of the 4 covariate univariate regressions is displayed in table 114; age was significantly associated with the time (seconds) to complete the Grooved Pegboard with the non-dominant hand, therefore it was included in the analysis as a covariate.

Variable	*b*	*SE B*	*B*	95% CI	*p*
Age	0.61	0.16	0.49	0.28 – 0.94	<0.005
Number of years in education	-1.07	0.94	-0.17	-2.96 – 0.81	0.258
Concussions (continuous)	-0.05	0.18	-0.04	-0.40 – 0.31	0.795
Concussions (categorical)	-2.59	3.54	-0.11	-9.72 – 4.55	0.469

Table 114 – Univariate regression analysis of variables predicting time to complete the Grooved Pegboard with the non-dominant hand

A two stage hierarchical regression was conducted to determine whether AL scores improved the prediction of time to complete the Grooved Pegboard with the non-dominant hand over and above age. The assumptions were checked initially and are reported in the Appendix E, section 1.21. Table 115 displays the regression statistics for each variable at the step it was entered and the change in R^2. The full model of age and AL scores was statistically significant (p <0.001); the addition of AL scores to the prediction of time to complete the Grooved Pegboard with the non-dominant hand (Model 2) significantly increasing the predictive capacity of the model by 10% (p <0.05, f^2 = 0.15). As AL scores increased, time (seconds) to complete the Grooved Pegboard with the non-dominant hand decreased.

Variable	*b*	*SE B*	*B*	95% CI	*p*	R^2	*Adjusted* R^2	ΔR^2
Model 1						0.24	0.22	-----
Age	0.61	0.16	0.49	0.28– 0.94	<0.005			
Model 2						0.34	0.30	0.10
Age	0.67	0.16	0.54	0.36 – 0.99	<0.001			
Allostatic load score	-1.86	0.75	-0.31	-3.37 – 0.36	<0.05			

Table 115- Hierarchical regression analysis of variables predicting time to complete the Grooved Pegboard with the non-dominant hand

8.7 Discussion

8.7.1 Principal findings

Despite frequent self-reports of concussion, AL was not associated with number of concussions in the retired international rugby players. This indicates that concussion does not contribute to wear-and-tear on allostatic systems over time. It is therefore unsurprising that there were no differences in AL scores between retired international rugby players late after repeat concussion, and comparison participants, and that AL was not associated with GOS-E ratings in the retired international rugby player group. Similarly, no relationship was found between self-ratings of depression and AL, except for a significant, moderate relationship between higher self-ratings of depression and higher metabolic component scores (higher triglyceride and creatinine levels and lower levels of albumin and high density lipoprotein), indicating an underlying metabolic pathway associated with depression in retired international rugby players.

Overall, the accumulation of AL did not explain cognitive function, except for a surprising significant inverse relationship between higher AL scores and faster performance speed in fine motor coordination after adjusting for age. This indicates that higher physiological dysfunction in the retired international rugby players, predicts better coordination performance. This finding contradicts the AL theory, which describes the accumulation of AL as having pathological consequences such as decline in physical performance. An explanation for this may lie in the likelihood that the lifestyles of elite rugby players is significantly different to the general population, such as having a larger muscle mass and better fitness levels, which brings into question the measurement of AL in this group.

8.7.2 Comparison with other studies

There are no other studies that consider AL and concussion in retired athletes. However based on the evidence that repeat concussion is likely to cause damage (Decq et al., 2016; Johnson et al., 2013; McKee et al., 2013), it was hypothesised that concussions frequency would correspond with the accumulation of AL. However the lack of association in this study indicates repeat concussions do not cause physiological dysregulation of the allostatic systems over time. The absence of a relation here is not due to the paucity of frequency of concussions in the rugby player group; the frequency of concussions in this study was high (median 6.5; IQR: 3, 17, compared to that in Decq et al. (2016) n = 239, median 2; IQR: 1, 3). It is likely that repeat concussion may have caused pathology or physiological damage in the rugby group in this study, and it is the assessment of AL that is not measuring this damage.

Consistent with this, no difference in AL scores was demonstrated between retired international rugby players late after repeat concussion and comparison participants. Nonetheless, this finding contrasts with that in study 3 (Chapter 7) where participants who had a single severe HI had significantly higher AL late after injury than comparison participants. This suggests that the accumulation of AL over time may be affected differently by repeat concussion than severe HI. An explanation for this may lie in the likelihood that the lifestyles of elite rugby players and most people with a severe HI are different.

Overall there was no significant relationship between AL and GOS-E ratings. Only 2 retired international rugby players were rated as ‘Disabled’ using the GOS-E, therefore unexpectedly the rugby players were largely functioning normally. This good health and low variability in outcome would also explain the lack of association between AL and cognitive function in the rugby player group. Nevertheless, this lack of finding contrasts with a number of studies that have demonstrated a relationship between cognitive function and AL. The tests of cognitive function used in the previous research were validated and assessed the same cognitive functions as this study; processing speed, verbal fluency, visuospatial and verbal memory, and executive function (Booth et al., 2015; Goldman et al., 2006; Karlamangla et al., 2014; Karlamangla et al., 2002; Seeman

et al., 2001; Seplaki et al., 2006). Thus the difference in finding is unlikely to be caused by the sensitivity of the cognitive tests used.

The absence of finding is also not due to a lack of cognitive impairment in the rugby player group; 13% had a score on the Montreal Cognitive Assessment that is categorised as 'mild cognitive impairment'. Post-hoc sub-analyses of those who were cognitively impaired on the MOCA (n = 15; mean AL score = -1.04, SD = 1.94) and those who were not impaired (n = 31; mean AL score = 0.17, SD = 2.94) showed no significant difference in AL scores (t = -1.45, p = 0.154, d = -0.05). This demonstrates further that physiological dysregulation is not associated with cognitive functioning in this sample of retired international rugby players.

Despite these findings contrasting with evidence that AL is associated with and cognitive impairment or decline based on healthy populations in the United States (Karlamangla et al., 2002; Seeman et al., 2001), Taiwan (Goldman et al., 2006; Seplaki et al., 2006), and Scotland (Booth et al., 2015); it is consistent with findings in study 3 (Chapter 7) that there was no relationship between AL and cognitive functioning late after severe HI. This indicates that the accumulation of AL following brain damage, whether severe (study 3) or repeat mild (study 4) is different to that observed in healthy aging populations, and which has previously demonstrated correlations with cognitive function.

This potential divergence in the accumulation of physiological dysregulation following repeat concussion may partly explain the unexpected associations between higher AL scores and faster time taken to complete a fine motor coordination task. This finding significantly contradicts the AL literature that shows an association between higher AL and lower physical functioning in terms of hand dexterity and grip strength for example (Gruenewald et al., 2009; Karlamangla et al., 2002). Further, it varies from the AL model, which describes how the accumulation of physiological damage, eventually leads to tertiary outcome such a poorer cognitive and physical functioning, disease and mortality (McEwen, 1998b, 2006a).

Further evidence that AL in elite sports players is different compared with normal populations is that there were no significant associations between AL scores, and any of the expected predictors of AL (table 84); even age or childhood deprivation

that were previously demonstrated in the Glasgow HI samples in Chapters 5-7. In the case of childhood deprivation scores, this may be due to the majority (58%) experiencing no deprivation during childhood; however there was a wide distribution of age (26-79) similar to other studies of healthy populations that have shown a significant increase in AL with age (Crimmins et al., 2003). One limitation of the assessment of AL in the elite player group for example, is the use of BMI, which may be high in rugby players due to muscle mass, which could skew AL scores higher, but may be associated with greater strength or agility; however this is only one of fifteen indicators of health used to construct the AL scores. It may be the development of AL is different in elite sports players due to lifestyle factors such as healthier diets and being very physically active. In order to understand the causes and consequences of AL in elite sports players, these findings needs to be replicated and investigated further using longitudinal study design.

Of note, the contradictory finding of an association between higher AL and faster time to complete a motor coordination task may be partly explained by criticism of the test used (the Grooved Pegboard test), as performance can be influenced by peripheral injury, such as arm or hand fracture (Wilde et al., 2010), which may be expected in the retired international rugby group, however this study does not have evidence for this.

In addition to functioning normally on the GOS-E, the rugby player group also did not have scores of depression higher than the 'normal' range. This could explain the absence of association between AL and scores of depression in the rugby player group. On the other hand a medium, positive relationship was found between scores of depression and metabolic component scores. As described previously, metabolic indicators of health are secondary outcomes of the AL model and part of the long-term stress response (McEwen, 2002). Major depression has been linked to increased peripheral blood inflammatory biomarkers, including cytokines (Alesci et al., 2005; Krishnadas & Cavanagh, 2012; Lanquillon, Krieg, Bening-Abu-Shach, & Vedder, 2000). Cytokines are primary mediators in the AL model (McEwen, 1998b; McEwen & Wingfield, 2003), thus long-term depression and inflammation may cause metabolic indicators (secondary outcomes) to adjust and increase their normal operating range. There is evidence of a link between depression and metabolic syndrome (Kinder, Carnethon, Palaniappan, King, &

Fortmann, 2004), however considering the scores of depression in the retired international rugby players were classified as 'normal', it is difficult to compare these results with other studies and to conclude anything concrete from the finding. Also due to the cross-sectional assessment of AL in this study, the interpretation of the temporal relationship between these two variables is limited.

8.7.3 Strengths and limitations

Retired international rugby players, being middle class, do not tend to have childhood deprivation and they take better care of their health on average, therefore AL is different in elite level athletes. If this is the case, the method of producing the AL scores, by combining together all the data from the 4 studies in this thesis (as described in Chapter 3), may have hindered the exploration of accumulated physiological damage in the retired international rugby players. The reason for doing this was in having a larger sample to create the indicator z-score, the standard error of the data would be reduced (Gravetter & Wallnau, 2016). Future research investigating AL in elite athletes may want to consider using a larger sample of just athletes to create z-scores. This would enable exploration of whether it is the case that AL is the same in elite athletes as in the general population.

The participants in this study may not represent the population of retired international rugby players due to a sampling bias. The proportion of participants who responded to the initial invitation letter was only 22% of the potential participant pool (n = 350). The demographics, history of concussion and health status of the 78% who did not participate is unknown. It is possible that some retired international rugby players who were psychologically attributing current complaints to the belief that (repeated) concussion had caused these symptoms may avoid taking part in this research, as men generally avoid seeking help for health related issues (Courtenay, 2000; Mansfield, Addis, & Mahalik, 2003; Sharpe & Arnold, 1998). There may also be a survival bias in the group recruited to this study, including the exclusion of those who no longer had the capacity to consent to take part, which may have been linked to repeat concussion.

It is important to note that 56.5% of the retired international rugby players in this sample played in the pre-professional era where frequency and severity of concussions may have been less than in the current professional era of rugby union and monitoring of concussion and readiness for return to play following concussion was assessed differently. Therefore the results of this study may not be generalizable to the current players of professional rugby. Another limitation of the generalisability of these findings is the sample recruited were elite level rugby players, who may be different to non-international players in terms of time spent playing and training for rugby, and therefore potentially exposure to risk of concussion and physical fitness, which might affect the accumulation of AL. Non-elite rugby players may be less likely to have repeat concussion and therefore less likely to be affected; thus these findings cannot be generalised to other levels of rugby playing beyond elite level.

Another limitation of this study is that concussion history was based on self-report. Although a common method of collecting this data in studies of similar design, the absence of objective information about the frequency and severity of head injuries renounces the quality of this assessment of concussion incidents. Further, agreement between recorded incidence of concussion and self-report in sports is argued to be poor (Kerr et al., 2015).

A strength of this study is the attempt to assess the links between AL, repeat concussions, cognitive function, and disability outcome in retired international rugby players, rather than using self-report measures of symptom complaint, which can be susceptible to the misattribution of common complaints found in healthy individuals as being caused by historical concussions (Iverson & Lange, 2003). Also a wide range of cognitive tests were used in order to assess potential cognitive impairments, which can vary extensively following repeat mild HI (Binder, 1986; Iverson & Lange, 2003; Ponsford et al., 2002). In addition, the use of a comparison group with experience of no more than one concussion further enabled the exploration of the effect of repeat concussion on AL accumulation.

8.7.4 Implications of findings

Higher AL is linked to pathological processes underlying increased risk of illness and mortality; however there were no suggestions that repeat concussion was

associated with increased AL. AL also does not explain current cognitive functioning in retired international rugby players; yet they were largely not cognitively impaired.

Nevertheless the data from this study may provide useful for future follow-up of these participants. Prospective or longitudinal studies are required to fully understand the impact of repeat concussion on cognitive and physical health late in life. Although age-related cognitive decline has been demonstrated from the age of 20, the speed of decline has been shown to rapidly increase after the age of 60; twice as great in measures of speed of processing and four times as great in measures of memory (Salthouse, 2009). At the time of assessment, 60.1% of the retired international rugby player group were younger than 60 years old. Therefore the participants in this study need to be followed-up at a later time point when the likelihood of impairment is higher if chronic neuropathological processes are associated with repetitive concussion. The data from this study would provide a helpful baseline of cognitive functioning and AL.

8.8 Conclusions

The findings of this study do not support the view that repeat concussion is associated with increased AL in retired international rugby players. As a result of this, AL is not a helpful predictor of outcomes in this group of elite athletes, including global disability and specific cognitive tests, except for fine motor control using the dominant and non-dominant hand. Finally there was no evidence of a difference in AL, and therefore pathological processes underlying the increased risk of illness and death, between retired international rugby players and comparison participants. A limitation of this study is the low variability in terms of outcome in the rugby group who were generally not impaired. Based on the findings in this study, future research should explore the consequences of AL in elite athletes.

This study concludes the experimental chapters; the next chapter provides a synthesis and evaluation of the results from all 4 empirical studies in this thesis.

Chapter 9 General discussion

Background

This chapter brings together and evaluates the strengths and limitations of the results of the four empirical studies within this thesis, whilst considering the potential direction for future research.

Methods

The findings from across the 4 studies within this thesis are critically summarised and interpreted within the context of four overarching research questions: 1) Does allostatic load (AL) explain disability outcome after head injury (HI)? 2) Does AL explain change in disability outcome after HI? 3) Do HI participants have higher AL scores than non-HI comparison participants? And 4) Does AL explain cognitive outcome later after HI? The impact of the results from the systematic search in Chapter 2 on the AL literature is also explored.

Results

Using 4 empirical studies, measuring outcome at different time points after HI, and a range of severity of HI, the studies within this thesis yielded little evidence to support the hypothesis that AL explains cognitive or disability outcome or change in outcome over time after HI.

Conclusions

The results in this thesis demonstrate that the utility of AL in explaining outcome after HI is limited; AL did not explain disability or cognitive outcome after HI. Differences in AL between HI and comparison participants late after injury may explain a proportion of the increased risk of pathology associated with disease and mortality observed late after HI. These results are novel and contribute to the investigation of outcome after HI. However replication of the findings and further research is needed to validate measures of AL, and to help improve outcomes and quality of life for HI patients and their families.

In this thesis, I investigated whether allostatic load (AL) explains the variability of outcome after head injury (HI) at different time points after injury. This allowed consideration of AL before (studies 1 and 2) and after (study 3) an opportunity for chronic effects of severe HI to have an impact on AL, and of late effects following multiple mild HI (study 4). This chapter will consider the main findings, strengths, and limitations of this research, before going on to evaluate the practical application of the AL model, and the implications for future research.

9.1 Principle findings across the studies in this thesis

Here, the findings of the four studies are summarised in the context of the overarching research questions.

9.1.1 Does allostatic load explain disability outcome after head injury?

Overall, AL was not associated with disability outcome. There was a significant relationship between higher neuroendocrine component scores (higher levels of aldosterone and lower levels of dehydroepiandrosterone) at discharge from hospital and greater disability 6 months later (Chapter 6). This finding indicates that dysregulation of primary mediators of allostasis may reduce the ability of the brain to recover within 6 months of discharge from hospital, leading to greater disability. However replication and more detailed investigation of the mechanism are required. For example, identifying differences in physical and psychological aspects of the recovery process following HI in participants with high and low neuroendocrine functioning, and recording recovery up to 6 months after discharge from hospital, will allow a greater understanding of the association observed in this research. If this finding is replicated, intervention may be possible to improve outcome, for example by reducing levels of neuroendocrine indicators near to injury with medication, preventing possible pathophysiological effects and improving recovering from brain damage.

There were no obvious trends in terms of AL or the other component scores explaining disability outcome after HI in any study. The AL theory considers the impact of genetic predisposition, early life events, lifestyle behaviours, habits and health-related choices, personal coping mechanisms, stressful events and

subjective interpretation of them, and social relationships, on the ability of the body to cope with physiological adaptation (McEwen, 1998b; McEwen & Wingfield, 2003). These factors can explain individual differences in physiological reactions, and the physiological dysregulation resulting from chronic over or underproduction of primary mediators of allostasis in response to an external challenge. However the results from this thesis indicate these factors, and/or the resulting physiological dysregulation do not predict or explain disability outcome after HI.

9.1.1.1 Reliability and validity of findings

There are possible factors that might reduce the reliability and validity of these findings; these are the samples, and the assessment of disability outcome, and AL.

9.1.1.1.1 Samples

It is unlikely that the absence of a significant relationship between AL and disability outcome was due to bias in the samples recruited. The participants seem generally representative of the Glasgow population with HI (Thornhill et al., 2000) and the four studies span a range of severity of HI and time since injury.

9.1.1.1.2 Assessment of disability outcome

The Glasgow Outcome Scale-Extended (GOS-E; Wilson et al., (1998)) was chosen because it is the most widely used measure of outcome after HI (McMillan et al., 2015; Shukla, Devi & Agrawal, 2011). In addition, GOS ratings could be generated from the GOS-E in order to investigate change in outcome from 6 months post-discharge and late after injury in study 3 (Chapter 7). The GODS was developed from the GOS-E and validated against it with the purpose of being used with HI patients in inpatients settings (McMillan et al., 2013). Therefore there was an excellent research advantage to be able to assess GODS of individuals still in inpatients settings and GOS-E of those in the community in study 2 (Chapter 6) and combine the results to explore the same outcome. These assessments were also chosen to permit comparison with results from other Glasgow HI studies that used these outcome measures and report change in disability outcome over time (McMillan et al., 2012; Whitnall et al., 2006).

The GOS-E has been criticised for not being sensitive to the wide range of deficits experiences in those with relatively good outcome (Hall, Bushnik, Lakisic-Kazazic, Wright, & Cantagallo, 2001) and recent reviews have concluded that the GOS-E is recommended in combination with other emotional psychosocial, health-related, and neuropsychological tests, as a more complete assessment of outcome after HI (Kosty & Stein, 2013; Shukla et al., 2011). However there is no evidence that combinations of this kind improve the sensitivity of the GOS-E (McMillan et al., 2015). Therefore, the GOS-E is a valid and reliable measure of disability outcome after HI, and using it, the studies in this thesis consistently found no evidence of a relationship with AL.

9.1.1.1.3 Assessment of allostatic load

In Chapter 2 section 2.2.7, the systematic search concluded that the indicators of AL that I used and the method of constructing an AL score were as optimal as possible. Therefore the lack of association between AL and disability outcome is unlikely to be due to these methods given that AL has been associated with chronic health conditions in other studies.

9.1.1.2 Conclusions

The results from the 4 studies in this thesis show little evidence for the utility of AL in explaining disability outcome after HI. Therefore it does not seem to be the case that greater AL, makes individuals vulnerable to a poorer outcome after HI. The finding of a relationship between neuroendocrine component scores at hospital discharge and disability outcome 6 months later may have consequences for intervention but requires replication and further study. However overall, there seems to be little empirical justification for significant investment in research on AL as a predictor of outcome after HI. Given the novelty of this research, definitive conclusions cannot be made. However this work provides an important and original contribution to the HI literature, by presenting data on the relationship between AL and outcome after HI at different time points.

9.1.2 Does allostatic load explain change in disability outcome after head injury?

Overall, evidence to support this hypothesis was not found. The only significant finding was a moderate inverse relationship between change in disability between 6 months post-discharge and assessment late after HI and metabolic component scores assessed late after injury (Section 7.6.7.2.1). This is a novel finding, which might suggest that increase in disability over time is a stressor that modifies the typical production of primary allostatic mediators, causing metabolic indicators to adjust their normal operating ranges and in this case increase. An explanation for this may lie in the likelihood that the lifestyles of individuals with worsening disability are less active and potentially less healthy. An alternative explanation is that change in disability is an effect of higher metabolic components scores. However due to the cross-sectional assessment of AL, the direction of the association cannot be determined.

Nonetheless, an implication of this finding is that chronically high metabolic indicators can predispose individuals to serious pathophysiology morbidity. Therefore it would be valuable to investigate this finding further; attempting replication using a longitudinal study design to understand the temporal relationship between metabolic component scores assessed at multiple time points, alongside change in disability. Also, it would be helpful to revisit this Glasgow HI group to investigate lifestyle factors, to see if higher metabolic component scores, or worsening disability outcome, were associated with less physical activity or poorer diets. This information would enable consideration of possible interventions in the development of high metabolic indicators, to inhibit the development of potential morbidities.

The remaining AL and component scores were not associated with change in disability, in any study. The reliability and validity of these findings considers the same factors as 9.1.1.1. Therefore it can be concluded that based on the findings in this thesis, the development in disability after brain damage over time is independent of the accumulation of AL. Besides the association between change in disability outcome and metabolic component scores late after injury, studies did not unveil potential factors that predict change disability over time. Again, this finding makes a unique and timely contribution to the literature around

outcome and change in outcome after HI. The paucity of evidence for a relationship between AL and change in disability after HI indicates that it is not a priority for HI researchers to continue examining AL. However the finding that 46% of participants experienced change in disability late after HI (a median of 27 years after injury), highlights that this group should not be ignored by health professionals when they are residing back in the community. Further research needs to be conducted into factors that explain change in disability late after HI.

Recent HI literature has found value in using multivariable prognostic modelling in predicting outcome early after HI (Majdan, Brazinova, Rusnak, & Leitgeb, 2017; Marmarou et al., 2007; Murray et al., 2007). However there remains little research focussing on factors that explain late outcome or change in outcome late after injury. The findings in this study demonstrate the need to identify factors that predict worsening disability over time, and multivariable prognostic modelling may assist in this investigation.

9.1.3 Do head injury participants have higher allostatic load scores than non- head injured comparison participants?

Early after HI at hospital discharge (study 1, Chapter 5), HI participants had a significantly higher AL than comparison participants, however this difference did not remain at 6 months post-discharge in the same group (study 2, Chapter 6), indicating that the initial difference may have been due to acute physiological deregulation caused by the HI. The wider implication of this is that AL in the head injured group is similar to that in the non-head injured group prior to HI. This in turn suggests that later high mortality rates following HI are not explained by a relatively high AL prior to injury. Despite this and as hypothesised, HI participants had significantly higher AL scores, specifically metabolic and anthropometric component scores, late after injury than comparison participants. This suggests that brain damage may alter the production of primary mediators of allostasis (neuroendocrine stress hormones), which over time cause the secondary outcomes (metabolic and anthropometric indicators) of allostasis to increase.

There are a number of conditions (figure 3, Chapter 2) that alter the production of primary mediators of allostasis, and which, over time modify the regulation and normal operating ranges of secondary biological systems (such as metabolic,

anthropometric, and cardiovascular), eventually leading to poor health, diseases, and mortality (McEwen & Stellar, 1993; Seeman et al., 2001). This could imply that the higher metabolic and anthropometric component scores in the HI participants are consequences of ineffective or overactive management of the primary allostatic mediators, than the non-head injured comparison participants. This might be explained by disability following HI being a long-term stressor, for example increasing cognitive effort to perform tasks.

Another explanation for the increased AL in the HI group could be maladaptive coping styles or changes in lifestyle after injury, which are unhealthier than comparison participants. Higher metabolic biomarkers (or decreased metabolic 'healthy' biomarkers such as HDL) and anthropometric physical measures of health are associated with conditions such as obesity, insulin resistance and metabolic syndrome (Eckel et al., 2005). The etiology of these conditions is multifactorial, ranging from the influence of genes, excess energy consumption and insufficient energy expenditure, to side effects of medication (Aronne et al., 2009; Park et al., 2003). Inadequate sleep is also a risk factor for obesity and sleep disorders are common after HI (Castriotta et al., 2007; Gangwisch et al., 2005; Orff et al., 2009; Ponsford et al., 2012). Therefore the AL of the HI participants could be a result of factors such as smoking, diet, sleep quality, and physical activity. Unfortunately in this study, further information about lifestyle such as diet and sleep habits were not assessed. Therefore it is difficult to elucidate the cause of higher metabolic and anthropometric component scores in the HI group. However it is not simply lifestyle behaviours that cause AL to accumulate, it is a combination of genetic predisposition, early life events, social relationships, stressful life events with health-related choice and lifestyle behaviours (McEwen, 1998b). These factors would be difficult to assess retrospectively and combine into a model of risk of AL. Further, the appeal and ease of measuring AL is that it is the end-point physiological result of all of these factors on health. However it remains difficult to make recommendations about how to delay the faster increase of AL following HI based on the data collected in this study.

Higher AL is associated with increased risk of morbidities and mortality (Goldman et al., 2006; Seeman et al., 1997); therefore an implication of higher AL late after injury than comparison participants is that AL may explain some of the underlying

pathology linked with the increased risk of mortality reported later after HI (McMillan et al., 2011; McMillan et al., 2014). Although as the magnitude of the effect is small, AL may only in part explain the increased risk of mortality late after HI.

9.1.3.1 Reliability and validity of findings

The assessment of AL and the matching criteria of the HI and non-HI groups are factors that might reduce the reliability and validity of the findings from this research question.

9.1.3.1.1 Assessment of allostatic load

As described above, there is no evidence that better indicators of health or method of constructing AL scores are available.

9.1.3.1.2 Matching of groups

In study 1 and 2 (Chapter 5 and 6) HI participants were matched exactly for gender, and SIMD (2012) quintile as an indicator of social deprivation, and within 5 years for age; differences in these characteristics were explored and adjusted for in unmatched groups (study 3 and 4, Chapters 7 and 8).

9.1.3.1.2.1 SIMD (2012) quintiles

Categorising the datazones into quintiles, as was done in this thesis for ease of matching groups, may be less sensitive than SIMD (2012) datazones. Despite this, SIMD is recommended and widely used as an indicator of deprivation in Scotland (Bishop et al., 2004). Therefore although possibly less sensitive, SIMD (2012) quintiles are a valid and reliable assessment of social deprivation, and in some analyses, datazones were used.

9.1.3.1.2.2 Other potential confounders of allostatic load

There are many other potential confounders of AL not controlled for in this research, for example physical activity, dietary intake, alcohol consumption, or sleep duration (Hickson et al., 2012). Accumulation of AL is differentially affected by lifestyle, genetic, social, and biological factors (McEwen, 1998b), thus the

matching criteria in this thesis may be considered crude. Despite this, it would be very difficult to match groups on all the factors that may contribute to the accumulation of AL.

There is plentiful further information that with hindsight could have been collected, which may have been helpful to the interpretation of the differences in AL between groups. For example, information about the health and lifestyle of participants, especially prior to study commencement, would help to understand specific causes of increased metabolic and anthropometric component scores in study 3 (Chapter 7). Further, there were other factors that were not assessed but are though to counter the accumulation of AL such as reliance, positive coping mechanisms, social support, and positive psychosocial experiences (McEwen & Wingfield, 2003; Seeman, Singer, Ryff, Dienberg, & Levy-Storms, 2002; Weinstein, Goldman, Hedley, Yu-Hsuan, & Seeman, 2003). However when designing this research, the comfort of the HI participants was considered, therefore assessment time and the opportunity to collect information was limited. If strong evidence is found to adjust for other covariates of AL, future studies should consider this when deciding on a sample size. If not treated as a covariate, then measuring other lifestyle factors would enable a better understanding of the specific causes of high AL, in order to consider interventions.

9.1.3.2 Conclusion

There is evidence that HI is associated with a small increase in AL late after injury, however this difference is unlikely to fully explain the increased risk of death found late after HI (McMillan et al., 2011; McMillan et al., 2014). Nonetheless this association should direct studies to investigate further information regarding lifestyle in the Glasgow HI cohort, which may clarify this finding.

9.1.4 Does allostatic load explain cognitive outcome later after head injury?

The only significant finding in the investigation of AL and cognitive function was counterintuitive; higher AL scores were associated with faster time to complete a fine motor co-ordination task in a group of retired international rugby players (Chapter 8, Section 8.6.7.7 and 8.6.7.8). It is likely that with a history of healthy diets and intensive physical activity, the accumulation of AL is different in elite

athletes. This group is also likely to have above average skills in motor co-ordination due to their experience in playing sports, which may also partly explain the unusual finding. It would be valuable to investigate AL further in elite sports players, to understand whether the consequences of chronic physiological dysregulation are the same or different as for the general population.

The remaining results in study 3 and 4 (Chapter 7 and 8) demonstrated that AL was not associated with cognitive performance late after hospitalised HI or after multiple concussions in retired international rugby players. This contrasts with research showing that higher AL is associated with poorer cognitive function in healthy aging populations (Booth et al., 2015; Goldman et al., 2006; Karlamangla et al., 2002; Seeman et al., 1997; Seplaki et al., 2006). This implies that the accumulation of AL following brain damage may be different to that observed in these healthy populations, and which has previously demonstrated correlations with cognitive function. The other possibility is cognitive impairment following HI is different to cognitive decline that occurs naturally with age, and which therefore is associated with the accumulation of AL.

9.1.4.1 Reliability and validity of findings

There are possible factors that might impact on the reliability and validity of these findings; these are the samples and measures.

9.1.4.1.1 Samples

The participants in Chapters 7 and 8 were recruited late after injury, when it would be more likely that an effect of age and long-term effects of HI on cognitive functioning would be detectable (Corkin et al., 1989; Himanen et al., 2006). A further strength was the exploration of AL and cognitive function in both mild and severe HI participants. It may be useful to follow-up these participants, or a larger sample, at an older age when the chance of observing significant cognitive decline is increased; however as AL plateaus in the 6th decade of life (Crimmins et al., 2003), this may limit the likelihood of any effect of AL being detected. The retired international rugby players reported a relatively high number of concussions and the average age was not too dissimilar compared to other studies. Therefore the

lack of association between AL and cognitive function following HI is unlikely to be due to bias in the samples.

9.1.4.1.2 Measures

As discussed above, there exists no evidence of a better method of constructing an AL score. The assessments of cognitive function are commonly used, validated, and some in particular were sensitive to detecting cognitive impairment. Therefore it is also unlikely that the lack of relationship was due to the range of cognitive tests used.

9.1.4.2 Conclusion

The evidence from this thesis indicates that AL is not associated with cognitive functioning late after HI. This finding makes an important and original contribution to the HI literature. Nevertheless, the results should be confirmed in a larger study, potentially assessing other prognostic factors that may affect cognitive outcome late after HI. There is value in following-up the participants from study 3 and 4 (Chapter 7 and 8) in the future to test whether AL predicts cognitive decline as has been demonstrated in previous AL literature (Goldman et al., 2006; Seeman et al., 1997; Seplaki et al., 2006).

9.2 Other limitations and strengths of the studies in this thesis

Specific limitations and strengths relating to each study have been discussed in the preceding chapters, and those relating to the specific research questions outlined above. However, the research presented in this thesis must be interpreted within the context of some general limitations and strengths.

9.2.1 Limitations

9.2.1.1 The generalisability of the sample

The participants in study 1, 2, and 3 (Chapters 5-7) were recruited from Glasgow hospitals, therefore they are representative of the Glasgow population, which is predominantly Caucasian. This limited the generalisability of the results in these studies to other populations that are more ethnically diverse. The retired

international rugby players in study 4 (Chapter 8) were all Caucasian, which is typical for retired elite Scottish rugby players therefore generalisability of these findings is not an issue in relation to that population.

There may also be a volunteer bias in all the studies in this thesis. Volunteers in the general population have been shown to be more educated, intelligent, approval-motivated, sociable, and likely to have a more affluent social background than non-volunteers (Rosenthal & Rosnow, 1975). It is unknown whether these differences are the same for the HI population, which would lead to biases in the HI sample. Another potential volunteer issue is the health or disability of those who did not come forward may be worse. For example, study 4 (Chapter 8) showed no relationship between concussion and ratings of depression; however other studies have found a higher rate of major depressive disorder following repeat concussion (Decq et al., 2016; McKee et al., 2013). Ratings of depression for retired international rugby players in study 4 were all 'normal'. It is possible that rugby players who had higher ratings of depression were less inclined to volunteer to take part. Unfortunately the demographics and health status of those who did not volunteer are unknown. Thus, the study samples may not fully represent the target populations, raising questions regarding the validity of generalising the findings to other HI populations. In addition to this, there is potential survival bias in the longitudinal studies. Late after injury (study 3, Chapter 7), only survivors could take part in the study; even so, if AL was a strong predictor of disability, it would be expected that some signs of an effect would be visible.

9.2.1.2 Sample size

The number of participants in all the studies was at or near to the estimated sample size. The effect sizes were extremely small, and most of the *p* values were far from being significant, thus there is no reason to suggest power is an issue in these studies.

9.2.1.3 Study design

The cross-sectional design of study 1 and 4 (Chapter 5 and 8) limits the interpretation of findings in terms of determining causality. Study 2 and 3

(Chapters 6 and 7) were longitudinal studies and therefore are limited in retention of recruitment. Corrigan et al. (2003) illustrates longitudinal HI research attrition could be due to death, inability to locate or interview, or refusal to take part at follow-up, and the loss of subjects from HI studies are likely to experience: a history of substance abuse, be socioeconomically disadvantaged, and have more severe motor deficits. This potentially causes a bias in the sample that is successfully follow-up, again limiting the generalisability of the findings to the wider HI population.

9.2.2 Strengths

9.2.2.1 Research novelty

A primary strength of this research is it is the first to investigate AL and outcome after HI. Despite some limitations described above, this thesis makes a unique contribution to the literature. The findings in this thesis signify that AL mostly does not help to explain the heterogeneity in disability or cognitive outcome after HI, although it may contribute to our understanding of increased risk of mortality late after injury. This is valuable knowledge to contribute to the broader investigation of what factors explain or predict outcome after HI. Future research can consider the findings of this thesis when formulating their research hypotheses.

9.2.2.2 Allostatic load score

There is strength in the range of indicators of health collected for modelling AL. Whilst not exhaustive, it was significantly broader than other AL research, and most importantly it represented all 5 recommended biological components (Juster et al., 2010). As described above, a systematic search in Chapter 2 (section 2.2.7), provided no evidence that any other indicators were better, or that a better method exists for constructing AL scores.

9.2.2.3 Study design

There are strengths in the design of the studies in this thesis. The use of different HI populations facilitated the exploration of outcome after HI and AL at different points since injury, and in mild and severe HI populations. The longitudinal design

of study 2 and 3 (Chapters 6 and 7), enabled the investigation of change in disability over time after HI. Specifically, the findings of Chapter 6 (late after HI) will contribute to the relatively small number of studies that have investigated change in disability late after HI (Hammond et al., 2004; McMillan et al., 2012; Whitnall et al., 2006).

9.2.2.4 The use of comparison groups

The use of comparison groups adds strength to the studies in this thesis. HI groups were matched exactly in gender and SIMD (2012) quintile, and within 5 years for age, to non-HI comparison participants, or differences in characteristics were adjusted for in the analyses. This enabled the exploration of the effect of having a HI or repeat concussion on AL.

9.3 The implications of this work for the allostatic load literature

The systematic search in Chapter 2 demonstrated there exists no evidence base of a more reliable and valid method for constructing AL than that used in the studies in this thesis. This combined with some counterintuitive findings, particularly in Chapter 8, bring into question whether the practice of measuring of AL is robust and whether the construct of AL itself adds value to measuring individual biomarkers.

The idea that physiological damage accumulates over the lifetime, as a result of genetics, early life events, lifestyle choices, and stressful events, has logical appeal. Indeed chronic stress is associated with an increased risk of stress-related diseases and pathology (McEwen, 1998b). For this reason, the prospect of being able to assess the physiological impact of all of these factors and generate testable predictions is appealing; particularly in a framework that focuses on the individual within social environmental context. However, this thesis has highlighted some limitations in the practical application of AL; somewhere between the theory and creating a measurable construct.

A key issue raised by this thesis is that there is no agreement in the literature about what is the best way to assess AL and there are no studies that test the validity or reliability of different measures of AL. Most importantly, there is no

one paper or study that demonstrates a measure of AL has high construct and concurrent validity, in that it is significantly associated with a number of known predictor variables with theoretical grounding, for example age, social deprivation, physical functioning, and mortality. The large AL literature taken as a whole shows these relationships in multiple different studies, however individual papers only ever report correlations with one or two of these factors. However there are some inconsistencies in these papers in terms of the methods used.

These issues have an impact on the AL literature and studies that attempt to operationalise AL; it may be that it is more complicated than simply combining indicators of health data. When indicators of health have different roles, within diverse biological systems, it might be too crude to combine them together into one score. The AL model argues that multiple biological systems need to be assessed; their interacting pattern of dysregulation is an important part of the AL model. Nevertheless it may be the case that a much more complicated construction of AL is needed to reflect these complex and inter-connected biological systems.

Despite these limitations, a model that views disease pathways in terms of individual experiences within their environments is a useful guide. Nonetheless, there remain challenges in determining ways to capture all the variables that contribute to AL; it is clearly necessary to examine the reliability and validity of the measures of AL. As discussed in Chapter 3, the method of creating an AL score in this thesis considered the directional relationship of each indicator of health with all-cause mortality; however this is not common practise in the AL literature. Having stronger evidence for the use of biomarkers and consideration of the nature of each indicator would be a good place to start in moving towards generating a consensus regarding a theoretically reliable and valid measure of AL.

A significant issue raised following the systematic search of AL literature in Chapter 2, is that a full meta-analyses or systematic review of the current AL literature is not currently meaningful due to the lack of consistency in language, choice of indicators, methods of constructing AL scores, the population tested, outcomes assessed, and covariates adjusted for in the AL literature. This has critical implications for the future of AL literature and model as it is lacking a

strong evidence base from which future research can expand and develop the literature.

Nevertheless, a possible if costly study that would benefit the AL literature at this time, would be a study to test the validity, reliability, and predictive models of AL, by using analysis such as principal component analysis or factor analysis in conjunction with measures of a wide number of indicators, all the known methods for constructing AL scores, and a multitude of outcomes known to be consequences of high AL such as illness or mortality from, and in a large, healthy, and representative population based sample. A longitudinal design would also enable the concurrent observation of the relationship between the accumulation of AL and the development of ill-health. This study has not yet been conducted, but it would add great value to the AL literature, as currently, the variability in measures of AL questions the validity of the methods, and prevents the comparison of data across studies.

Finally, future research investigating AL should consider collecting large amounts of information regarding lifestyle, which may behave as covariates of AL, or descriptors of the causes of increased AL. With these issues resolved in the field of AL, researchers can take guidance from a gold-standard method for measuring AL and utilise this potentially helpful tool in other clinical populations beyond HI.

9.4 Direction for future research

This research does not support the use of AL as a predictor of outcome after HI. The novelty of this research means replication of the findings is required before definitive conclusions can be made. Nonetheless, some findings in this study are worthy of further study:

- The relationships between neuroendocrine component scores at hospital discharge and disability outcome at 6 month follow-up requires replication and further investigation. For example, as discussed in Chapter 6, potential further exploration of the differences in psychology and physical aspects of recovering between those with high and low neuroendocrine indicators early after injury may elucidate details about the relationship between neuroendocrine functioning and later disability outcome after HI. Another

remaining question related to whether there is a cause or effect relationship between HI and AL late after injury. This would require a longitudinal study, following-up HI participants from early after HI until late after injury, measuring AL at multiple time points to track to development of the accumulation of AL. It would also be valuable to track to development of AL in a group of matched comparison participants to compare any differences in the accumulation of AL, to understand the cause of higher AL in the participants in study 3 (Chapter 7).

- The relationships between change in disability from 6 months post- discharge to late after injury and metabolic component scores at late follow-up requires replication and further study. Similarly, a longitudinal study is necessary to investigate this finding further, observing the progression of change in disability, the accumulation of metabolic component scores, and measuring details about lifestyle, in order to understand the temporal relationship between these factors, what are the important factors, and whether intervention wold be beneficial.

Future research should aim to replicate these findings ideally, and to explore AL as a factor in a larger, multifactorial prospective study examining predictors of disability outcome and mortality over several years. Importantly however, as discussed above, much work is first required to establish an agreed measure of AL and method of scoring that is both valid and reliable.

As yet, so much is unknown about the factors that predict outcome after HI. Although this study found little evidence a model of chronic life stress affecting outcome after HI, there seems to be value in adopting longitudinal designs in HI studies, different time points since HI, different severities, in order to do a comprehensive investigation of chronic effects of HI over time. Future HI research should consider using multivariable prognostic modelling to analyse a large number of potential predictors of outcome after HI, and focus on disability and cognitive outcome and change in outcome late after HI.

9.5 Conclusions

In this thesis, I have investigated AL and outcome after HI using four diverse studies. The results demonstrate that the utility of AL in explaining outcome after HI may be limited. AL did not explain disability or cognitive outcome after HI. Differences in AL between HI and comparison participants late after injury may explain a proportion of the increased risk of pathology associated with disease and mortality observed late after HI. These results are novel and contribute to the investigation of outcome after HI, however much remains unknown. Further research is necessary to validate measures of AL, and to help improve outcomes and quality of life for HI patients and their families.

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Appendices

Appendix A

- Communication

- Ethical approval

- Research and development approval

Appendix B

- Participant Information Sheet

- Participant Consent Form

Appendix C

- Assessment tools

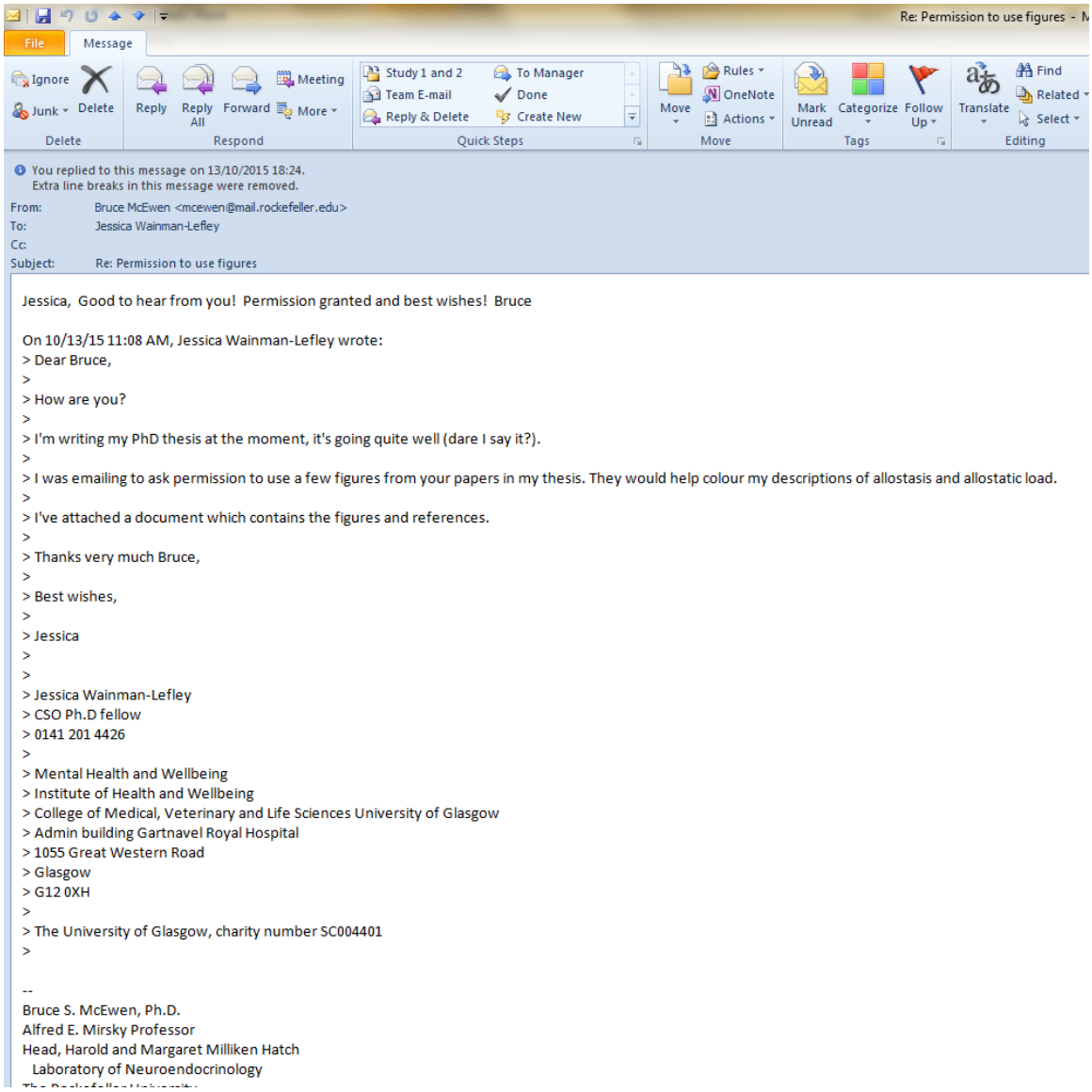
Appendix D

- Supplementary data

Appendix E

- Assumptions of regression

Appendix A: Research communication



Re: Permission to use figures - M

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You replied to this message on 13/10/2015 18:24.
Extra line breaks in this message were removed.

From: Bruce McEwen <mcewen@mail.rockefeller.edu>
To: Jessica Wainman-Lefley
Cc:
Subject: Re: Permission to use figures

Jessica, Good to hear from you! Permission granted and best wishes! Bruce

On 10/13/15 11:08 AM, Jessica Wainman-Lefley wrote:
> Dear Bruce,
>
> How are you?
>
> I'm writing my PhD thesis at the moment, it's going quite well (dare I say it?).
>
> I was emailing to ask permission to use a few figures from your papers in my thesis. They would help colour my descriptions of allostasis and allostatic load.
>
> I've attached a document which contains the figures and references.
>
> Thanks very much Bruce,
>
> Best wishes,
>
> Jessica
>
>
> Jessica Wainman-Lefley
> CSO Ph.D fellow
> 0141 201 4426
>
> Mental Health and Wellbeing
> Institute of Health and Wellbeing
> College of Medical, Veterinary and Life Sciences University of Glasgow
> Admin building Gartnavel Royal Hospital
> 1055 Great Western Road
> Glasgow
> G12 0XH
>
> The University of Glasgow, charity number SC004401
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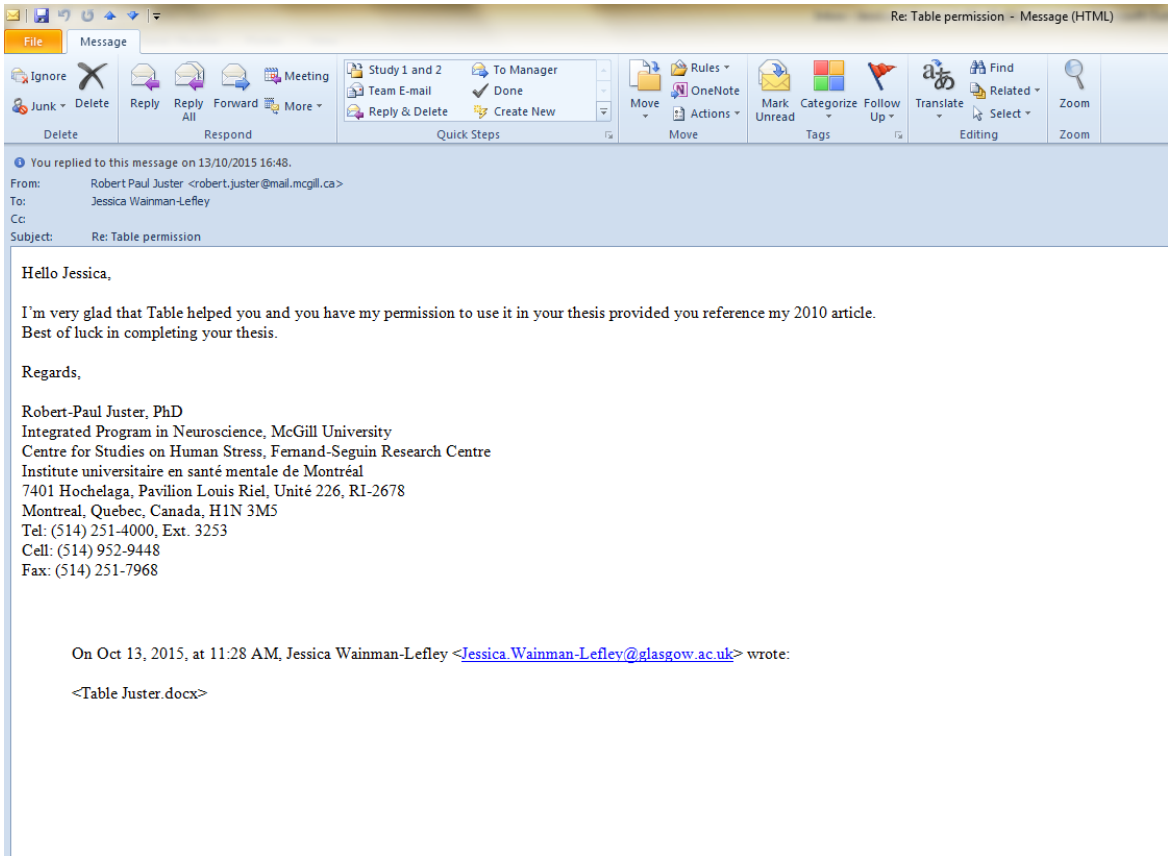
Bruce S. McEwen, Ph.D.
Alfred E. Mirsky Professor
Head, Harold and Margaret Milliken Hatch
Laboratory of Neuroendocrinology

Screen shot of email giving permission to use diagrams from McEwen (2006a) and McEwen (1998a)



Re: Table permission - Message (HTML)

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Study 1 and 2 | Team E-mail | Reply & Delete | To Manager | Done | Create New | Quick Steps

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You replied to this message on 13/10/2015 16:48.

From: Robert Paul Juster <robert.juster@mail.mcgill.ca>
To: Jessica Wainman-Lefley
Cc:
Subject: Re: Table permission

Hello Jessica,

I'm very glad that Table helped you and you have my permission to use it in your thesis provided you reference my 2010 article.
Best of luck in completing your thesis.

Regards,

Robert-Paul Juster, PhD
Integrated Program in Neuroscience, McGill University
Centre for Studies on Human Stress, Fernand-Seguin Research Centre
Institute universitaire en santé mentale de Montréal
7401 Hochelaga, Pavilion Louis Riel, Unité 226, RI-2678
Montreal, Quebec, Canada, H1N 3M5
Tel: (514) 251-4000, Ext. 3253
Cell: (514) 952-9448
Fax: (514) 251-7968

On Oct 13, 2015, at 11:28 AM, Jessica Wainman-Lefley <Jessica.Wainman-Lefley@glasgow.ac.uk> wrote:

<Table Juster.docx>

Screen shot of email giving permission to use diagrams from Juster et al. (2010)

NHS Greater Glasgow & Clyde ethics approval letter Study 1 and 2 (Chapter 5 and 6)

WoSRES
West of Scotland Research Ethics Service

NHS Greater Glasgow and Clyde

Professor Thomas McMillan
Professor of Clinical Neuropsychology
1st Floor, Mental Health and Wellbeing
Admin building, Gartnavel Royal hospital
1055 Great Western Road
Glasgow
G12 0XH

West of Scotland REC 5
Ground Floor - Tennent Building
Western Infirmary
38 Church Street
Glasgow
G11 6NT

Date 11 January 2013

Direct line 0141 211 2102
E-mail sharon.macgregor@ggc.scot.nhs.uk

Dear Professor McMillan

Study title: **Allostatic Load and health outcome in adults at discharge and at 6 months following a head injury, in comparison to matched control participants.**
REC reference: **12/WS/0315**
IRAS project ID: **115839**

I refer to Ms Wainmann-Lefley's recent letter, which was received on 7th January 2013, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Mrs Sharon Macgregor, sharon.macgregor@ggc.scot.nhs.uk.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management

permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		26 November 2012
GP/Consultant Information Sheets (Participants & Control)	1	03 October 2012
Other: Health Information to be taken from Head Injury patient's medical notes		
Participant Consent Form: Head Injury Participant	2	12 November 2012
Participant Consent Form: Control	3	07 January 2013
Participant Information Sheet: Control	3	07 January 2013
Participant Information Sheet: Head Injury	3	07 January 2013
Protocol	1	14 November 2012
Questionnaire: General Information (Control)		
Questionnaire: General Information (Head Injury)		
Questionnaire: Glasgow Outcome at Discharge Scale		
Questionnaire: Multidimensional Health Locus of Control Scale (Form A)		

Questionnaire: Perceived Stress Scale		
Questionnaire: Glasgow Outcome Scale - Extended		
Questionnaire: Rehabilitation/Treatment Questionnaire		
Questionnaire: The Alcohol Use Disorders Identification Test: Interview Version		
Questionnaire: Rosenberg Self-Esteem Scale		
Questionnaire: HADS		
REC application	1	23 November 2012
Response to Request for Further Information		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/WS/0315 Please quote this number on all correspondence

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

for
Dr Gregory Ofili
Chair

Enclosures: "After ethical review – guidance for researchers"

Copy to: Erica Packard, NHS Greater Glasgow and Clyde

NHS Greater Glasgow & Clyde Research & Development approval letter for Study 1 and 2 (Chapter 5 and 6)

Coordinator/Administrator: Dr Erica Packard/Mrs Elaine O'Neill
Telephone Number: 0141 211 6208
E-Mail: erica.packard@ggc.scot.nhs.uk
Website: www.nhsggc.org.uk/r&d

R&D Management Office
Western Infirmary
Tennent Institute
1st Floor 38 Church Street
Glasgow, G11 6NT,

5 February 2013

Prof Tom McMillan
University of Glasgow
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow G12 0XH

NHS GG&C Board Approval

Dear Prof McMillan,

Study Title:	**Allostatic Load and health outcome in adults at discharge and at 6 months following a head injury, in comparison to matched control participants.**
Principal Investigator:	**Prof Tom McMillan**
GG&C HB site	**All locations**
Sponsor	**NHS Greater Glasgow and Clyde**
R&D reference:	**GN12CP212**
REC reference:	**12/WS/0315**
Protocol no: (including version and date)	**V1; 14/11/12**

I am pleased to confirm that Greater Glasgow & Clyde Health Board is now able to grant **Approval** for the above study. **PhD Student can not perform venepuncture until evidence of competency has been received by the R&D office.**

Conditions of Approval

1. **For Clinical Trials** as defined by the Medicines for Human Use Clinical Trial Regulations, 2004
   a. During the life span of the study GGHB requires the following information relating to this site
      i. Notification of any potential serious breaches.
      ii. Notification of any regulatory inspections.

It is your responsibility to ensure that all staff involved in the study at this site have the appropriate GCP training according to the GGHB GCP policy (www.nhsggc.org.uk/content/default.asp?page=s1411), evidence of such training to be filed in the site file.

NHS
Greater Glasgow and Clyde

2. **For all studies** the following information is required during their lifespan.
   a. Recruitment Numbers on a monthly basis
   b. Any change of staff named on the original SSI form
   c. Any amendments – Substantial or Non Substantial
   d. Notification of Trial/study end including final recruitment figures
   e. Final Report & Copies of Publications/Abstracts

Please add this approval to your study file as this letter may be subject to audit and monitoring.

Your personal information will be held on a secure national web-based NHS database.

I wish you every success with this research study

Yours sincerely,

E Packard

Dr Erica Packard
Research Co-ordinator

Cc: Ms Jessica Wainman-Lefley

Tayside NHS Research & Development approval Study 1 and 2 (Chapter 5 and 6)

NHS
Tayside

07 November 2013

Mr Douglas Gentleman
Centre for Brain Injury Rehabilitation
Royal Victoria Hospital
Jedburgh Road
Dundee
DD2 1SP

Dear Mr Gentleman,

R & D MANAGEMENT APPROVAL - TAYSIDE

Title: Allostatic Load and health outcome in adults at discharge and at 6 months following a head injury, in comparison to matched control participants.

Chief Investigator: Prof Tom McMillan

Principal Investigator: Mr Douglas Gentleman

Tayside Ref: 2013NF05 **NRS Ref: NRS13/NE108**

REC Ref: 12/WS/0315

EudraCT Ref: N/A **CTA Ref: N/A**

Sponsor(s): NHS Greater Glasgow & Clyde

Funder(s): CSO

Many thanks for your application to carry out the above project here in NHS Tayside. I am pleased to confirm that the project documentation (as outlined below) has been reviewed, registered and Management Approval has been granted for the study to proceed locally in Tayside.

Approval is granted on the following conditions:-

- ALL Research must be carried out in compliance with the Research Governance Framework for Health & Community Care, Health & Safety Regulations, data protection principles, statutory legislation and in accordance with Good Clinical Practice (GCP).
- All amendments to be notified to TASC R & D Office.
- All local researchers must hold either a Substantive Contract, Honorary Research Contract, Honorary Clinical Contract or Letter of Access with NHS Tayside where required (http://www.nihr.ac.uk/systems/Pages/systems_research_passports.aspx).
- TASC R & D Office to be informed of change in Principal Investigator, Chief Investigator or any additional research personnel locally.

- Notification to TASC R & D Office of any change in funding.
- As custodian of the information collated during this research project you are responsible for ensuring the security of all personal information collected in line with NHS Scotland IT Security Policies, until destruction of this data.
- All eligible studies will be added to the UKCRN Portfolio http://public.ukcrn.org.uk/. Recruitment figures for eligible studies must be recorded onto the Portfolio every month: This is the responsibility of the lead UK site. If you are the lead, or only, UK site, we can provide help or advice with this. For information, contact Charles Weller – (01382) 383822 – charles.weller@nhs.net or Liz Livingstone – (01382) 383872 – elivingstone@nhs.net.
- Annual reports are required to be submitted to TASC R & D Office with the first report due 12 months from date of issue of this management approval letter and at yearly intervals until completion of the study.
- Notification of early termination within 15 days or End of Trial within 90 days followed by End of Trial Report within 1 year to TASC R & D Office.
- You may be required to assist with and provide information in regard to audit and monitoring of study.

Please note you are required to adhere to the conditions, if not, NHS management approval may be withdrawn for the study.

Approved Documents

Document	Version	Date
Protocol	2.1	27/09/13
IRAS R & D Form		
SSI Form		
General information questionnaire – head injury	2	30/08/13
General information questionnaire – control	2	30/08/13
Head injury PIS	3	07/01/13
Control PIS	3	07/01/13
Consent head injury	3.1	20/05/13
Consent control	3.1	20/05/13
GP letter	1.1	20/05/13
Health information list	1	26/11/12
Disability rating scale	1	20/11/12
Glasgow outcome scale – extended		
HADS		
Multidimensional health locus of control scale (form a)		
Perceived stress scale		
Rehabilitation/treatment questionnaire		
Rosenberg Self Esteem Scale		
Glasgow outcome at discharge		
AUDIT		
Advert	1	Aug 2013
REC AM04		06/11/13
REC AM03		04/06/13
REC AM 05/04/13		12/03/13
REC favourable opinion		11/01/13
Funding letter		24/08/12
CV – Douglas Gentleman		14/10/13
CV – Thomas McMillan		13/08/12

CV – Jessica Wainman-Lefley		**26/09/11**
CV – Jill Pell		
CV – Jonathan Cavanagh		**09/06/11**

May I take this opportunity to wish you every success with your project.

Please do not hesitate to contact TASC R & D Office should you require further assistance.

Yours sincerely,

Elizabeth Coote
R&D Manager

TAyside medical **S**cience **C**entre (TASC)
Ninewells Hospital & Medical School
TASC Research & Development Office
Residency Block, Level 3
George Pirie Way
Dundee DD1 9SY
Email: liz.coote@nhs.net
Tel: 01382 383876 Fax: 013812 740122

c.c.
Jessica Wainman-Lefley
Thomas McMillan
NRSPCC (for NRS studies)

Letter to the General Practitioner of the head injury participants in Study 1 (chapter 5)

University of Glasgow

NHS Greater Glasgow and Clyde

Professor T. M. McMillan
Chair in Clinical Neuropsychology
0141-211-0354

Ref: TM/JWL/PR

Date:

Dear Dr.

***RE:* Allostatic Load and Health Outcome in Adults Following Head Injury**

***RE:* (CHI:)**

You may know that the above patient, who I believe is on your list, was admitted to hospital with a head injury recently.

Your patient has consented to take part in the above study; I have enclosed the information sheet for your records. You are not required to do anything for this research; this letter is just for information. Should you have any concerns please do not hesitate to contact me.

Yours sincerely,

Tom McMillan
Professor of Clinical Neuropsychology
M App Sci, PhD, FBPsS

Jessica Wainman-Lefley
Ph.D Student
Tel: 0141 211 0651

Pauline Rankin
Secretary to Professor T McMillan
0141 211 0354
Mental Health and Wellbeing
Admin Building, Gartnavel Royal Hospital

Reminder letter Study 2 (Chapter 6)

University of Glasgow

NHS Greater Glasgow and Clyde

Professor T. M. McMillan
Chair in Clinical Neuropsychology
0141-211-0354

Ref: TM/JWL/PR

Date:

Dear

***RE:* Allostatic Load and Health Outcome in Adults Following Head Injury**

As you may remember, I visited you at discharge from hospital following your head injury around 5 months ago. I am writing to thank you for your help and to remind you that the second part of the study is due soon. It would involve a short interview, a few measures of your health and a small blood sample, much like when I first met with you. This second part of the study is very important as it allows me to understand more about your recovery and health outcome following head injury.

I would be very grateful if you could get in touch with me on either of these numbers: **0141 211 0651** or **07546 509 008.** You can ask me any questions you might have and we can organise a suitable time and place to meet. You will receive a £25 voucher to thank you for your time at this follow-up meeting. I have enclosed the Information Sheet for your interest.

Yours sincerely,

Jessica Wainman-Lefley
Ph.D Fellow
Tel: **0141 211 0651**
Or **07546 509 008**

Professor Tom McMillan
Professor of Clinical Neuropsychology
M App Sci, PhD, FBPsS

Pauline Rankin
Secretary to Professor T McMillan
0141 211 0354
Mental Health and Wellbeing
Admin Building, Gartnavel Royal Hospital

Version 1: 03/10/2013

NHS Greater Glasgow & Clyde ethics approval letter for Study 3 (Chapter 7)

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

Professor Thomas McMillan
1st Floor, Mental Health and Wellbeing
Admin building, Gartnavel Royal Hospital
1055 Great Western Road
Glasgow
G12 0XH

West of Scotland REC 5
Ground Floor - Tennent Building
Western Infirmary
38 Church Street
Glasgow
G11 6NT

Date 22 December 2014

Direct line 0141 211 2102
E-mail WoSREC5@ggc.scot.nhs.uk

Dear Professor McMillan

Study title: **An investigation of heterogeneity of outcome late after head injury**
REC reference: **14/WS/1145**
IRAS project ID: **159844**

Thank you for your email of 19 December 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Mrs Sharon Macgregor, WoSREC5@ggc.scot.nhs.uk. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the

study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Cover Letter]		03 November 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Client Letter]		30 July 2013
GP/consultant information sheets or letters [GP letter]	2	27 November 2014
GP/consultant information sheets or letters [Blood biomarker GP letter]	2	19 December 2014
Letter from funder [Award letter from CSO]		24 August 2012
Letters of invitation to participant [Participant Invitation Letter]	2	27 November 2014
Non-validated questionnaire [An Investigation of Heterogeneity of Outcome: General Questionnaire]	2	24 July 2014
Other [Consent letter with revised A6-1 summary of study]	1	01 December 2014
Participant consent form [Participant consent form]	2	27 November 2014
Participant information sheet (PIS) [Participant Information Sheet]	2	27 November 2014
REC Application Form [REC_Form_05112014]		05 November 2014
Research protocol or project proposal [Protocol Version]	5	27 November 2014
Response to Request for Further Information [email]		19 December 2014
Summary CV for Chief Investigator (CI) [CV Tom McMillan]		14 October 2014
Summary CV for student [Jessica Wainman-Lefley CV]		25 July 2014
Summary CV for supervisor (student research) [CV Tom McMillan]		14 October 2014
Validated questionnaire [AUDIT]		
Validated questionnaire [GHQ 28]		
Validated questionnaire [HADS]		
Validated questionnaire [MMSE]		
Validated questionnaire [RSE scale]		
Validated questionnaire [PSScale]		
Validated questionnaire [Symbol digit modalities test]		
Validated questionnaire [Stroop test]		
Validated questionnaire [WAIS]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

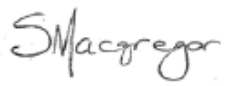
HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

14/WS/1145	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely



for
Dr Gregory Ofili
Chair

Enclosures: "After ethical review – guidance for researchers"

Copy to: Miss Emma-Jane Gault, University of Glasgow
Dr Erica Packard, NHS Greater Glasgow and Clyde

NHS Greater Glasgow & Clyde Research & Development approval letter for Study 3 (Chapter 7)

2. **For all studies** the following information is required during their lifespan.
   a. Recruitment Numbers on a quarterly basis
   b. Any change of staff named on the original SSI form
   c. Any amendments – Substantial or Non Substantial
   d. Notification of Trial/study end including final recruitment figures
   e. Final Report & Copies of Publications/Abstracts

Please add this approval to your study file as this letter may be subject to audit and monitoring.

Your personal information will be held on a secure national web-based NHS database.

I wish you every success with this research study

Yours sincerely,

EPackard

Dr Erica Packard
Research Co-ordinator

Cc:

Letter from Professor McMillan to General Practitioners in Study 3 (Chapter 7)

University of Glasgow

NHS Greater Glasgow and Clyde

Professor T.M.McMillan
Chair in Clinical Neuropsychology
0141-211-0354

Ref:TM/GP/PR

Date

GP title -name
GP-Address
GP-Post code

Dear [Title] [Surname]

RE: [patient name-DOB – address]

The above patient, who I believe is on your list, had a head in the past and was included in a follow-up study that investigated the effects of the injury. The study took place more than a decade ago and was published (Millar et al JNeurology Neurosurgery and Psychiatry 2003; 74, 1047-52). I have received ethics approval to contact patients to carry out a further follow-up to determine outcome very late after injury.

Participants will be seen at the Clinical Research Facility at the Western Infirmary or Glasgow Royal Infirmary. The assessment will take about an hour and a half. The attached information sheet gives further details, but in brief, the assessment involves interview, questionnaires, cognitive tests, non-invasive assessment of basic physiology (blood pressure and forced expiratory volume) and a blood sample.

I would be most grateful if you could let me know if there are any reasons why we should not contact your patient; e.g. they are deceased or lack the capacity to consent. A copy of the information sheet, consent form and letter to the patient is enclosed. For your convenience there is a response sheet and a stamped addressed envelope attached.

If you would like further information or wish to discuss this, please let me know. I am extremely grateful for your help.

Yours sincerely

Tom McMillan
Professor of Clinical Neuropsychology

Version 1: 10/07/2014

GP Reply Sheet:

An Investigation of Heterogeneity of Outcome Late after Severe Head Injury

Patient Name:

Date of Birth:

Address:

[ ] Uncertain – please telephone GP surgery

[ ] No: Patient died on (date)...../...../.....

[ ] Not happy for patient to be contacted.

Reason: .....

[ ] Patient no longer with this practice

[ ] Other

Reason: .....

Signed by GP: .....

Print name: .....

Date: ...../...../.....

Version 1: 10/07/2014

Letter from Professor Teasdale to potential participant in Study 3 (Chapter 7)

Professor GM Teasdale
Mental Health and Wellbeing
Institute of Health and Wellbeing
University of Glasgow
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow G12 0XH
0141-211-0354

Ref:GMT/JWL/LM

Date:

Name
Address
Post code

Dear *[Title] [Surname]*

You kindly took part in a study on the effects of head injury over ten years ago. This has helped us to understand about long term effects. To understand more about the after effects of head injury even longer after injury, my colleague Professor Tom McMillan is conducting a new study and I am writing to ask if you are willing to meet with his team with a view to taking part.

I enclose a copy of the information sheet, which summarises what is involved. **The interview would take place at the Western Infirmary or Glasgow Royal Infirmary.** Your travel expenses can be reimbursed and there will be £20 for you in vouchers for your time as indicated on the information sheet.

If you think it may be upsetting for you to talk about the event that caused the injury, you should ask a close friend or family member to be present at the time of the interview.

Thank you for considering this request. If you are willing meet with Professor McMillan's team with a view to taking part in the study please make contact with Lin MacLean: Linda.Maclean@glasgow.ac.uk (0141 211 3901) who is a research worker on the project. You can also contact Professor Tom McMillan who is supervising the study on the above number.

I am extremely grateful for your help.

Yours sincerely

Professor Sir Graham Teasdale

Version 3: 05.01.15

Ethics approval letter for Study 4 (Chapter 8)

University of Glasgow | College of Medical, Veterinary & Life Sciences

22nd January 2014

Dear Professor T McMillan

MVLS College Ethics Committee

Project Title: The Long term Health Outcomes of Participation in Elite Level Rugby
Project No: 200130062

The College Ethics Committee has reviewed your application and has agreed that there is no objection on ethical grounds to the proposed study. They are happy therefore to approve the project, subject to the following conditions

- Project end date: January 2016
- The research should be carried out only on the sites, and/or with the groups defined in the application.
- Any proposed changes in the protocol should be submitted for reassessment, except when it is necessary to change the protocol to eliminate hazard to the subjects or where the change involves only the administrative aspects of the project. The Ethics Committee should be informed of any such changes.
- You should submit a short end of study report to the Ethics Committee within 3 months of completion.

Yours sincerely

Prof. Andrew C. Rankin
Deputy Chair, College Ethics Committee

Appendix B: Participant information sheets and consent forms

Head injury Participant Information Sheet Study 1 and 2 (Chapter 5 and 6)

University of Glasgow

NHS Greater Glasgow and Clyde

HEAD INJURY PARTICIPANT INFORMATION SHEET

Allostatic load and health outcome in adults following head injury

Introduction

You are being invited to take part in a research study. Before you decide whether you want to take part, it is important for you to understand why the research is being carried out and what is involved. Please take time to read the following carefully and discuss it with friends or relatives if you wish. If you would like more information or if there is anything that is not clear please ask.

What is the purpose of the study?

We would like to have a greater understanding of the relationship between a head injury and the individual's health outcome later after injury. There is currently little evidence to help explain why some people recover better than others after a head injury. We are investigating 'allostatic load', which is an estimate of the stress that has accumulated in your body over your life-time. We want to see if allostatic load is related to recovery following head injury. If there is a relationship between the two, our greater understanding of outcome after head injury could lead to improvements in rehabilitation.

Why have I been chosen?

You have been admitted to hospital with a head injury and are between the ages of 16 and 64.

Do I have to take part in the study?

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?

There are two parts to the study. The first involves assessment in hospital that takes about 1-1.5 hours. This includes taking your consent, contact and health information. We would also like your permission to look at your medical notes to learn more about your health and the head injury. We will ask questions about any disability, your perception of stress and how in control of your health you feel. Finally we will calculate your allostatic load score by measuring your; height, weight, heart rate, blood pressure, breath volume, body mass index and take a small blood sample (to measure blood markers of stress). The second part of the study involves a follow- up 6 months after discharge from hospital. The above tests will be repeated and you will be asked a few further questions about your physical and psychological recovery from the head injury. The second assessment will take about 2 hours. There will be no risk to you when taking part in these research procedures.

Will I be paid for taking part?

You will not be paid, however you will receive a voucher to recompense you for your time. After the first assessment you will be given £15 in vouchers and after the second £25.

Will my taking part in the study be kept confidential?

Your GP will be notified that you have taken part in this research. Your identity and personal information will be completely confidential and known only to research fellow Jessica Wainman- Lefley and Professor Tom McMillan who leads the Head Injury Research Group. Findings from the study may be published in academic journals however your data will not be identifiable. Data will be stored for up to 10 years as we may decide to use it again for future research. It will be stored anonymously, in locked filing cabinets and then destroyed in confidential NHS shredders. Your study data may be examined by authorised individuals from the study sponsor, NHS Greater Glasgow and Clyde, and/or the regulatory authorities to ensure the study has been conducted to the proper standards.

Who is organising and paying for the research?

The research is organised by the Head Injury Research Team from The University of Glasgow. If you have any questions about the study, please contact the research fellow Jessica Wainman- Lefley on 0141 211 0651.

Who do I contact if I have a complaint about the study?

Please contact the Research and Development Department on 0141 211 2184.

Who do I contact for independent information about the study?

Please contact Dr. Sarah Wilson on 0141 211 3921.

Thank you for your time and co-operation.

Version 3: 07/01/2013

Comparison Participant Information Sheet Study 1 and 2 (Chapter 5 and 6)

University of Glasgow

NHS Greater Glasgow and Clyde

CONTROL PARTICIPANT INFORMATION SHEET

Allostatic load and health outcome in adults following head injury

Introduction

You are being invited to take part in a research study. Before you decide whether you want to take part, it is important for you to understand why the research is being carried out and what is involved. Please take time to read the following carefully and discuss it with friends or relatives if you wish. If you would like more information or if there is anything that is not clear please ask.

What is the purpose of the study?

We would like to have a greater understanding of the relationship between a head injury and the individual's health outcome later after injury. There is currently little evidence to help explain why some people recover better than others after a head injury. We ar investigating 'allostatic load', which is an estimate of the stress that has accumulated in your body over your life-time. It is important to compare the results of this for head injury patients to those of matched controls. We want to see if allostatic load scor is related to recovery following head injury. If there is a relationship between the two, our greater understanding of outcome after head injury could lead to improvements in rehabilitation.

Why have I been chosen?

You have been chosen to be part of a group of people without a head injury who will be compared with patients with a head injury and who are of similar age, gender and postcode.

Do I have to take part in the study?

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason.

What will happen to me if I take part?

The study involves an assessment that takes about 1-1.5 hours. This includes taking your consent, contact and health information. We will ask questions about your perception of stress and how in control of your health you feel. Finally we will calculate your allostatic load score by measuring your; height, weight, heart rate, blood pressure, breath volume, body mass index and take a sma blood sample (to measure blood markers of stress). There will be no risk to you when taking part in these research procedures. Your contact information will be stored incase we wish to contact you for further information regarding the study. However we wi only contact you if you give your consent for us to do so.

Will I be paid for taking part?

You will not be paid, however you will receive a voucher of £15 after the assessment to recompense you for your time.

Will my taking part in the study be kept confidential?

Your identity and personal information will be completely confidential and known only to research fellow Jessica Wainman-Lefley and Professor Tom McMillan who leads the Head Injury Research Group. Findings from the study may be published in academic journals however your data will not be identifiable. Data will be stored for up to 10 years as we may decide to use it agai for future research. It will be stored anonymously, in locked filing cabinets and then destroyed in confidential NHS shredders. You study data may be examined by authorised individuals from the study sponsor, NHS Greater Glasgow and Clyde, and/or the regulatory authorities to ensure the study has been conducted to the proper standards.

Who is organising and paying for the research?

The research is organised by the Head Injury Research Team from The University of Glasgow. If you have any questions about the study, please contact the research fellow Jessica Wainman- Lefley on 0141 211 0651.

Who do I contact if I have a complaint about the study?

Please contact the Research and Development Department on 0141 211 2184.

Who do I contact for independent information about the study?

Please contact Dr. Sarah Wilson on 0141 211 3921.

Thank you for your time and co-operation.

Version 3: 07/01/2013

Head injury participant consent form Sheet Study 1 and 2 (Chapter 5 and 6)

University of Glasgow

NHS Greater Glasgow and Clyde

Professor T.M.McMillan
Mental Health & Wellbeing
Gartnavel Royal Hospital
0141-211-0354

Patient Identification Number: ____

Consent Form (Head Injury Participant)

Title of Project: Allostatic load and health outcome in adults following head injury

Name of Researcher: Jessica Wainman-Lefley

Please Initial Box

1. I confirm that I have read and understand the information sheet dated 07/01/2013 (Version 3) for the above study. I have had the opportunity to consider the, information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from University of Glasgow, from regulatory authorities or from the NHS Board, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study ☐

5. I agree to take part in the above study, including having a blood sample taken. ☐

6. I agree to my data being retained for 10 years, including following loss of capacity. I understand this is for the purpose of future research and that all data will be destroyed confidentially after this period. ☐

7. I would like to be contacted about any future research. ☐

Name of Patient	Date	Signature
Name of Person taking consent	Date	Signature

Version 3.1: 20/05/2013

Comparison participant consent form Sheet Study 1 and 2 (Chapter 5 and 6)

University of Glasgow

NHS Greater Glasgow and Clyde

Professor T.M.McMillan
Mental Health & Wellbeing
Gartnavel Royal Hospital
0141-211-0354

Patient Identification Number: ____

Consent Form (Control Participant)

Title of Project: Allostatic load and health outcome in adults following head injury

Name of Researcher: Jessica Wainman-Lefley

Please Initial Box

1. I confirm that I have read and understand the information sheet dated 07/01/2013 (Version 3) for the above study. I have had the opportunity to consider the, information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected. ☐
3. I understand that data collected during the study, may be looked at by individuals from University of Glasgow, from regulatory authorities or from the NHS Board, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data. ☐
4. I agree to take part in the above study; including having a blood sample taken. ☐
5. I agree to my data being retained for 10 years, including following loss of capacity. I understand this is for the purpose of future research and that all data will be destroyed confidentially after this period. ☐
6. I would like to be contacted about any future research. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Version 3.1: 20/05/2013

Participant Information Sheet Study 3 (Chapter 7)

University of Glasgow | College of Medical, Veterinary & Life Sciences

NHS Greater Glasgow and Clyde

PARTICIPANT INFORMATION SHEET

An Investigation of Heterogeneity of Outcome Late after Severe Head Injury

You previously helped us in a research study on head injury and we would like you to help us once more. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
We are carrying out studies on head injury to investigate why outcome can be different in different people and why, in some, disabilities can change over time.

Why have I been chosen?
You have been chosen because you took part in a study with us before on head injury about ten years ago and seeing you again will help us to understand whether there has been any change in your health or abilities since we saw you last.

Do I have to take part?
It is up to you to decide whether or not to take part. You will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason.

What will happen to me if I take part?
You will be invited to attend for a single assessment lasting 60-90 minutes. This will involve: (i) a brief interview about recent health and history of head injury (ii) questionnaires about psychological wellbeing; (iii) tests of cognition such as concentration and memory; (iv) basic physical measurements such as blood pressure; (v) a 20ml blood sample (about four teaspoons) which we will use to check for markers we think may be relevant to outcome after a head injury. You will be offered vouchers for £20 that you can use in Tesco, Asda, Sainsburys or Boots to compensate you for your time.

Where will the assessment take place?
The assessment will take place in Glasgow. If you are unable to attend we can obtain some information by telephone. We would also like to contact you again for future follow-up study.

What do I have to do?
You just have to attend for the assessment and not have consumed alcohol on that day.

University of Glasgow | College of Medical, Veterinary & Life Sciences

NHS Greater Glasgow and Clyde

What are the possible disadvantages and risks of taking part?
There are no particular disadvantages to taking part. There can be temporary bruising at the needle site, but only occasionally do some people feel faint when a blood sample is being taken.

What are the possible benefits of taking part?
You will receive no direct benefit from taking part. The information collected in the study will give us a better understanding of any long term effects of head injury and may allow us to make recommendations for health service improvements.

Will my taking part in this study be kept confidential?
All information collected about you during the research will be kept strictly confidential. You will be identified by an identity number, and any information about you will have your name and address removed so that you cannot be recognised from it. Scientific publications arising from the research will not identify any individual. Findings from blood analyses will be copied to your GP.

What will happen to the results of the research study?
When the project is completed, the findings will be submitted for publication in peer reviewed international journals.

Who is organising and funding the research?
The research is organised by the University of Glasgow. The research is funded by the University of Glasgow, the Chief Scientist Office and by the Sackler Foundation.

Who has reviewed the study?
The project has been reviewed by the University of Glasgow College of Medical Veterinary and Life Sciences and by the West of Scotland NHS Ethics Committee.

Contact for Further Information
You can contact Lin MacLean: Linda.Maclean@glasgow.ac.uk (0141 211 3901) or Jessica Wainman-Lefley who will be arranging and carrying out the assessments: Jessica.Wainman-lefley@glasgow.ac.uk (0141 211 0651); or Professor Tom McMillan thomas.mcmillan@glasgow.ac.uk (0141 211 0354); who is organising the research.

Thank you for considering this request to take part in the study.

Participant consent form Sheet Study 3 (Chapter 7)

University of Glasgow | College of Medical, Veterinary & Life Sciences

NHS Greater Glasgow and Clyde

Participant ID Number: _____

CONSENT FORM

Title: An Investigation of Heterogeneity of Outcome Late after Severe Head Injury

		Please initial box
1)	I confirm that I have read and understand the information sheet dated 27/11/14 (Version 2) for the above study and have had the opportunity to ask questions.	☐
2)	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my legal rights being affected.	☐
3)	I agree to take part in the above study.	☐
4)	I agree that the researchers can obtain NHS records pertaining to any hospital admission that I have had.	☐
5)	I understand that anonymous data collected during the study, may be looked at by individuals from University of Glasgow, from regulatory authorities or from the NHS Board, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
6)	I agree to my blood analyses being copied to my GP	☐
7)	I agree to my data being retained for 10 years, including following loss of capacity. I understand this is for the purpose of future research ad that all data will be destroyed confidentially after this period.	☐
8)	I agree that I can be contacted about future studies on head injury.	☐

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

Institute of Health and Wellbeing
College of MVLS

27.11.14: V2

Retired International Rugby Player Participant Information Sheet Study 4 (Chapter 8)

University of Glasgow | College of Medical, Veterinary & Life Sciences

PARTICIPANT INFORMATION SHEET

The Long Term Health Outcomes of Participation in Elite Level Rugby

You are invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
We are carrying out studies to investigate the effects of exposure to head injury, in particular concussion late after injury in retired elite rugby players. We want to understand whether health is affected in the long term. We are recruiting and assessing retired rugby players (whether or not they have had a history of concussion) and will invite participants to consider taking part in a follow-up in a few years time. We are comparing rugby players to 'controls' who are similar in age and background.

Why have I been chosen?
You have been chosen because you are a either a retired rugby player that played at an elite level or are a 'control' who has not participated in organised contact sport beyond school level and have no history of head injury other than up to one concussion.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason.

What will happen to me if I take part?
You will be invited to attend for a single assessment lasting 60-90 minutes. This will involve:
(i) a brief interview about recent health and history of head injury (ii) questionnaires about psychological wellbeing; (iii) tests of cognition such as concentration and memory; (iv) basic physiological measurements such as blood pressure and lung capacity; (v) a 20ml blood sample (4 teaspoons) which we will test in this study for a variety of markers and genes we think may be of interest following head injury. In addition, we would like to store any leftover blood sample in the NHS Greater Glasgow and Clyde Bio-repository for future anonymised research studies.

Where will the assessment take place?
The assessment can take place in Glasgow, Edinburgh or London, whichever is most convenient for you. If you are unable to attend we can obtain some information by telephone. We would also like to contact you again for future follow-up study.

What do I have to do?
You just have to attend for the assessment and not have consumed alcohol on that day.

What are the possible disadvantages and risks of taking part?
There are no particular disadvantages to taking part. There can be temporary bruising at the needle site and occasionally some people can feel faint when a blood sample is being taken.

What are the possible benefits of taking part?
You will receive no direct benefit from taking part. The information collected in the study will give us a better understanding of any long term effects of repeated concussion in elite sportsmen and may help us to advise sports regulators, such as the Scottish Rugby Union, with regard to safer play.

Will my taking part in this study be kept confidential?
All information collected about you during the research will be kept strictly confidential. You will be identified by an ID number, and any information about you will have your name and address removed so that you cannot be recognised from it. Publications arising from the research will not identify any individual.

What will happen to the results of the research study?
When this project is completed, the findings will be presented to the Scottish Rugby Union to inform policy developments in this field. Thereafter, the data will be submitted for publication in peer reviewed international journals. We would retain part of the blood sample for future study.

Who is organising and funding the research?
The research is organised by the University of Glasgow. The research is funded by the University of Glasgow and by the Sackler Foundation.

Who has reviewed the study?
The project has been reviewed by the Scottish Rugby Union and by the University of Glasgow College of Medical Veterinary and Life Sciences Ethics Committee.

Contact for Further Information
You can contact Jessica Wainman-Lefley who will be arranging and carrying out the assessments: Jessica.Wainman.lefley@glasgow.ac.uk (0141 211 0651); or Professor Tom McMillan thomas.mcmillan@glasgow.ac.uk (0141 211 0354); or Dr Willie Stewart william.stewart@glasgow.ac.uk (0141 354 9535) who are organising the research.

Thank you for considering this request to take part in the study.

Retired International Rugby Player consent form Study 4 (Chapter 8)

University of Glasgow | College of Medical, Veterinary & Life Sciences

Centre Number:
Project Number:
Participant ID Number:

CONSENT FORM

The Long term Health Outcomes of Participation in Elite Level Rugby

	Please initial box
I confirm that I have read and understand the information sheet dated December 2013 (version 1) for the above study and have had the opportunity to ask questions	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected	☐
I agree that the researchers can obtain NHS records pertaining to any hospital admission with head injury that I have had	☐
I agree to take part in the above study	☐
I agree that I can be contacted about future related studies	☐

Name of participant	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

(1 copy for subject and 1 copy for researcher)

College of MVLS
Ethics Committee

December 2013: v1

Appendix C: Assessment tools

Glasgow Outcome Scale - Extended

Patient's name: _____ Date of interview: _____

Date of Birth: _____ Date of injury _____ Gender: M / F

Age at injury: _____ Interval post-injury: _____

Respondent: Patient alone ___ Relative/ friend/ carer alone ___ Patient + relative/ friend/ carer ___

Interviewer: _____

CONSCIOUSNESS

1. Is the head injured person able to obey simple commands, or say any words? ☐ 1 = No (VS) 2 = Yes

Anyone who shows ability to obey even simple commands, or utter any word or communicate specifically in any other way is no longer considered to be in the vegetative state. Eye movements are not reliable evidence of meaningful responsiveness. Corroborate with nursing staff. Confirmation of VS requires full assessment as in the Royal College of Physician Guidelines.

INDEPENDENCE IN THE HOME

2a Is the assistance of another person at home essential every day for some activities of daily living? ☐ 1 = No 2 = Yes
If "No" go to question 3a.

For a 'No' answer they should be able to look after themselves at home for 24 hours if necessary, though they need not actually look after themselves. Independence includes the ability to plan for and carry out the following activities: getting washed, putting on clean clothes without prompting, preparing food for themselves, dealing with callers, and handling minor domestic crises. The person should be able to carry out activities without needing prompting or reminding, and should be capable of being left alone overnight.

2b Do they need frequent help or someone to be around at home most of the time? ☐ 1 = No (Upper SD) 2 = Yes (Lower SD)

For a 'No' answer they should be able to look after themselves at home for up to 8 hours during the day if necessary, though they need not actually look after themselves.

2c Was assistance at home essential before the injury? ☐ 1 = No 2 = Yes

INDEPENDENCE OUTSIDE THE HOME

3a Are they able to shop without assistance? ☐ 1 = No (Upper SD) 2 = Yes

This includes being able to plan what to buy, take care of money themselves, and behave appropriately in public. They need not normally shop, but must be able to do so.

3b Were they able to shop without assistance before the injury? ☐ 1 = No 2 = Yes

4a Are they able to travel locally without assistance? ☐ 1 = No (Upper SD) 2 = Yes

They may drive or use public transport to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and instruct the driver.

4b Were they able to travel without assistance before the injury? ☐ 1 = No 2 = Yes

WORK

5a Are they currently able to work to their previous capacity? ☐ 1 = No 2 = Yes

If they were working before, then their current capacity for work should be at the same level. If they were seeking work before, then the injury should not have adversely affected their chances of obtaining work or the level of work for which they are eligible. If the patient was a student before injury then their capacity for study should not have been adversely affected.

5b How restricted are they? ☐
a) Reduced work capacity. 1 = a (Upper MD)
b) Able to work only in a sheltered workshop or non-competitive job, or currently unable to work. 2 = b (Lower MD)

5c Were they either working or seeking employment before the injury (answer 'yes') or were they doing neither (answer 'no')? ☐ 1 = No 2 = Yes

SOCIAL & LEISURE ACTIVITIES

6a Are they able to resume regular social and leisure activities outside home? ☐ 1 = No 2 = Yes

They need not have resumed all their previous leisure activities, but should not be prevented by physical or mental impairment. If they have stopped the majority of activities because of loss of interest or motivation then this is also considered a disability.

6b What is the extent of restriction on their social and leisure activities? ☐
a) Participate a bit less: at least half as often as before injury. 1 = a (Lower GR)
b) Participate much less: less than half as often. 2 = b (Upper MD)
c) Unable to participate: rarely, if ever, take part. 3 = c (Lower MD)

6c Did they engage in regular social and leisure activities outside home before the injury? ☐ 1 = No 2 = Yes

FAMILY & FRIENDSHIPS

7a Have there been psychological problems which have resulted in ongoing family disruption or disruption to friendships? ☐ 1 = No 2 = Yes

Typical post-traumatic personality changes: quick temper, irritability, anxiety, insensitivity to others, mood swings, depression, and unreasonable or childish behaviour.

7b What has been the extent of disruption or strain? ☐
a) Occasional - less than weekly 1 = a (Lower GR)
b) Frequent - once a week or more, but tolerable. 2 = b (Upper MD)
c) Constant - daily and intolerable. 3 = c (Lower MD)

7c Were there problems with family or friends before the injury? ☐ 1 = No 2 = Yes

If there were some problems before injury, but these have become markedly worse since injury then answer 'No' to Q7c.

RETURN TO NORMAL LIFE

8a Are there any other current problems relating to the injury which affect daily life? ☐ 1 = No (Upper GR) 2 = Yes (Lower GR)

Other typical problems reported after head injury: headaches, dizziness, tiredness, sensitivity to noise or light, slowness, memory failures, and concentration problems.

8b Were similar problems present before the injury? ☐ 1 = No 2 = Yes

If there were some problems before injury, but these have become markedly worse since injury then answer 'No' to Q8b.

Epilepsy:
Since the injury has the head injured person had any epileptic fits? No / Yes
Have they been told that they are currently at risk of developing epilepsy? No / Yes

What is the most important factor in outcome?
Effects of head injury ___ Effects of illness or injury to another part of the body ___ A mixture of these ___

Scoring: The patient's overall rating is based on the lowest outcome category indicated on the scale. Refer to Guidelines for further information concerning administration and scoring

1	Dead	☐
2	Vegetative State (VS)	
3	Lower Severe Disability (Lower SD)	
4	Upper Severe Disability (Upper SD)	
5	Lower Moderate Disability (Lower MD)	
6	Upper Moderate Disability (Upper MD)	
7	Lower Good Recovery (Lower GR)	
8	Upper Good Recovery (Upper GR)	

GLASGOW OUTCOME at DISCHARGE SCALE (GODS) v5

Name: **Date of Assessment:**

Date of Birth: **Time of Assessment:**

Ward: **Date of Injury:**

		Enter No	
Consciousness			
1a	Is the brain injured person conscious eg: able to obey simple commands, write, say any words or communicate by other means? • Could the absence of response be due to sedation? [Yes / No]* • Has the person been diagnosed as being in a vegetative state [Yes / No]* *Note: Corroborate with nursing staff.		1 – No 2 - Yes
Independence in the unit/ward			
2a	Does the person require nursing care or supervision every day for some activities of daily living? • For a 'No' answer they should be able to look after themselves for 24 hours although they need not actually look after themselves. • Independence includes the ability to plan for and carry out the following activities: getting washed, putting on clean clothes, able to prepare food for themselves (eg in the OT kitchen or during home leave), can appropriately deal with visitors/other patients and handle minor crises. • They should be able to carry out the above activities **without needing prompting**, supervision or reminding and should be believed to be capable of being left alone safely overnight. • They should not be a danger to themselves or others.		1 – No 2 - Yes
2b	Do they need frequent help or someone to be around for most of the time? • For a 'No' answer they should be thought able to look after themselves for up to 8 hours during the day if necessary, although they need not actually look after themselves.		1 – No (Upper SD) 2 – Yes (Lower SD)
2c	Was assistance at home essential before the injury?		1 – No 2 - Yes
2d	Is the person confused or disorientated? Has this been assessed using a PTA scale y/n : If yes name of scale: and score [ ] Could confusion or disorientation be a result of sedation? [Yes / No] • If the person is confused or disorientated for any reason, assume the answer is YES to 2a		1 – No (Upper SD) 2 – Yes (Lower SD)
2e	Does the person's behaviour cause severe disruption or difficulties with ward staff, visitors, other patients or carers • No: May be antisocial, irritable or passive/apathetic but are not a danger to self or others and do not require immediate or urgent attention • Yes: Severely disruptive or difficult and can be a danger to self or others. Requires immediate or urgent staff intervention and special measures to minimise risk such as additional staffing or regular sedation.		1 – No (Upper SD) 2 – Yes (Lower SD
Independence outside the unit/ward			
3a	Are they able to shop without assistance? • For example at the hospital shop could they plan what to buy, handle money appropriately and purchase a list of items successfully without assistance		1 – No (Upper SD) 2 - Yes
3b	Were they able to shop without assistance before the injury?		1 – No

			2 – Yes
4a	Are they able to travel outside the unit/ward safely without assistance? • They may walk, self propel a wheelchair, drive or use public transport to get around. Examples include visiting the hospital shop independently and safely or travelling home and returning on pass successfully and safely. Use of a taxi is sufficient if the person can phone for it themselves and instruct the driver.		1 – No (Upper SD) 2 - Yes
4b	Were they able to travel without assistance before the injury?		1 – No 2 - Yes
Work			
5a	Are they thought to be able to work to their previous capacity? • This pertains to ability to return to work within a week of discharge, and specifically to the advice they would be given at discharge. If they were working before, then their capacity for work should be at the same level. If they were seeking work before, then the injury should not have adversely affected their chances of obtaining work or the level of work for which they are eligible. If the patient was a student before their injury then their capacity for study should not have been adversely affected.		1 – No 2 - Yes
5b	How restricted do you think they are? a) Reduced work capacity b) Able to work only in a sheltered workshop or non-competitive job, or unable to work		1 = a (Upper MD) 2 = b (Lower MD)
5c	Were they either working or seeking employment before the injury (answer 'Yes') or were they doing neither (answer 'No')		1 – No 2 - Yes
Social and leisure activities			
6a	Are they able to participate in regular social and leisure activities in the ward? • This includes interacting socially and appropriately with other patients, therapists, staff and visitors. It includes taking an interest in others and in television or radio or newspapers or other reading. If they do not participate in the majority of social or leisure activities or therapy because of loss of interest or motivation then this is also considered a disability. • The person should be engaging in the activity intellectually and a judgement needs to be made this regard; eg check by simply by asking them what they are/have recently been watching, reading or listening to.		1 – No 2 - Yes
6b	What is the extent of restriction of their social and leisure capabilities? a) Mild: spend half the waking day or more demonstrating some social or intellectual interest b) Moderate: spend less than half the waking day demonstrating some social or intellectual interest c) Severe: rarely if ever, demonstrate an intellectual or social interest		1 = a (Lower GR) 2 = b (Upper MD) 3 = c (Lower MD
6c	Did they engage in regular social and leisure activities outside the home before the injury?		1 – No 2 - Yes
Social relationships			
7a	Are there psychological problems which result in disruption or difficulties in social relationships with ward staff, family, visitors, other patients or carers • Typical post brain injury personality changes: quick temper, irritability, aggression, anxiety, insensitivity to others, mood swings and depression, and unreasonable or childish behaviour		1 – No 2 - Yes
7b	What is the impact of the psychological problems?		

	a) Occasional problems that do not have any severe or persisting impact. b) Problems are evident, but are tolerable and occur less than daily. Causes strain but this is intermittent. c) A cause of continual and severe strain and upset on a daily basis. Could lead or has led to breakdown in family relationships.		1 = a (Lower GR) 2 = b (Upper MD) 3 = c (Lower MD
7c	Were there problems of this kind before the injury? • If there were some problems before the injury but these have become remarkably worse since the injury then answer 'No' to 7c		1 – No 2 - Yes
Return to normal life			
8a	Are there any other current problems relating to the injury which have a negative impact on daily life? • Other typical problems reported after brain injury: headaches, dizziness, tiredness, sensitivity to noise or light, slowness, memory failures, and concentration difficulties		1 – No (Upper GR) 2 – Yes (Lower GR)
8b	Were similar problems present before the injury? • If there were some problems before injury, but these have become markedly worse since the injury then answer 'No' to 8b		1 – No 2 - Yes

What is the most important factor affecting progress (tick)?

Effects of head injury ___ Effects of illness or injury to another part of the body ___ A mixture of these ___

Scoring: The overall rating is based on the lowest outcome category indicated on the scale*.

Refer to the GODS Guidelines for further information concerning administration and scoring

1 Dead
2 Not conscious
3 Lower Severe Disability (Lower SD)

4 Upper Severe Disability (Upper SD)
5 Lower Moderate Disability (Lower MD)
6 Upper Moderate Disability (Upper MD)
7 Lower Good Recovery (Lower GR)
8 Upper Good Recovery (Upper GR)

*Patients scoring less than 7 should not be discharged to the community without care support.

Box 4

The Alcohol Use Disorders Identification Test: Interview Version

Read questions as written. Record answers carefully. Begin the AUDIT by saying "Now I am going to ask you some questions about your use of alcoholic beverages during this past year." Explain what is meant by "alcoholic beverages" by using local examples of beer, wine, vodka, etc. Code answers in terms of "standard drinks". Place the correct answer number in the box at the right.

1. How often do you have a drink containing alcohol?
   (0) Never [Skip to Qs 9-10]
   (1) Monthly or less
   (2) 2 to 4 times a month
   (3) 2 to 3 times a week
   (4) 4 or more times a week

2. How many drinks containing alcohol do you have on a typical day when you are drinking?
   (0) 1 or 2
   (1) 3 or 4
   (2) 5 or 6
   (3) 7, 8, or 9
   (4) 10 or more

3. How often do you have six or more drinks on one occasion?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily
   Skip to Questions 9 and 10 if Total Score for Questions 2 and 3 = 0

4. How often during the last year have you found that you were not able to stop drinking once you had started?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

5. How often during the last year have you failed to do what was normally expected from you because of drinking?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

7. How often during the last year have you had a feeling of guilt or remorse after drinking?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

9. Have you or someone else been injured as a result of your drinking?
   (0) No
   (2) Yes, but not in the last year
   (4) Yes, during the last year

10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?
    (0) No
    (2) Yes, but not in the last year
    (4) Yes, during the last year

Record total of specific items here

If total is greater than recommended cut-off, consult User's Manual.

MULTIDIMENSIONAL HEALTH LOCUS OF CONTROL SCALE (FORM A)

Name: .....

Date: ..... **Record Number:** .....

This is a questionnaire designed to determine the way in which different people view certain important health-related issues. Each item is a belief statement with which you may agree or disagree. Beside each statement is a scale which ranges from strongly disagree (1) to strongly agree (6). For each item we would like you to circle the number that represents the extent to which you disagree or agree with the statement. The more strongly you agree with a statement, then the higher will be the number you circle. The more strongly you disagree with a statement, then the lower will be the number you circle. Please make sure that you answer every item and that you circle **only one** number per item. This is a measure of your personal beliefs: obviously, there are no right or wrong answers.

Please answer these items carefully, but do not spend too much time on any one item. As much as you can, try to respond to each item independently. When making your choice, do not be influenced by your previous choices. It is important that you respond according to your actual beliefs and not according to how you feel you should believe or how you think we want you to believe.

	Strongly disagree	*Moderately disagree*	*Slightly disagree*	*Slightly agree*	*Moderately agree*	*Strongly agree*
1. If I get sick, it is my own behaviour which determines how soon I get well again.	1	2	3	4	5	6
2. No matter what I do, if I am going to get sick, I will get sick.	1	2	3	4	5	6
3. Having regular contact with my doctor is the best way for me to avoid illness.	1	2	3	4	5	6
4. Most things that affect my health happen to me by accident.	1	2	3	4	5	6
5. Whenever I don't feel well, I should consult a medically trained professional.	1	2	3	4	5	6
6. I am in control of my health.	1	2	3	4	5	6
7. My family has a lot to do with my becoming sick or staying healthy.	1	2	3	4	5	6
8. When I get sick, I am to blame.	1	2	3	4	5	6
9. Luck plays a big part in determining how soon I will recover from an illness.	1	2	3	4	5	6
10. Health professionals control my health.	1	2	3	4	5	6
11. My good health is largely a matter of good fortune.	1	2	3	4	5	6
12. The main thing which affects my health is what I myself do.	1	2	3	4	5	6
13. If I take care of myself, I can avoid illness.	1	2	3	4	5	6
14. When I recover from an illness, it's usually because other people (for example, doctors, nurses, family, friends) have been taking good care of me.	1	2	3	4	5	6
15. No matter what I do, I'm likely to get sick.	1	2	3	4	5	6
16. If it's meant to be, I will stay healthy.	1	2	3	4	5	6
17. If I take the right actions, I can stay healthy.	1	2	3	4	5	6
18. Regarding my health, I can only do what my doctor tells me to do.	1	2	3	4	5	6

PERCEIVED STRESS SCALE

Name: .....

Date: ..... **Record Number:** .....

Instructions

The questions in this scale ask you about your feelings and thoughts during the last month. In each case, you will be asked to indicate how often you felt or thought a certain way. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer each question fairly quickly. That is, don't try to count up the number of times you felt a particular way, but rather indicate the alternative that seems like a reasonable estimate.

For each question choose from the following alternatives:

0 = never
1 = almost never
2 = sometimes
3 = fairly often
4 = very often

1. In the last month, how often have you been upset because of something that happened unexpectedly? ☐
2. In the last month, how often have you felt that you were unable to control the important things in your life? ☐
3. In the last month, how often have you felt nervous and stressed? ☐
4. In the last month, how often have you dealt with irritating life hassles? ☐
5. In the last month, how often have you felt that you were effectively coping with important changes that were occurring in your life? ☐
6. In the last month, how often have you felt confident about your ability to handle your personal problems? ☐
7. In the last month, how often have you felt that things were going your way? ☐
8. In the last month, how often have you found that you could not cope with all the things you had to do? ☐
9. In the last month, how often have you been able to control irritations in your life? ☐
10. In the last month, how often have you felt that you were on top of things? ☐
11. In the last month, how often have you been angered because of things that happened that were outside of your control? ☐
12. In the last month, how often have you found yourself thinking about things that you have to accomplish? ☐
13. In the last month, how often have you been able to control the way you spend your time? ☐
14. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them? ☐

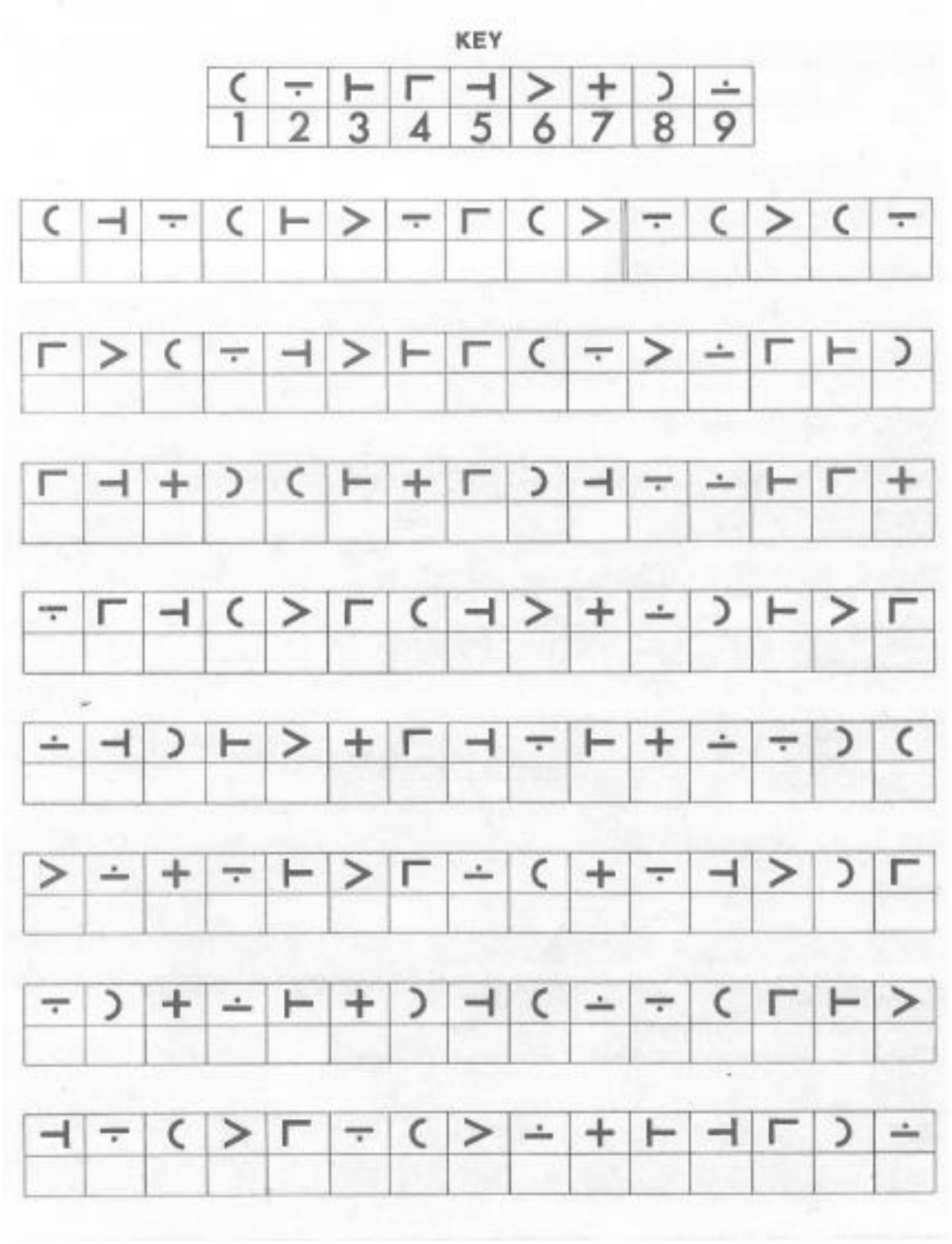
The Stroop Colour-Word Test form

Form C-W Stimulus Sheet

BLUE	GREEN	RED	GREEN
GREEN	BLUE	GREEN	TAN
RED	RED	BLUE	RED
TAN	BLUE	TAN	TAN
GREEN	TAN	RED	BLUE
BLUE	RED	TAN	TAN
RED	GREEN	BLUE	GREEN
TAN	TAN	TAN	RED
RED	GREEN	RED	GREEN
BLUE	BLUE	BLUE	RED
RED	RED	RED	BLUE
TAN	TAN	TAN	GREEN
BLUE	GREEN	BLUE	TAN
TAN	RED	GREEN	BLUE
RED	BLUE	TAN	GREEN
BLUE	GREEN	BLUE	RED
GREEN	RED	TAN	GREEN
TAN	GREEN	BLUE	TAN
GREEN	BLUE	RED	GREEN
TAN	TAN	GREEN	BLUE
RED	GREEN	BLUE	TAN
BLUE	RED	GREEN	BLUE
RED	TAN	BLUE	GREEN
TAN	BLUE	GREEN	RED
RED	TAN	RED	BLUE
TAN	RED	GREEN	GREEN
GREEN	TAN	TAN	RED
TAN	GREEN	RED	BLUE

PAR Psychological Assessment Resources, Inc./P.O. Box 998/Odessa, FL 33556/TOLL-FREE 1-800-331-TEST

The Symbol Digit Modalities Test



The Wechsler Memory Scale-Revised test of Narrative Memory

LOGICAL MEMORY I Administer both stories. Score 1 point for each correct item (see Appendix A in Manual for Scoring Criteria).	Score
Story A	
Anna / Thompson / of South / Boston /, employed / as a cook /	_____
in a school / cafeteria /, reported / at the City Hall / Station /	_____
that she had been held up / on State Street / the night before /	_____
and robbed / of fifty-six dollars /. She had four /	_____
small children /, the rent was due /, and they had not eaten /	_____
for two days /. The police / touched by the woman's story /,	_____
took up a collection / for her /.	_____
Max. = 25 Total Story A	
Story B	
Robert / Miller / was driving / a ten-ton / truck /	_____
down a highway / at night / in the Mississippi / Delta /,	_____
carrying eggs to Nashville /, when his axle / broke /.	_____
His truck skidded / off the road /, into a ditch /.	_____
He was thrown / against the dashboard / and was badly shaken /	_____
There was no traffic / and he doubted that help would come /.	_____
Just then his two-way radio / buzzed /. He quickly answered /,	_____
"This is Grasshopper /."	_____
Max. = 25 Total Story B	
Max. = 50 Total Sum of Stories A + B	

Record clock time _____

The Wechsler Memory Scale-Revised test of Verbal Paired Associates

VERBAL PAIRED ASSOCIATES I If the examinee answers all eight items correctly on the third set, discontinue the subtest. Otherwise, present Sets IV, V, and VI until all eight items are correct.

SET I	Recall	Easy	Hard
Metal—Iron	Fruit		
Baby—Cries	Obey		
Crush—Dark	Rose		
School—Grocery	Baby		
Rose—Flower	Cabbage		
Obey—Inch	Metal		
Fruit—Apple	School		
Cabbage—Pen	Crush		
	Total		

SET II	Recall	Easy	Hard
Rose—Flower	Cabbage		
Cabbage—Pen	Baby		
Obey—Inch	Metal		
Fruit—Apple	School		
School—Grocery	Rose		
Metal—Iron	Crush		
Crush—Dark	Fruit		
Baby—Cries	Obey		
	Total		

SET III	Recall	Easy	Hard
Baby—Cries	Obey		
Crush—Dark	Fruit		
School—Grocery	Baby		
Rose—Flower	Metal		
Cabbage—Pen	Crush		
Fruit—Apple	School		
Obey—Inch	Rose		
Metal—Iron	Cabbage		
	Total		

SET IV	Recall	Easy	Hard
Crush—Dark	School		
Cabbage—Pen	Metal		
Fruit—Apple	Obey		
Obey—Inch	Crush		
Baby—Cries	Fruit		
Rose—Flower	Baby		
Metal—Iron	Cabbage		
School—Grocery	Rose		
	Total		

SET V	Recall	Easy	Hard
Fruit—Apple	Rose		
School—Grocery	Crush		
Rose—Flower	Baby		
Cabbage—Pen	Metal		
Metal—Iron	Obey		
Crush—Dark	Cabbage		
Baby—Cries	School		
Obey—Inch	Fruit		
	Total		

SET VI	Recall	Easy	Hard
Metal—Iron	Baby		
Rose—Flower	Fruit		
Crush—Dark	Cabbage		
Baby—Cries	Rose		
Obey—Inch	School		
Fruit—Apple	Obey		
Cabbage—Pen	Crush		
School—Grocery	Metal		
	Total		

Total Sets I-III	Max. Easy = 12	Max. Hard = 12	Max. Total = 24	

VISUAL REPRODUCTION I Use VRI Copying Sheet.

Hand used: ____ Right ____ Left

Item	Score (see Visual Reproduction Scoring Summary)	
1		Observations:
2		
3		
4		
Max. = 41 Total		

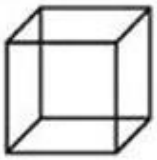
The Montreal Cognitive Assessment

MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube



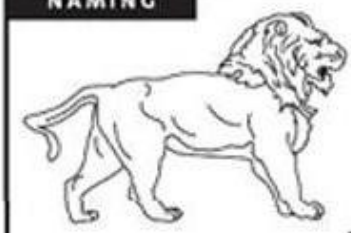
[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING



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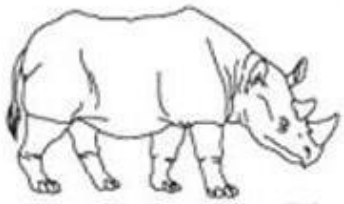

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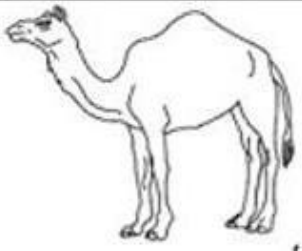

[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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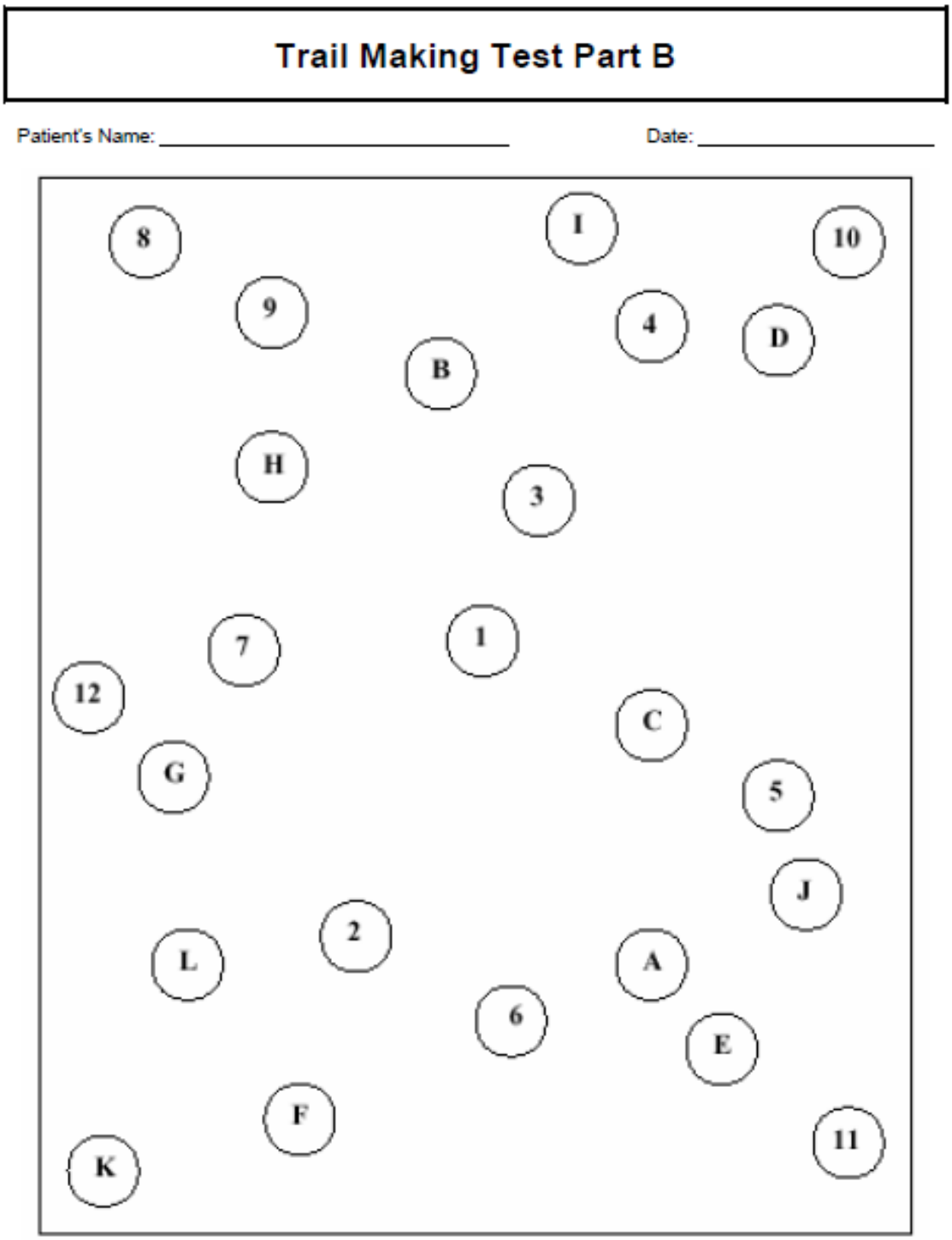
Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

www.mocatest.org

The Trail Making Test: Part B



The Auditory Verbal Learning Task

ID No: Initials: Date: Researcher:

Auditory Verbal Learning Task

- I am going to read a list of words. Listen carefully because, when I stop, I would like you to tell me as many of the words as you can remember. It doesn't matter in what order you repeat them. Just tell me as many words as you can remember. Ready?
(read words at a rate of 1 every second)

Drum		Parent		Nose	
Curtain		Moon		Turkey	
Bell		Garden		Colour	
Coffee		Hat		House	
School		Farmer		River	

Trial 1 Score (/15) ☐

- Now I am going to read that same list of words again and, again, when I stop, I want you to tell me as many of the words as you remember, *including all the words that you told me the first time*. Again, you can tell me the words in any order. Ready? (read list again)

Drum		Parent		Nose	
Curtain		Moon		Turkey	
Bell		Garden		Colour	
Coffee		Hat		House	
School		Farmer		River	

Trial 2 Score (/15) ☐

- Now I am going to read the list to you again. As before, when I stop, I want you to tell me as many of the words as you remember, in any order, *including all the words that you have already told me.*

Drum		Parent		Nose	
Curtain		Moon		Turkey	
Bell		Garden		Colour	
Coffee		Hat		House	
School		Farmer		River	

Trial 3 Score (/15) ☐

ID No: Initials: Date: Researcher:

- Now I am going to read the list to you again. As before, when I stop, I want you to tell me as many of the words as you remember, in any order, *including all the words that you have already told me.*

Drum		Parent		Nose	
Curtain		Moon		Turkey	
Bell		Garden		Colour	
Coffee		Hat		House	
School		Farmer		River	

Trial 4 Score (/15) ☐

- Now I am going to read the list to you again. As before, when I stop, I want you to tell me as many of the words as you remember, in any order, *including all the words that you have already told me.*

Drum		Parent		Nose	
Curtain		Moon		Turkey	
Bell		Garden		Colour	
Coffee		Hat		House	
School		Farmer		River	

Time Finished: **Trial 5 Score (/15)** ☐

(Allow 30mns before delayed recall)

Total Score (/75) ☐

Delayed Auditory Verbal Learning Task

Remember that list of words that I read to you earlier? I read the list to you five times and asked you to repeat as many as you could remember each time? Well, I'd like you to tell me as many of those words as you can remember now.

Drum		Parent		Nose	
Curtain		Moon		Turkey	
Bell		Garden		Colour	
Coffee		Hat		House	
School		Farmer		River	

Delayed Score (/15) ☐

History of concussion form for Study 4 (Chapter 8)

V2/Dec13/tm

Head Injury Assessment Form

1. What position(s) did you play in rugby?

2. What age did you start playing rugby?

3. How many years did you play rugby for?

4. When did you stop playing rugby?

5. How many international matches did you play in (estimate)?

6. Have you ever experienced any of the following symptoms after a blow or bang to the head? [We just want a single Yes /No].....

Headache
nausea/vomiting
drowsiness
confusion
difficulty remembering, poor concentration, feeling in a 'fog'
dizziness, unsteadiness on your feet
ringing in your ears or sensitivity to noise
blurred or disturbed vision , seeing stars
irritability, being more emotional, being anxious
difficulty sleeping

If YES how many times? .....

[If they have difficulty estimating; ask if more or less than 3 times? More or less than 5 times? More or less than 10 times? More or less than 20 times and increase by 10 etc until you get the answer]

V2/Dec13/tm

7. Have you ever been knocked out **AND** then admitted to hospital following a bang to the head? Y/ N

[Most likely this will be a small number; get information as clearly as possible for each occasion]

If Yes, list below:

Duration LoC	Approx duration admitted	Year of injury	Duration time off playing rugby	Which Hospital or where	Injury playing Rugby Y/N? If no – what were the circumstances

8. Have you ever been knocked out and **not** attended hospital Y/ N

If Yes: How many times:

[If they have difficulty estimating; ask if more or less than 3 times? More or less than 5 times? More or less than 10 times? More or less than 20 times and increase by 10 etc]

If any of these was for more than 5 minutes detail below:

Duration LoC	Approx duration admitted	Year of injury	Duration time off playing rugby	Which Hospital or where	Injury playing Rugby Y/N? If no – what were the circumstances

V2/Dec13/tm

9. How many times in total, including those already mentioned- have you been confused or disorientated for an hour or more after a blow or bang to the head or have gaps in your memory lasting an hour or more after a blow or bang to the head?

   0; 1; 2; 3; 4; 5; 6-10; 11-20; 21-30; 31-50; more than 50

10. Other than rugby, is there any other sport you have taken part in regularly? Have you ever had a blow to the head in any of these where you had any of the symptoms we discussed before? If yes ...how often [check whether they already included these above]

Q 1-5 rugby history
Q 6 overall number of HI
Q 7-9 estimate frequency of moderate and severe head injury
Q5-10 other sports history HI

Appendix D: Supplementary data

Outcome category (assigned number)	**Description of GOS-E criteria**	**Description of GODS criteria**
Upper Good Recovery (8)	• Are without problems related to effects of the head injury, or with symptoms that are having no effect on their daily lives.	• Are without problems related to effects of the head injury, or with symptoms that are having no effect on their daily lives.
Lower Good Recovery (7)	• Has minor problems that are having a negative effect on their daily lives e.g. headaches, concentration difficulties, dizziness, tiredness, slowness, sensitivity to noise or light and memory failures. • Restriction of social and leisure capabilities are "mild: spend half the waking day or more demonstrating some social or intellectual interest". E.g. loss of interest or motivation in activities they engaged in before the injury. • Psychological problems that are having an impact on social relationships are "occasional problems that do not have any severe or persisting impact". E.g. mood swings, anxiety, irritability, depression, insensitivity to others, unreasonable or childish behaviour, quick temper and aggression.	• Has minor problems that are having a negative effect on their daily lives e.g. headaches, concentration difficulties, dizziness, tiredness, slowness, sensitivity to noise or light and memory failures. • Restriction of social and leisure capabilities are "mild: spend half the waking day or more demonstrating some social or intellectual interest". E.g. taking an interest in the television, radio, newspapers, talking to staff and other patients, engaging in therapy. The person should also be engaging in the activity intellectually. • Psychological problems that are having an impact on social relationships are "occasional problems that do not have any severe or persisting impact". E.g. mood swings, anxiety, irritability, depression, insensitivity to others, unreasonable or childish behaviour, quick temper and aggression.
Upper Moderate Disability (6)	• Has a reduced work capacity compared with prior to injury. • Restriction of social and leisure activities outside the home, spending less than half the waking day demonstrating some social or intellectual interest.	• Has a reduced work capacity compared with prior to injury. • Restriction of social and leisure activities on the ward, spending less than half the waking day demonstrating some social or intellectual interest. E.g. taking an interest in the television, radio, newspapers, talking to

		staff and other patients, engaging in therapy.
	• Psychological problems that are having an impact on social relationships are "frequent, once a week, but tolerable". E.g. mood swings, anxiety, irritability, depression, insensitivity to others, unreasonable or childish behaviour, quick temper and aggression.	• Psychological problems that are having an impact on social relationships are "evident, but are tolerable and occur less than daily; causing strain but this is intermittent". E.g. mood swings, anxiety, irritability, depression, insensitivity to others, unreasonable or childish behaviour, quick temper and aggression.
Lower Moderate Disability (5)	• Able to work only in a sheltered workshop or non-competitive job, or currently unable to work. • They rarely if ever, demonstrate an intellectual or social interest in social and leisure activities outside the home. • Psychological problems that are having an impact on social relationships are "constant, on a daily basis and intolerable and could lead to breakdown in family relationships".	• Able to work only in a sheltered workshop or non-competitive job, or currently unable to work. • They rarely if ever, demonstrate an intellectual or social interest in social and leisure activities in the ward. • Psychological problems that are having an impact on social relationships "cause continual and severe strain and upset on a daily basis and could lead to breakdown in family relationships".
Upper Severe Disability (4)	Questions concerning independence in and outside of the home. • They can look after themselves for 8 hours at home, but not over the space of 24 hours in the home e.g. preparing food, putting on clean clothes, dealing with callers, and handling minor domestic crises, unsupervised, unprompted and not needing reminding. • Cannot travel locally without support, e.g. safely use public transport, or phone for a taxi	Questions concerning independence in and outside of the ward or unit. • They can look after themselves for 8 hours on the ward, but not over the space of 24 hours; requiring nursing care or supervision on the ward e.g. getting washed and dressed, preparing food in the OT kitchen, dealing appropriately with other patients and visitors, and dealing with minor crises, unsupervised, unprompted and not needing reminding. • Cannot travel outside the ward/unit safely without assistance e.g. walk or self-propel a wheelchair, either to

	themselves and instruct the driver. • Cannot <u>shop</u> without support, e.g. plan what to buy, use money and behave appropriately in public.	visit the hospital shop independently, or travel home on pass and return safely and successfully using public transport or taxis. • Cannot <u>shop</u> without support, e.g. plan what to buy, use money and behave appropriately in public at the hospital shop.
Lower Severe Disability (3)	• Person needs frequent help or someone to be around for most of the time e.g. unable to look after themselves for up to 8 hours during the day; they require support with preparing food, putting on clean clothes without prompting, dealing with callers, or handling minor domestic crises. • Behaviour is severely disruptive, causing them to be a danger to themselves or others • They are confused or disorientated.	• Person needs frequent help or someone to be around for most of the time e.g. unable to look after themselves for up to 8 hours during the day; they require support or supervision with getting washed and putting on new clothes unprompted, preparing food in the OT kitchen, dealing appropriately with other patients and visitors, and with minor crises. • Behaviour is severely disruptive, causing them to be a danger to themselves or others. Requires staff intervention. • They are confused or disorientated.
Not conscious (2)	• They are unconscious e.g. unable to communicate by any means or obey simple commands.	• They are unconscious e.g. unable to communicate by any means or obey simple commands.
Dead (1)	• Person is dead	• Person is dead.

Table 1 – Description of disability criteria of The Glasgow Outcome Scale- Extended and the Glasgow Outcome at Discharge Scale

Author	Biomarkers	Immune	Neuroendocrine	Cardiovascular	Metabolic	Anthropometric	Other
Allsworth 2005	11	3: Alb, CRP, CR	*	3: SBP, DBP, FEV	4: TC, HDL, GH, Trig	1: BMI	
Barboza 2014	14	4: IGF1, CRP, fib, IgE	2: salivary cort (2TP)	4: HR, FEV, SBP, DBP	4: HDL, LDL, trig, GH	*	
Bellatorre 2011	11	3: CRP, fib, Alb	*	3: SBP, DBP, HR	4: TC, HDL, Trig, Pgluc	1: WHr	
Bellingrath 2008	17	4: CRP, fib, TNFα, D-dimer	4: DHAS, Cort, EPI, NE	2: SBP, DBP	5: GH, HDL, TC, trig, Fgluc	2: BMI, WhR	
Brody 2014a, 2013a, 2013b	7	1: CRP	3: Cort, EPI, NE	2: SBP, DBP	*	1:BMI	
Brody 2014b, 2013c	6	*	3: Cort, EPI, NE	2: SBP, DBP	*	1:BMI	
Carroll 2013	18	3:CRP, fib, IL-6	4: urinary NE, EPI, Cort (2TP)	3: SBP, DBP, HR	4: HDL, LDL, trig, gluc, insulin	waist CC	2: low and high freq HRV
Chen 2014	6	*	3: Cort, NE, EPI	2: SBP, DBP	*	1:BMI	
Clark 2014	9	2: CRP, IL6	*	2: SBP, DBP	GH, trig, TC, HDL	WHr	
De Castro 2010	6	1: CRP	1: Cort	2: SBP, DBP	*	2: BMI, WhR	
Deuster 2011	5	1: CRP		2: SBP, DBP	1: Insulin	1: Body fat	
Dich 2014, 2015a	9	2: CRP, IL-6	*	SBP, DBP	4: Fasting insulin, HDL, LDL, trig	1 BMI	
Dich 2015b	9	2:CRP, IL6	*	SBP, DBP	4:Trig, HDL, TC, GH	1:WHr	
Doamekpor 2013	8	3:CRP, CR, sAlb	*	3: SBP, DBP, HR	2:HDL, TC	*	
Duru 2012	10	2: Alb, CRP	*	2: SBP, DBP	4: TC, trig, HCY, GH, eGFR	1:WHr	
Evans 2014	10	2: Alb, CRP	*	4: SBP, DBP, HR,	3:HDL, GH, TC, HCY	1: BMI	
Gale 2015	9	2: Alb, CRP	*	3: SBP, DBP, HR	3: TC, HDL, GH	1:WHr	
Gallo 2010	12	3: CRP, IL6, TNFα	3: NE, EPI, Cort	2: SBP, DBP	3: HDL, rTC/HDL, GH	2 BMI, waist CC	
Gay 2015	10	3: CRP, IL-6, TNFα	*	3: SBP, DBP, HR	3: TC, HDL, GH	1: BMI	

Geronimus 2006	10	3: CRP, CRc	*	2: SBP, DBP	4: GH, trig HCY, TC	1: BMI	
Glover 2006	10	*	4: DHAS, Cort, NE, EPI	2: SBP, DBP	3: HDL, TC, GH	1: BMI	
Goertzal 2006	11	3: CRP, Alb, IL6	5: ALDO, sCort, DHAS, NE, EPI	2: SBP, DBP	*	1:WHr	
Gustafsson 2011, 2012, 2014	12	1: CRP	1: Cort	2: SBP, DBP	6: Fgluc, TC, HDL, trig, APOA1, ApoB	2: BMI, WhR	
Hampson 2009	7	*	*	2: SBP, DBP	5: TC, Trig, Fgluc, UP, rTC/HDL	2: BMI, WhR	
Hansen 2014	14	3: CRP, IL6, TNFα	*	2: SBP, DBP	5: gluc, GH, HDL, LDL, trig	3: BMI, WhR Body fat,	
Hasson 2009	12	*	1: DHAS	3: SBP, DBP, HR	6: GH, TC, HDL, LDL, rLDL/HDL, trig, prolactin	1:WHr	
Hux 2015	10	3: CRP, Alb, IL6	*	3: SBP, HR, PP	3: TC, HDL, trig	1: BMI	
Hux 2014	9	3: CRP, Alb, Cr	*	2: SBP, DBP	3: GH, HDL, TC	1: BMI	
Jung 2014	11	3: CR, IL-6 and TNFα	3: Cort, NE, EPI	3: SBP, DBP, HR	CRu	2: BMI, body fat	
Juster 2011, 2012	15	3: CRP, amylase, fib	2: Cort, DHAS	2: SBP, DBP	7: CR, Alb, TC, Insulin, GH, Trig, HDL	1:WHr	
Juster 2013	15	3:CRP, IL6, TNFα	1: Cortl	3: SBP, DBP, HR	6: Insulin, gluc, HOMA, HDL, LDL, Trig	2: BMI, WhR	
Juster 2013	21	4: IL6, TNFα, CRP, fib	6: EPI, NE, DA, Cort (2TP), DHAS	2: SBP, DBP	7: sAlb, CRu, insulin, GH, TC, HDL, trig	2: BMI, WhR	
Kaestner 2010	10	3: CRP, CRc	*	2: SBP, DBP	4: GH, trig, TC, HCY, Alb	1: BMI	
Kinnunen 2005	8	*	2: DHAS, EPI	2: SBP, DBP	3: HDL, GH, trig	1:WHr	
Krause 2012	11	2: CRP, IL6	3: Cort, NE, EPI	2: SBP, DBP	3: TC, HDL, GH	1:WHr	
Langelaan 2007	8	1: CRP	*	2: SBP, DBP	4: TC, HDL, gluc, HbA1C	1: BMI	
Li 2007	11	*	*	*	9: HDL, LDL, TC, GH, Trig, HOMA- IR,	2: BMI, WhR	

					HOMA- β, apM1, Visfatin		
Lindfors 2006	7	*	*	3: SBP, DBP, FEV	3: TC, HDL, GH	1:WHr	
Lipowicz 2013	11	2: CRc, ESR	3: BU, ALP, TPP	3: SBP, DBP, FEV	2:Gluc, TC	1: % fat distribution	
Masterson 2015	6	1: CRP	*	2: SBP, DBP	3: Trig, HDL, glucose	1: waist circumference	
Mair 2011	16	9: CRP, IL-6, TNFα, IL-1, IL-10, HSV-1, EBV–VCA, EBV–EA, EBNA	*	2: SBP, DBP	4: rTC/HDL, GH, Trig, HDL	1: BMI	
McCaffery 2012	10	2: IL6- CRP	*	2: SBP, DBP	4: fasting gluc, insulin, HDL, trig	2: BMI, WhR	
Morrison 2013	10	3:CRP, CR, Alb	*	3: SBP, HR, PP	4: TC, HDL, GH, HCY	*	
Naswall 2011	8	*	*	4: SBP, DBP, HR, FEV	3: GH, HDL, TC	1:WHr	
Nicod 2014	20	4: CRP, IL-6, IL-1β, TNFα	*	3: SBP, DBP, HR	9: insulin, gluc, leptin, adiponectin, HDL, TC, Trig, ApoB, HCY	2: BMI, WhR	Oxidative stress (2): GGT, UA
Nugent 2015	13	1 :CRP	3: DHAS, cort, EPI	3: SBP, DBP, HR	3: HDL, TC, GH	2: BMI, WhR	
Robertson 2015	9	2:CRP, Alb	*	3: SBP, HR, PP	3: GH, TC, HDL	1:WHr	
Rosenberg 2014	9	2:CRP, Alb	*	3: SBP, HR, PP	3: TC, HDL, GH	1:WHr	
Schnorpfeil 2003	14	3: Alb, CRP, TNFα	4: Cort, DHAS, NE, EPI	2: SBP, DBP	3: GH, TC, HDL	2: BMI, WhR	
Schulz 2012, 2013	7	*	*	2: SBP, DBP	4: HDL, TC, Gluc, trig	1:WHr	
Seeman 2010	18	3: CRP, IL6, fib	4: Cort (2TP), NE, EPI	3: SBP, DBP, HR,	5: HDL, LDL, trig, insulin, Fgluc	1: waist CC	2: HRV (low/ high freq power)

Seeman 2014	17	3: CRP, IL-6, fib	3: NE, EPI, Cort	3: SBP, DBP, HR	5: HDL, LDL, trig, gluc, insulin	1: waist CC	2: HRV (low/ high freq power)
Singer 1999	9	*	4: DHAS, Cort, NE, EPI	2: SBP, DBP	3: HDL, GH, rTC/HDL	1:WHr	
Sjors 2013	13	1: CRP	1: Cort	2: SBP, DBP	6: HDL, LDL, rTC/HDL, Trig, Insulin, Gluc, GH	2: BMI, WhR	
Solis 2015	14	3: IGF1, CRP, fib	2: Cort (2TP)	4: SBP, DBP, HR, FEV	4: HDL, LDL, trig, GH	*	
Song 2014	11	1: CRP	4: DHAS, cort, NE, EPI	2: SBP, DBP	3: GH, HDL, rTC/HDL	1:WHr	
Sun 2007	13	2:Fib, CRP	2: Cort, adnephrin	2: SBP, DBP	3: GH, TG, rTC/HDL, IGR	2: BMI, WHr	
Tanaka 2011	9	CRP	*	2: SBP, DBP	6: HDL, Chol, TC, Trig, HGB, insulin resis	1: WHr	
Tomfohr 2013	11	2:CRP, IL6	3: NE, EPI Cort	2: SBP, DBP	3: Fgluc, HDL, rTC/HDL	1: WHr	
Upchurch 2015	11	2:Fib, CRP	DHAS	2: SBP, DBP	4: TC, HDL, trig, gluc	2: BMI, WHr	
Upchurch 2015	10	2: Alb, CRP	*	4: SBP, DBP, HR, HCY	3: GH, HDL, TC	1: BMI	
Vie 2014	10	1: CRP	*	3: HR, SBP, DBP	4: TC, trig, HDL, gluc	2: BMI, WHr	
Von Thiele 2006	13	*	1: DHAS	3: HR, SBP, DBP	8: trig, gluc, GH, HDL, LDL, Chol, rLDL/HDL, prolactin, TC	1: WHr	
Wallace 2013	9	*	*	2: SBP, DBP	6: TC, HDL, LDL, trig, gluc, insulin	1: waist CC	
Wallace 2013	9	2: Fib, WBC	*	2: SBP, DBP	4: TC, trig, gluc, insulin	1:BMI	
Wallace 2013	5	*	2: DHAS, Cort	1: SBP	*	2: GH, TC	
Westerlund 2012, 2013	12	1: CRP	1: Cort	2: SBP, DBP	6: Fgluc, TC, HDL, trig APOA1, ApoB	2: BMI, WHr	
Widom 2015	9	3: CC, Alb, CRP	*	3: SBP, DBP, FEV	3: HDL, GH, rTC/HDL	*	

Zota 2013	7	3: CRP, CR, Alb	*	*	3: GH, trig, HDL	1: waist CC	

Table 2 - Blood biomarkers and physical measures of health used in papers retrieved from systematic search.

* = No biomarkers measured from this component, Alb = Albumin, Aldo = Aldosterone, ALP = alkaline phosphatase activity, apM1 = adiponectin, APOA1 = apolipoprotein A1, ApoB = apolipoprotein B, BMI = Body Mass Index, BU = bilirubin, CC = circumference, * = No biomarkers measured from this component, Alb = Albumin, Aldo = Aldosterone, ALP = alkaline phosphatase activity, apM1 = adiponectin, APOA1 = apolipoprotein A1, ApoB = apolipoprotein B, BMI = Body Mass Index, BU = bilirubin, CC = circumference, Chol = Cholesterol, Cort = cortisol, CR = Creatinine, CRc = Creatinine clearance, CRP = C-reactive protein, Cru = urinary creatinine, DA = dopamine, DBP = diastolic blood pressure, DHAS = dehydroepiandrosterone, EBV–VCA = Latent EBV-capsid antigen, EBV–EA = early antigen (EA), EBNA = EBV nuclear antigen, eGFR = estimated Glomerular Filtration Rate, EPI = epinephrine, ESR = erythrocyte sedimentation rate, FEV – Forced expiratory volume, Fgluc = fasting glucose, Fib = fibrinogen, GGT = Gamma-glutamyl transferase, GH = Glycated haemoglobin, Gluc = glucose, HDL = high-density lipoprotein cholesterol, HGB = haemoglobin, HOMA- IR = homeostasis model assessment-insulin resistance, HOMA- β = homeostasis model assessment β –cell function, HR = heart rate, HRV = heart rate variability, HCY = Homocysteine, IGF-1 = Insulin-like growth factor 1, IL-1 = Interleukin-1, IL-10 = Interleukin-10, IL-1 β = Interleukin- β, IL-6 = Interleukin-6, IgE = Immunoglobulin E, HSV-1 = Herpes simplex viruses, IL-6 = interleukin 6, LDL = low-density lipoprotein cholesterol, NE = norepinephrine, pGluc = Plasma glucose, PP = pulse pressure, rLDL/HDL = Ratio of low-density lipoprotein cholesterol to high-density lipoprotein cholesterol, rTC/HDL = Ratio of Total cholesterol to high-density lipoprotein cholesterol, sAlb = serum albumin, sCort = serum cortisol, SBP = systolic blood pressure, TC = total cholesterol, TNF α = Tumor necrosis factor α, TPP = total plasma protein, Trig = triglycerides, UA = Uric acid, UP = urinary protein, WBC = white blood cell count, WHr = Waist- to-hip ratio.

Article	CRP	IL-6	TNFα	HDL	Trig	Albumin	Creatinine	SBP	DBP	FEV	HR	WHr	BMI	Aldosterone	DHEAS
Allsworth 2005	√			√	√	√	√	√	√	√			√		
Barboza 2014	√			√	√			√	√	√	√	√			
Bellator 2011	√			√	√	√		√	√		√	√			
Bellingrath 2008	√		√	√	√			√	√			√	√		√
Brody 2014, 2013a, 2013b	√							√	√				√		
Brody 2014b, 2013c								√	√				√		
Carroll 2013	√	√		√	√			√	√		√				
Chen 2014								√	√				√		
Clark 2014	√	√		√	√			√	√			√			
De Castro 2010	√							√	√			√	√		
Deuster 2011	√							√	√						
Dich 2014, 2015a	√	√		√	√			√	√				√		
Dich 2015b	√	√		√	√			√	√			√			
Doamekpor 2013	√			√		√	√	√	√						
Duru 2012	√				√	√		√	√			√			
Evans 2014	√				√	√		√	√		√		√		
Gallo 2010	√	√	√	√				√	√				√		
Gale 2015	√			√		√		√	√		√	√			
Gay 2015	√	√	√	√				√	√		√		√		
Geronimus 2006	√				√		√	√	√				√		
Glover 2006				√				√	√				√		√
Goertzal 2006	√	√				√		√	√			√		√	√
Gustafsson 2011, 2012, 2014	√			√	√			√	√			√	√		
Hampson 2009					√			√	√			√	√		
Hansen 2014	√	√	√	√	√			√	√			√	√		
Hassen 2009				√	√			√	√		√	√			√
Hux 2015	√	√		√	√	√		√	√		√		√		
Hux 2014	√			√		√	√	√	√				√		
Jung 2014		√	√				√	√	√		√		√		
Juster 2012, 2011	√			√	√	√	√	√	√			√			√
Juster 2013	√	√	√	√	√			√	√		√	√	√		
Kaestne 2010	√				√	√	√	√	√				√		
Kinnunen 2005				√	√			√	√			√			√
Krause 2012	√	√		√				√	√			√			
Langelaan 2007	√			√				√	√				√		

	CRP	IL-6	TNFα	HDL	Trig	Albumin	Creatinine	SBP	DBP	FEV	HR	WHr	BMI	Aldosterone	DHEAS
Li 2007				√	√			√	√			√	√		
Lindfors 2006				√				√	√	√		√			
Lipowicz 2013							√	√	√	√					
Mair 2011	√	√	√	√	√			√	√				√		
Masterson 2015	√			√	√			√	√						
McCaffery 2012	√	√		√	√			√	√			√	√		
Morrison 2013	√			√		√	√	√	√		√				
Naswall 2011				√				√	√	√	√	√			
Nicod 2014	√	√	√	√	√			√	√		√	√	√		
Nugent 2015	√			√				√	√		√	√	√		√
Robertson 2015	√			√		√		√	√		√	√			
Rosenberg 2014	√			√		√		√	√		√	√			
Schnorpfeil 2013	√		√	√		√		√	√			√	√		√
Schulz 2012, 2013				√	√			√	√			√			
Seeman 2010	√	√		√	√			√	√		√				
Seeman 2014	√	√		√	√			√	√						
Singer 1999				√				√	√			√			√
Sjors 2013	√			√	√			√	√			√	√		
Soli 2015	√			√	√			√	√	√	√				
Song 2014	√			√				√	√			√			√
Sun 2007	√				√			√	√			√	√		
Tanaka 2011	√			√	√			√	√			√			
Tomfohr 2013	√	√		√				√	√			√			
Upchurch 2015	√			√	√			√	√			√	√		√
Upchurch 2015	√			√		√		√	√				√		
Vie 2014	√			√	√			√	√		√	√	√		
Von Thiele 2006				√	√			√	√		√	√			√
Wallace 2013				√	√			√	√						
Wallace 2013					√			√	√				√		
Wallace 2013								√							√
Westerlund 2012, 2013	√				√			√	√			√	√		
Widom 2015	√			√		√	√	√	√	√					
Zota 2013	√			√	√	√	√	√	√						

Table 3 - Papers retrieved from systematic search which have measured the same blood biomarkers and physical measures of health as in this research

Chronic co-morbidities (frequency)		
Alcohol excess (11)	Hepatitis B positive (1)	Pancreatitis (2)
Asthma (5)	Hepatitis C positive (2)	Psoriasis (1)
Eczema (2)	High blood pressure (1)	Type 2 diabetes (2)
Epilepsy (3)	Liver cirrhosis (1)	

Table 4 – Type and frequency of chronic co-morbidities experienced by 35 head injury participants at discharge from hospital in Study 1(Chapter 5)

Chronic co-morbidities (frequency)		
Arthritis (2)	Crohn's disease (1)	Liver disease (1)
Asthma (5)	Depression (1)	Muscular dystrophy (1)
Coeliac disease (1)	High cholesterol (1)	Osteoporosis (1)

Table 5 - Type and frequency of chronic co-morbidities experienced by 35 comparison participants in Study 1 (Chapter 5)

Medication (frequency)		
Amlodipine (3) [2]	Glucazide (1)	Omeprazole (9)
Amoxicillin (4)	Haloperidol (2)	Ondansetron (1)
Atarax (1)	Humalog Mix 50-50 (1)	Oramorph (1)
Augmentin (1)	Ibuprofen (9) [1]	Paracetamol (20)
Bendroflumethiazide (2) [2]	Insulin (1)	Phenoxymethylpenicillin (1)
Benzylpenicillin (1)	Intrasite gel (1)	Phenytoin sodium (3)
Carbocysteine (1)	Keppra (3)	Phosphate sandoz (1)
Chlorhexidin (1)	Lacri-Lube SOP ointment (1)	Pred Forte drops (1)
Clexane (3)	Lactulose (9)	Pregabalin (1)
Clonazepam (1)	Lantis (1)	Propanalol (4) [2]
Coamoxiclav (1)	Lanzeprado (1)	Ranitidine (2)
Co-codamol (6) [1]	Latchelose (1)	Risperidone
Codeine phosphate (5) [1]	Laxido (1)	Sando-K
Conotrane cream (1)	Levetiracetam (3)	Senna (6)
Creon (1)	Lisinopril (1) [2]	Seretide (1) [1]
Cyclizine (2)	Lorazepam (1)	Sertraline (1)
Daktacort Hydrocortisone Cream (1)	Lotriderm cream (1)	Slow sodium (1)
Diazapam (1)	Magnesium glycerophosphate (2)	Sodium bicarbonate (1)
Diclofenac (1) [1]	Matazepine (1)	Sodium docusate (1)
Dicloren (1) [1]	Methadone (2)	Sodium valporate (2)
Dihydrocodeine (4) [1]	Metoclopramide (1)	Stematil (1)
Doxycyline (1)	Metronidazole (1)	Temazepam (1)
Enalapril (1) [2]	Micolette (1)	Thiamine (15)
Enoxaparin (2)	Miconazole (1)	Tiotropium (1)
Ensure plus (4)	Mirtazapine (1)	Trazadone (1)
Escitalopram (1)	Mometasone furoate (1) [1]	Zopiclone (1)
Eumovate (1)	Morphine (4)	
Exocin (1)	Mucogel (1)	
Ferrousfumarate (1)	Naproxen (1) [1]	
Fluctoxicillin (1)	Nazipam (1) [2]	
Fluoxetine (2)	Nictotine patch (5)	
Gentisone eardrops (2)	Omeprazole (1)	

Table 6 – Medication taken by 35 head injury participants at discharge from hospital in Study1 (Chapter 5) [1] = Anti-inflammatory, [2] = Blood pressure reducing

Medication (frequency)	
Aspirin (2) [1]	Omeprazole (3)
Azathioprine (1) [1]	Propanalol (1)
Calcium (1)	Ramipril (1) [2]
Flomaxtra (1)	Sabutamol (1) [1]
Fluoxetine (1)	Seretide (2) [1]
Hormone Replacement Therapy (1)	Simvastatin (1) [1]
Ibuprofen (3) [1]	Solpedol (1)
Micronore (1)	Thyroxine (1)
Mirtazapine (1)	Venlafaxine (1)
Nasinex (1)	Vescore (1)

Table 7 – Medication taken by 35 comparison participants in Study 1(Chapter 5) [1] = Anti-inflammatory, [2] = Blood pressure reducing

Chronic co-morbidities (frequency)		
Alcohol excess (2)	Ex IVDU (4)	Pancreatitis (2)
Asthma (5)	Hepatitis B positive (1)	Psoriasis (1)
Eczema (1)	Hepatitis C positive (1)	Sciatica (1)
Epilepsy (2)	High blood pressure (1)	Type 2 diabetes (1)

Table 8 – Type and frequency of chronic co-morbidities experienced by 28 head injury participants 6 months after discharge from hospital in Study 2 (Chapter 6)

Chronic co-morbidities (frequency)		
Arthritis (2)	Depression (1)	High cholesterol (1)
Asthma (3)	Diabetes (1)	Liver disease (1)
Crohn's disease (1)	High blood pressure (1)	Osteoporosis (1)

Table 9 - Type and frequency of chronic co-morbidities experienced by 28 comparison participants in Study 2 (Chapter 6)

Medication (frequency)		
Amitriptyline (1)	Inhaler (1) [1]	Prochlorperazine (1)
Amlodipine (3) [2]	Keppra (1)	Propanalol (4) [2]
Aspirin (1) [1]	Ketoprofen (1) [1]	Ramaprol (1) [2]
Azathioprine (1) [1]	Lactulose (1)	Rasperidone (1)
Bendroflumethiazide (1) [2]	Lamictal blue (1)	Ritalin (1)
Bisoprolol (1) [2]	Levetiracetam (1)	Sabutamol (1)[1]
Budesonide (1)	Lidocraine patches (1)	Sertraline (1)
Cipraflaxine (1)	Loperamide (1)	Sodium valporate (1)
Citalopram (1)	Lopressor (1) [2]	Thiamine (8)
Cocodamol (1) [1]	Mirtazapine (2)	Trazadone (3)
Dehydrocodeine (1)	Naproxen (2) [1]	Vastatin (1) [1]
Diazepam rectal solution (2)	Nefopam (1)	Versatis (1)
Diprobase (1)	Nortriptyline (1)	Zomig (1)
Enalapril (1) [2]	Omeprazole (4)	Zopiclone (2)
Epilem (1)	Oxycontin (1)	
Flucloxocillin (1)	Paracetamol (7)	
Fluoextine (3)	Paroxetine (1)	
Gabapentin (1)	Phenytoin sodium (3)	
Ibuprofen (1) [1]	Pregabalin (1)	

Table 10 - Medication taken by 28 head injury participants 6 months after discharge from hospital in Study 2(Chapter 6)[1] = Anti-inflammatory, [2] = Blood pressure reducing

Medication (frequency)	
Aspirin (1) [1]	Ramipril (1) [2]
Azathioprine (1) [1]	Seretide (1) [1]
Calcium (1)	Simvastatin (1) [1]
Flomaxtra (1)	Solpedol (1)
Ibuprofen (2) [1]	Thyroxine (1)
Inhaler (2) [1]	Venlafaxine (1)
Nasinex (1)	Vescore (1)
Omeprazole (3)	

Table 11 - Medication taken by 28 comparison participants in Study 2 (Chapter 6)[1] = Anti-inflammatory, [2] = Blood pressure reducing

Chronic co-morbidities (frequency)		
alcohol excess	Eczema	Type 2 Diabetes
Asthma	Epilepsy (2)	Underactive thyroid
Blood clots (2)	Haemacromatosis	
Celiac disease	strokes (multiple)	

Table 12 – Type and frequency of chronic co-morbidities experienced by 41 head injury participants late after injury in Study 3 (Chapter 7)

Medication (number of participants)	
Albuterol (1) [1]	Lansoprazole (1)
Amlopdipine (1)	Levothyroxine (1)
Amplidine (1) [2]	Lisinopril (1) [2]
Asacol (1)	Lortasan (1) [2]
Aspirin (1) [1]	Metformin (1)
Atenolol (2) [2]	Naproxen (1) [1]
Atorvastatin (3) [1]	Odocol 3D (1)
Bendroflumethiazide (3) [2]	Omeprazole (4)
Buscopan (1)	Paracetamol (1)
Citalopram (2)	Simvastatin (2) [1]
Clopidogrel (1)	Sitlex (1)
Co-codomol (3)	Statin (1) [1, 2]
Co-dydramol (1)	Suboxone (1)
Deferasirox (1)	Tegretol (3)
Diazepam (1)	Temazepam (1)
Diprobase (1)	Thiamine (2)
Doxycyline (1)	Tramadol (1)
Etidrocal (1)	Xarelto (1)

Table 13 – Medication taken by 41 head injury participants late after injury in Study 3 (Chapter 7) [1] = Anti-inflammatory, [2] = Blood pressure reducing

Chronic co-morbidities (frequency)		
Acid reflux (1)	Depression (1)	Liver disease (1)
Arthritis (3)	High blood pressure (1)	Muscular dystrophy (1)
Asthma (6)	High cholesterol (1)	Osteoporosis (1)
Coeliac disease (1)	Crohn's disease (1)	Type 2 diabetes (2)

Table 14 - Type and frequency of chronic co-morbidities experienced by 47 comparison participants in Study 3 (Chapter 7)

Medication (number of participants)	
Aspirin (2) [1]	Nasinex (1)
Azathioprine (1) [1]	Omeprazole (3)
Cephalexin (1)	Propanalol (1) [2]
Citalopram (1)	Ramipril (1) [2]
Elocon cream (1)	Sabutamol (1) [1]
Finastiride (1)	Sandostatin (1) [2]
Fluoxetine (1)	Seratide (2)
Glycoside (1)	Simvastatin (2) [1]
Hormone Replacement Therapy (1)	Solpedol (1)
Ibuprofen (3) [1]	Steroid nasal spray (1) [1]
Inhaler (3) [1]	Thyroxine (1)
Metamorphine (1)	Venlafaxine (1)
Mirtazapine (1)	Ventalin (1)

Table 15 – Medication taken by 47 comparison participants in Study 3 (Chapter 7) [1] = Anti-inflammatory, [2] = Blood pressure reducing

Chronic co-morbidities (frequency)		
Arthritis (8)	Deep vein thrombosis (1)	High cholesterol (1)
Asthma (2)	Depression (1)	Parkinson's Disease (1)
Atrial Fibrillation (1)	Heart Condition (1)	
Sciatica (1)	High Blood Pressure (2)	

Table 16 – Type and frequency of chronic co-morbidities experienced by 46 retired international rugby players in Study 4 (Chapter 8)

Chronic co-morbidities (frequency)		
Arthritis (1)	High Blood Pressure (2)	Hypertension (2)
Atrial fibrillation (1)	High cholesterol (2)	Stomach ulcer (1)

Table 17 - Type and frequency of chronic co-morbidities experienced by 29 comparison participants in Study 4 (Chapter 8)

Medication (number of participants)	
Amitriptyline (1)	Glyceryl Spray (1)
Aspirin (3) [1]	Ibuprofen (1) [1]
Azathioprine (1) [1]	Lisinopril (2) [2]
Bisoprolol Fumarate (2) [2]	Methotrexate (1) [1]
Budesanite (1) [1]	Montelukast (1) [1]
Cetirizine (1)	Omeprazole (1)
Citralopam (1)	Pentasa (1) [1]
Clopidogrel (1)	Ramapril (1) [2]
Corticosteroid nasal spray (1) [1]	Ropinirole (1)
Diclofenic (1) [1]	Seretide (1) [1]
Fesoterodine (1)	Statins (5) [1 2]
Flecainide Acetate (1)	Steroid injection (1) [1]
Flixonase (1) [1]	Telfast (1)
Fostair (1) [1]	Warfarin (2)
Glucosamine (1)	Zomig (1)

Table 18 – Medication taken by 46 retired international rugby players in Study 4 (Chapter 8) [1] = Anti-inflammatory, [2] = Blood pressure reducing

Medication (number of participants)	
Amlopidine (2) [2]	Irbesartan (1) [2]
Aspirin (1) [1]	Lisinopril (3) [2]
Atorvastrium (1) [2]	Nytol (1)
Bendroflumethiazide (2) [2]	Omeprazole (2)
Bepridil (1)	Ramapril (1) [2]
Candesartan (2)	Setraline (1)
Citralopam (1)	Sotalol (1)
Clarinex (1)	Statins (4) [1, 2]
Coenzyme Q10 (1)	Steroid cream (1) [1]
Doxazosin (1) [2]	Tamsulosin (1)
Finastiride (1)	Thiamine (2)
Flomaxtra (1)	Warfarin (1)

Table 19 – Medication taken by 29 comparison participants in Study 4 (Chapter 8)[1] = Anti-inflammatory, [2] = Blood pressure reducing

Appendix E: Assumptions of regressions

1.1: Chapter 5, Hypothesis 1

The assumptions of a hierarchical regression for the association between participant group and allostatic load (AL) scores, adjusting for age, gender, SIMD (2012) quintiles, and childhood deprivation scores:

The analysis of standard residuals showed that the data contained outliers (minimum standard residual = -2.00, maximum standard residual = 2.31). Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.72, VIF = 1.39; gender, tolerance = 0.90, VIF = 1.11; SIMD (2012) quintile, tolerance = 0.68, VIF = 1.48; childhood deprivation score tolerance = 0.70, VIF = 1.44; participant group, tolerance = 0.97, VIF = 1.04). The data met the assumption of independent errors (Durbin-Watson value = 1.97). The histogram of standardised residuals indicated that the data contained normally distributed errors (Figure 1), as did the normal P-P plot of standardised residuals, which showed points that were close to the line (Figure 2). The scatterplot of standardised predicted values showed that the data met the assumptions of homogeneity of variance and linearity (Figure 3). The data also met the assumption of non-zero variances (AL scores, variance = 6.66; age, variance = 199.39, gender, variance = 0.18; SIMD (2012) quintile, variance = 2.00; childhood deprivation scores, variance = 1.27; participant group, variance = 0.25).

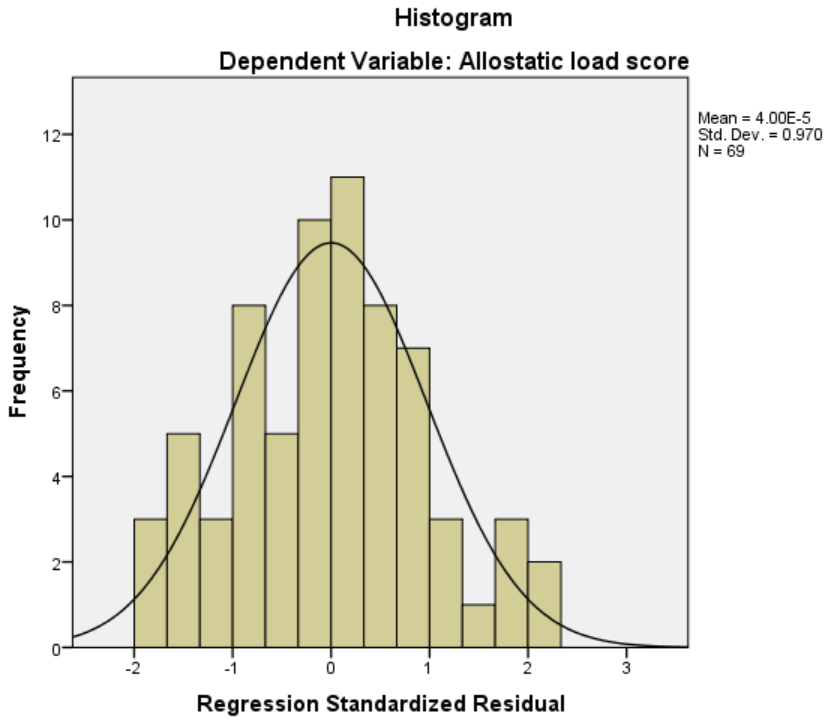


Figure 1 - Histogram of the regression standardised residual

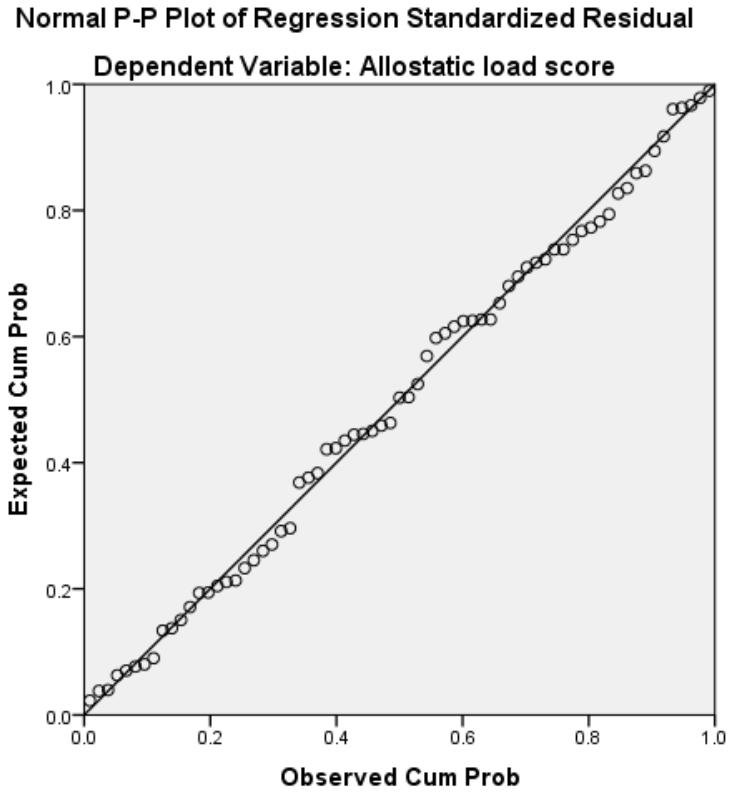


Figure 2 - Normal P-P plot of regression standardized residual

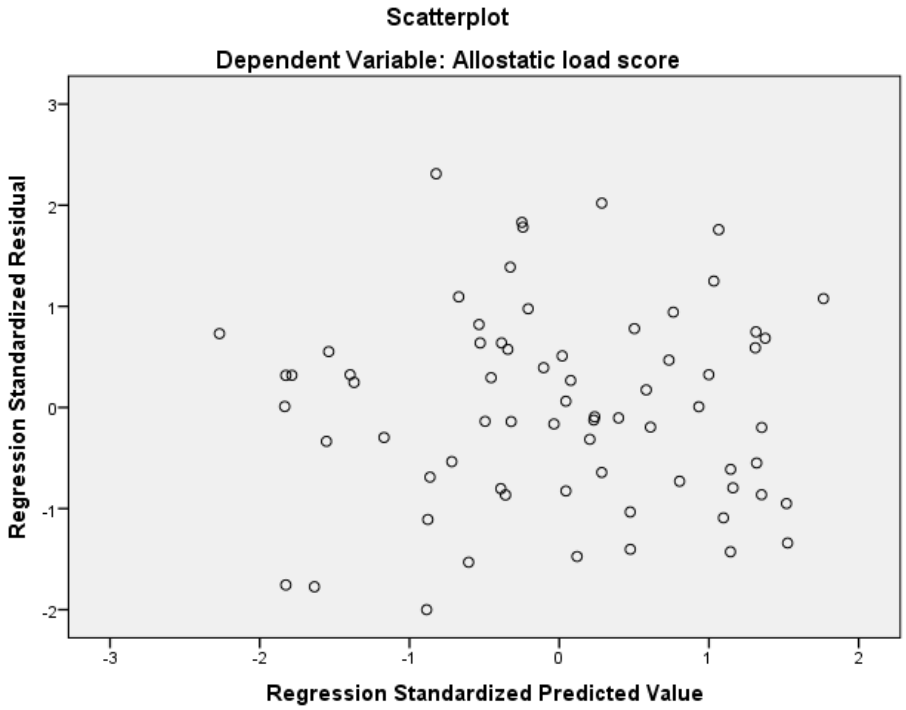


Figure 3 - Scatterplot of the regression standardized residual and regression standardized predicted value

1.2: Chapter 5, Hypothesis 2

Variable	X^2	*p*
Allostatic load	13.94	0.083
Cardiovascular	12.66	0.124
Neuroendocrine	8.27	0.408
Immune	12.65	0.124
Metabolic	1.43	0.990
Anthropometric	1.71	0.989

Table 20 - The assumption of proportional odds

Variable	Tolerance	VIF	Variable	Tolerance	VIF
Allostatic load	0.93	1.07	Age	0.93	1.07
Cardiovascular	0.94	1.06	Age	0.94	1.06
Neuroendocrine	0.96	1.04	Age	0.96	1.04
Immune	1.00	1.00	Age	1.00	1.00
Metabolic	0.98	1.02	Age	0.98	1.02
Anthropometric	1.00	1.00	Age	1.00	1.00

Table 21 - The assumption of collinearity

1.3: Chapter 6, Hypothesis 4

The assumption of proportional odds for the association between change in Glasgow Outcome ratings between hospital discharge and 6 months follow-up, and AL scores at both time points:

Allostatic load measured at	X^2	*p*
Discharge from hospital	3.11	0.796
6 months follow-up	4.13	0.530

Table 20 - Ordinal logistic regression analysis of the relationship between change in Glasgow Outcome ratings between hospital discharge and 6 months follow-up and allostatic load scores at both time points

The assumption of proportional odds for the association between change in Glasgow Outcome ratings between hospital discharge and 6 months follow-up, and AL component scores at both time points:

Variable	X^2	*p*
Component score at hospital discharge		
Cardiovascular	6.03	0.420
Neuroendocrine	6.09	0.413
Immune	4.67	0.571
Metabolic	5.81	0.445
Anthropometric	4.48	0.612
Component score at 6 months follow-up		
Cardiovascular	9.62	0.087
Neuroendocrine	1.35	0.929
Immune	4.48	0.483
Metabolic	3.49	0.613
Anthropometric	7.50	0.186

Table 21- Ordinal logistic regression analysis of the relationship between change in Glasgow Outcome ratings between hospital discharge and 6 months follow-up and allostatic load component scores at both time points

1.4: Chapter 7, Hypothesis 1

The assumptions of a hierarchical regression for the association between participant group and AL score, adjusting for age and childhood deprivation score:

The analysis of standard residuals showed that the data contained outliers (minimum standard residual = -1.77, maximum standard residual = 3.37). One

comparison participant had a standardised residual value of 3.37, which is defined as an outlier as it is above the value of 3.0, although only just (Tabachnick & Fidell, 2007). The data was checked and the participant had a high but correct allostatic index score, therefore it was left in the analysis. Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.81, VIF = 1.23; childhood deprivation, tolerance = 0.84, VIF = 1.20; participant group; tolerance = 0.91, VIF = 1.10). The data met the assumption of independent errors (Durbin-Watson value = 2.25). The histogram of standardised residuals indicated that the data contained normally distributed errors (Figure 4), as did the normal P-P plot of standardised residuals, which showed points that were close to the line (Figure 5). The scatterplot of standardised predicted values showed that the data met the assumptions of homogeneity of variance and linearity (Figure 6). The data also met the assumption of non-zero variances (age, variance = 165.94; childhood deprivation, variance = 1.15; AL score, variance = 8.92; participant group, variance = 0.25).

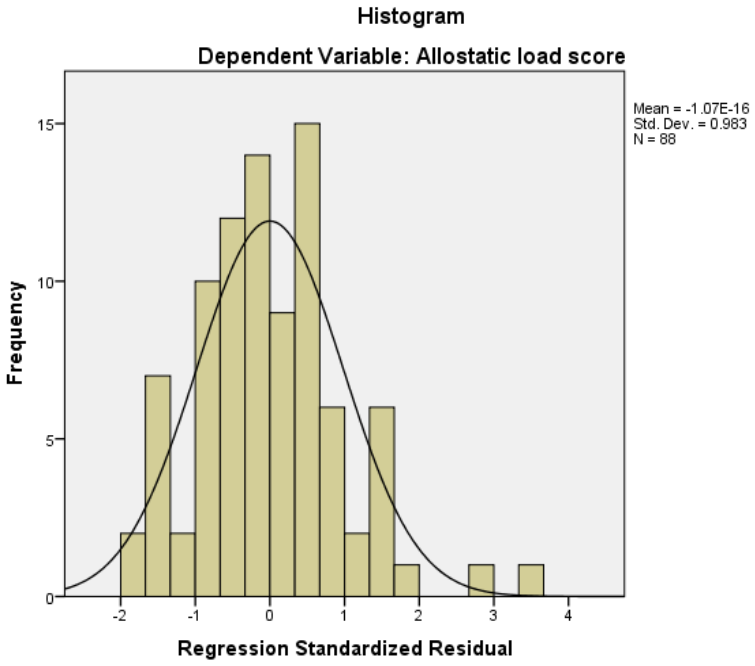


Figure 4- Histogram of the regression standardised residual

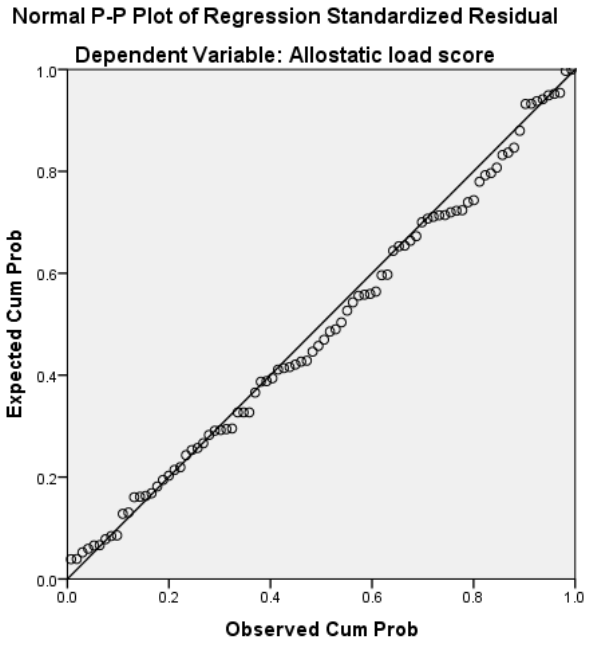


Figure 5- Normal P-P plot of regression standardized residual

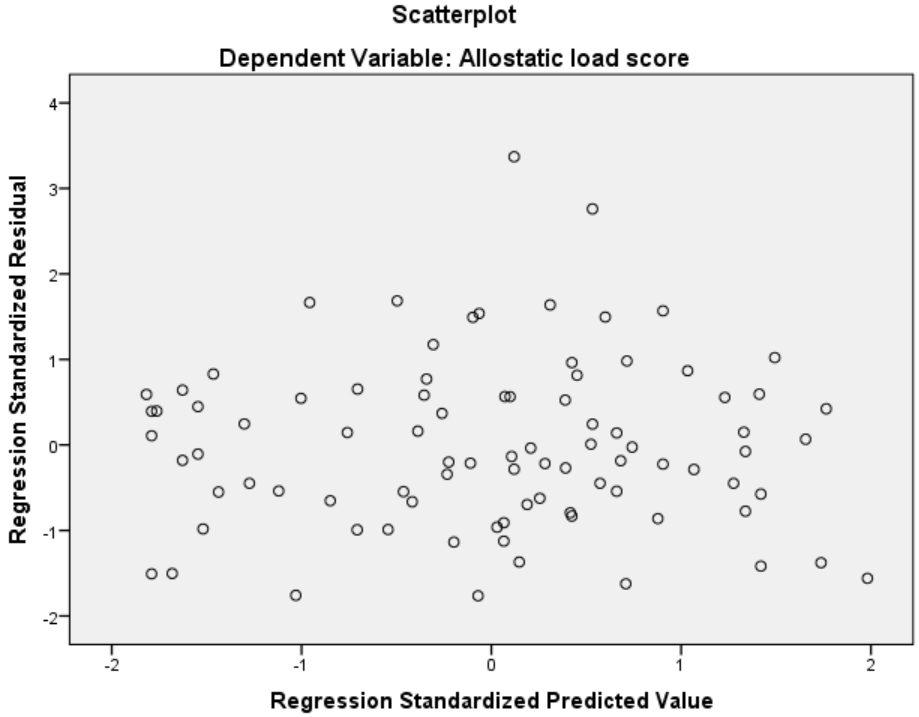


Figure 6 - Scatterplot of the regression standardized residual and regression standardized predicted value

1.5: Chapter 7, Hypothesis 1

The assumptions of a hierarchical regression for the association between participant group and cardiovascular component score, adjusting for age and gender:

The analysis of standard residuals showed that the data contained no outliers (minimum standard residual = -2.25, maximum standard residual = 2.49). Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.92, VIF = 1.08; gender, tolerance = 1.00, VIF = 1.00; participant group, tolerance = 0.92, VIF = 1.08). The data met the assumption of independent errors (Durbin-Watson value = 2.00). The histogram of standardised residuals indicated that the data contained errors that may have small positive skew, (Figure 7), however with a small sample size of residuals the normal P-P plot of standardised residuals is a better indicator of normality, and this showed points that were approximately close to the line, particularly at either end of the line (Figure 8). The scatterplot of standardised predicted values showed that although the data were not totally evenly distributed, they were not of concern and so met the assumptions of homogeneity of variance and linearity (Figure 9). The data also met the assumption of non-zero variances (cardiovascular component scores, variance = 1.00; age, variance = 165.94, gender, variance = 0.22; participant group, variance = 0.25).

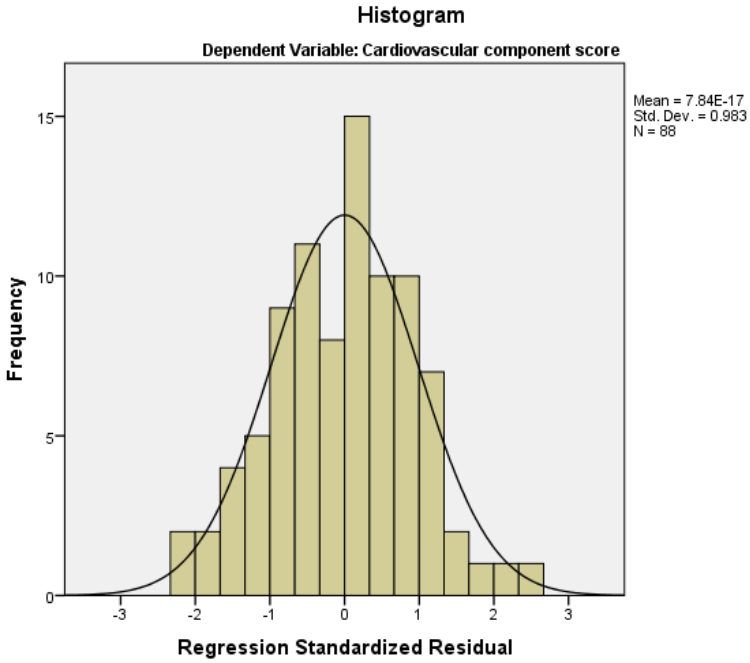


Figure 7 - Histogram of the regression standardised residual

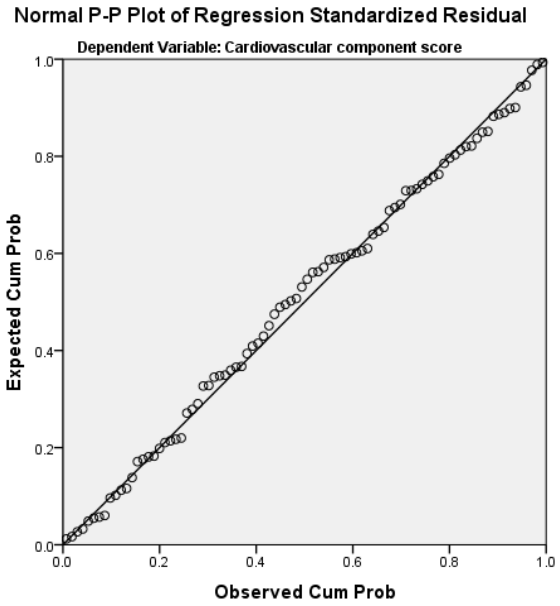


Figure 8 - Normal P-P plot of regression standardized residual

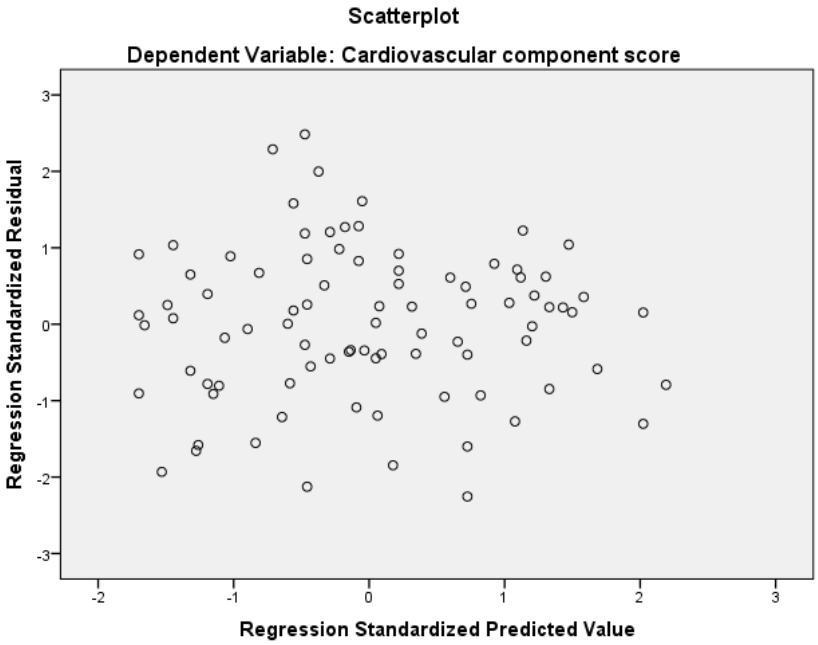


Figure 9 - Scatterplot of the regression standardized residual and regression standardized predicted value

1.6: Chapter 7, Hypothesis 1

The assumptions of a hierarchical regression for the association between participant group and neuroendocrine component score adjusting for age:

The analysis of standard residuals showed that the data contained no outliers (minimum standard residual = -2.19, maximum standard residual = 2.53). Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.93, VIF = 1.08; participant group, tolerance = 0.93, VIF = 1.08). The data met the assumption of independent errors (Durbin-Watson value = 2.00). The histogram of standardised residuals indicated that the data contained errors that may have small positive skew, (Figure 10), however with a small sample size of residuals the normal P-P plot of standardised residuals is a better indicator of normality, and this showed points that were approximately close to the line, particularly at either end of the line (Figure 11). The scatterplot of standardised predicted values showed that although the data were not totally evenly distributed, they were not of concern and so met the assumptions of homogeneity of variance and linearity (Figure 12). The data also met the

assumption of non-zero variances (neuroendocrine component scores, variance = 0.95; age, variance = 165.94; participant group, variance = 0.25).

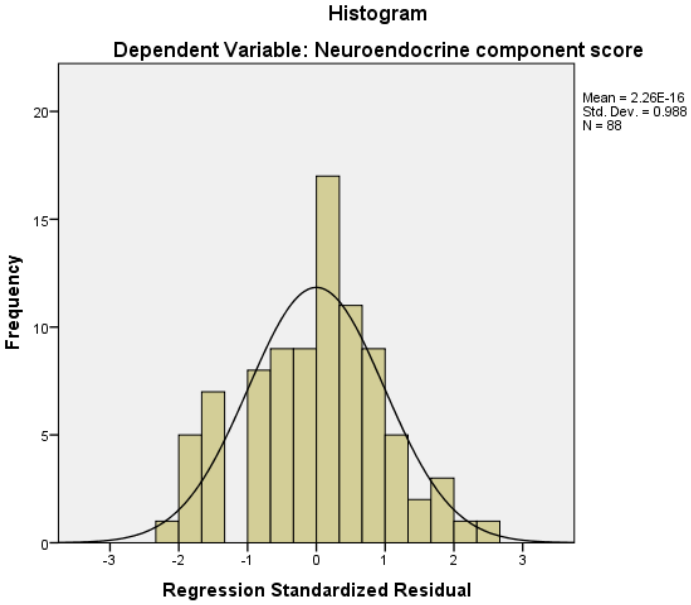


Figure 10 - Histogram of the regression standardised residual

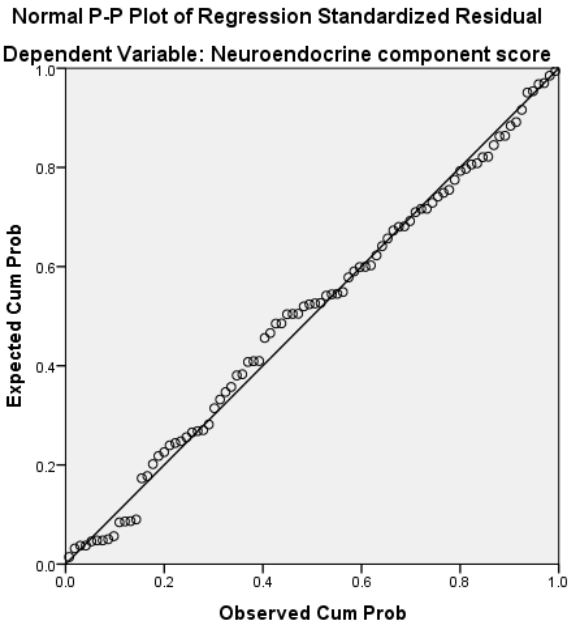


Figure11 - Normal P-P plot of regression standardized residual

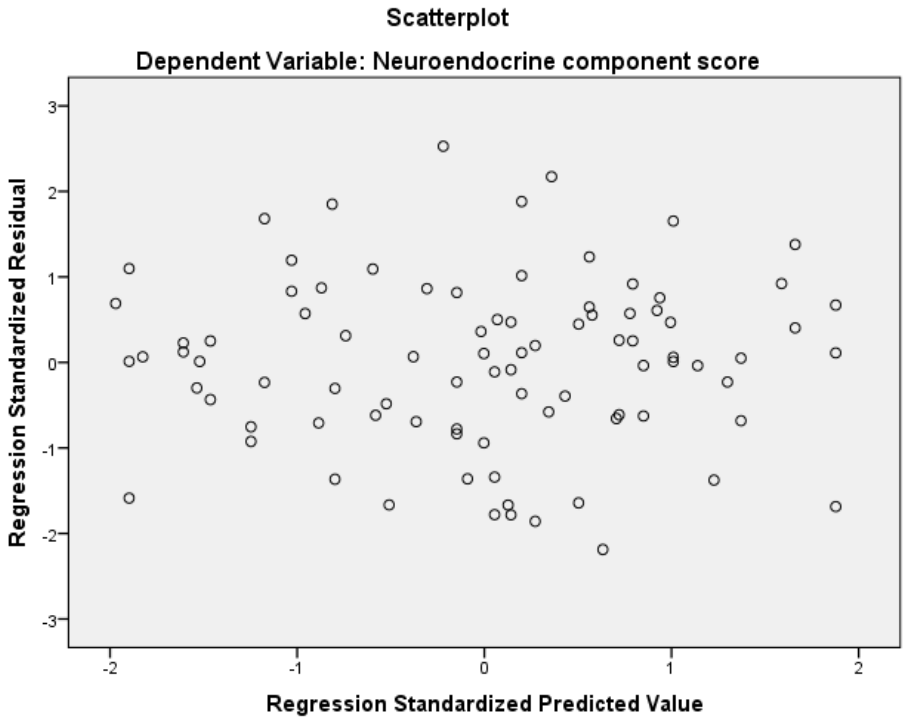


Figure 12 - Scatterplot of the regression standardized residual and regression standardized predicted value

1.7: Chapter 7, Hypothesis 1

The assumptions of a hierarchical regression for the association between participant group and anthropometric component score, adjusting for age:

The analysis of standard residuals showed that the data contained no outliers (minimum standard residual = -1.75, maximum standard residual = 2.75). Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.93, VIF = 1.08; participant group, tolerance = 0.93, VIF = 1.08). The data met the assumption of independent errors (Durbin-Watson value = 2.11). The histogram of standardised residuals indicated that the data contained errors that may have small positive skew, (Figure 13), however with a small sample size of residuals the normal P-P plot of standardised residuals is a better indicator of normality, and this showed points that were approximately close to the line, particularly at either end of the line (Figure 14). The scatterplot of standardised predicted values showed that although the data were not totally evenly distributed, they were not of concern and so met the assumptions of

homogeneity of variance and linearity (Figure 15). The data also met the assumption of non-zero variances (anthropometric component scores, variance = 1.44; age, variance = 165.94; participant group, variance = 0.25).

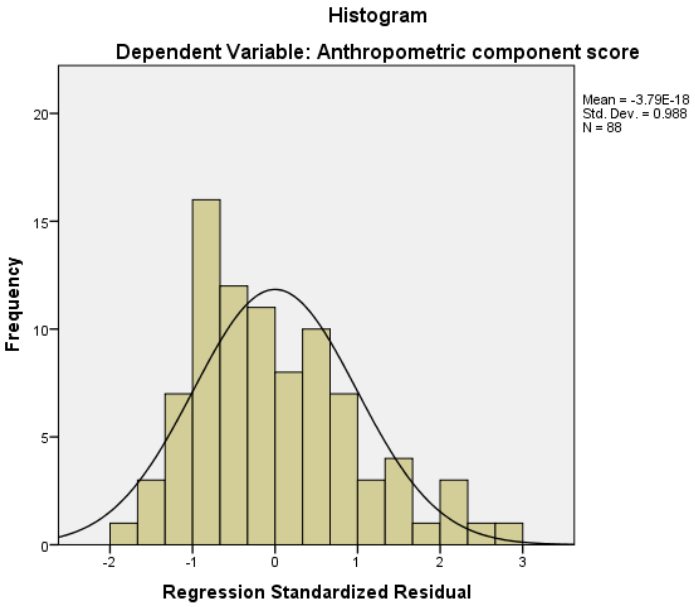


Figure 13 - Histogram of the regression standardised residual

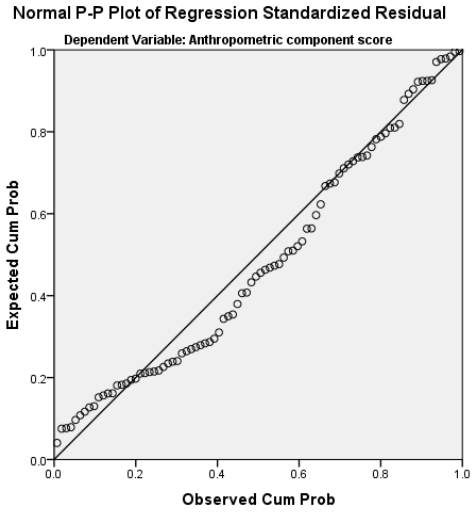


Figure 14 - Normal P-P plot of regression standardized residual

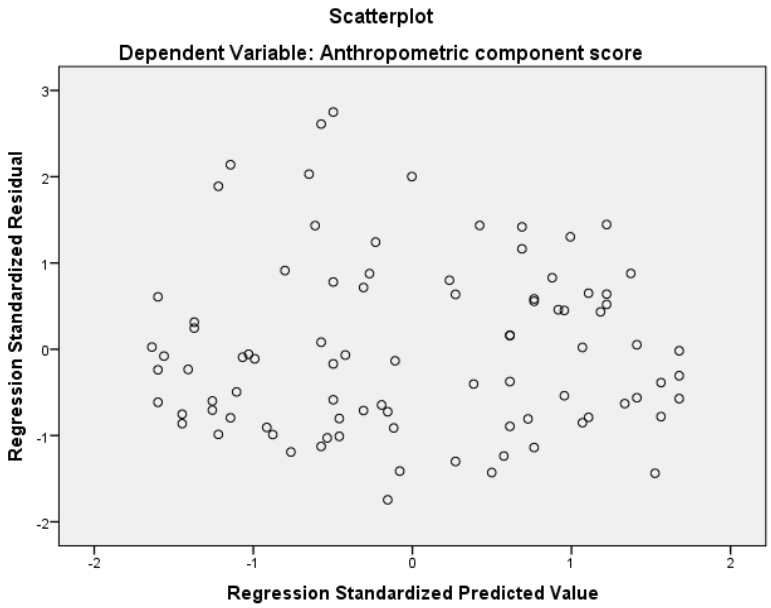


Figure 15 - Scatterplot of the regression standardized residual and regression standardized predicted value

1.8: Chapter 7, Hypothesis 1

The assumptions of a hierarchical regression for the association between participant group and metabolic component score, adjusting for gender:

The analysis of standard residuals showed that the data contained no outliers (minimum standard residual = -1.87, maximum standard residual = 3.08). Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (gender tolerance, = 1.00, VIF = 1.00, participant group, tolerance = 1.00, VIF = 1.00). The data met the assumption of independent errors (Durbin-Watson value = 2.01). The histogram of standardised residuals indicated that the data contained errors that may have small positive skew, (Figure 16), however with a small sample size of residuals the normal P-P plot of standardised residuals is a better indicator of normality, and this showed points that were approximately close to the line, particularly at either end of the line (Figure 17). The scatterplot of standardised predicted values showed that although the data were not totally evenly distributed, they were not of concern and so met the assumptions of homogeneity of variance and linearity (Figure 18). The data also met the

assumption of non-zero variances (metabolic component scores, variance = 1.06; gender, variance = 0.22; participant group, Variance = 0.25).

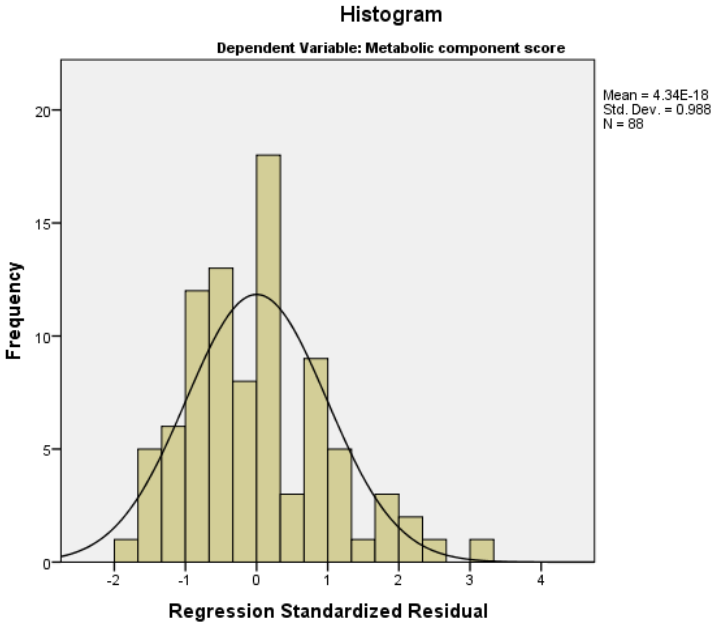


Figure 16 - Histogram of the regression standardised residual

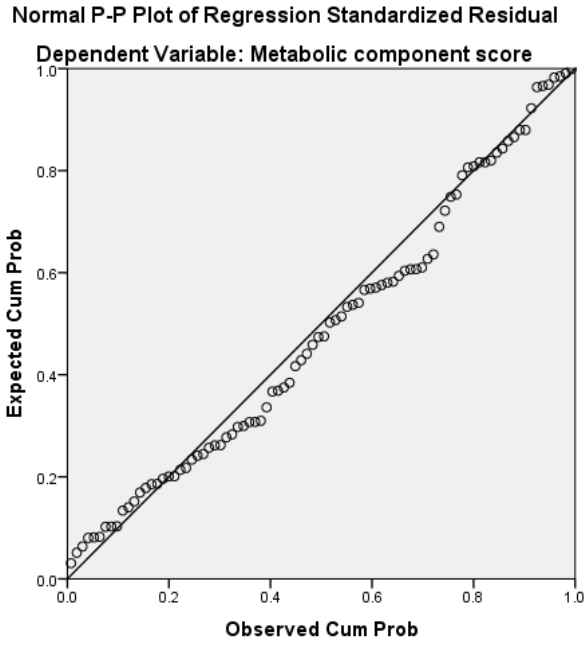


Figure 17 - Normal P-P plot of regression standardized residual

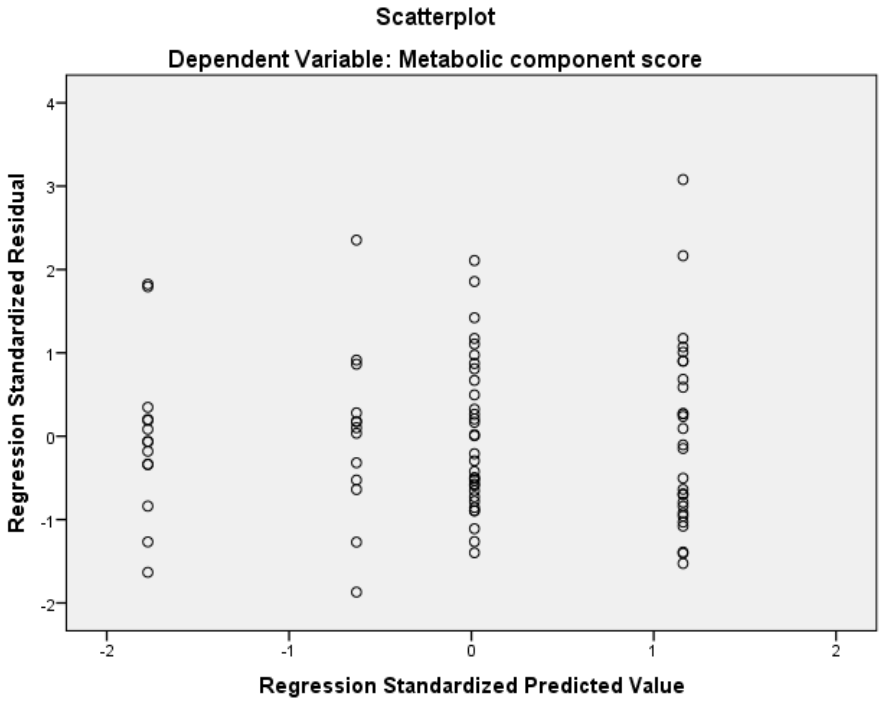


Figure 18 - Scatterplot of the regression standardized residual and regression standardized predicted value

1.9: Chapter 7, Hypothesis 3

The assumptions of a hierarchical regression for the association between AL score and symbol digit modalities test score, adjusting for age:

The analysis of standard residuals showed that the data contained no outliers (minimum standard residual = -2.00, maximum standard residual = 2.00). Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.98, VIF = 1.02; AL score, tolerance = 0.98, VIF = 1.02). The data met the assumption of independent errors (Durbin-Watson value = 2.46). The histogram of standardised residuals indicated that the data contained normally distributed errors (Figure 19), as did the normal P-P plot of standardised residuals, which showed points that were close to the line (Figure 20). The scatterplot of standardised predicted values showed that the data met the assumptions of homogeneity of variance and linearity (Figure 21). The data also met the assumption of non-zero variances (symbol digit modalities test score, variance = 188.22; age, variance = 138.80; AL score, variance = 6.10).

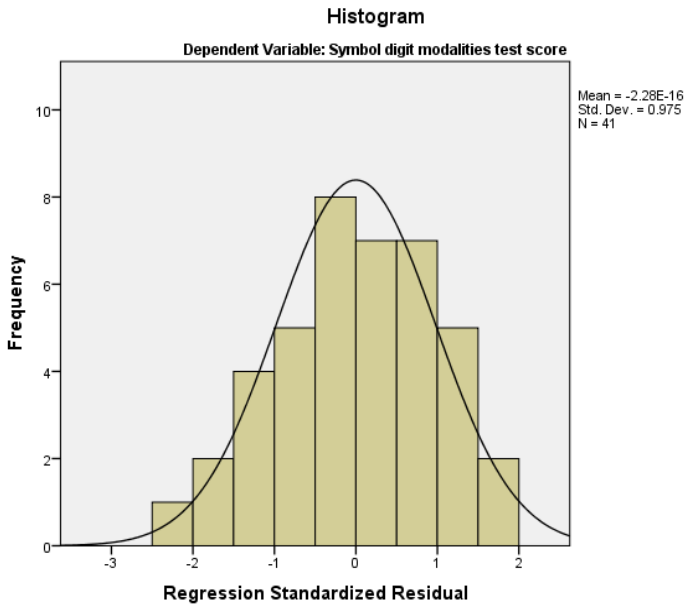


Figure 19 - Histogram of the regression standardised residual

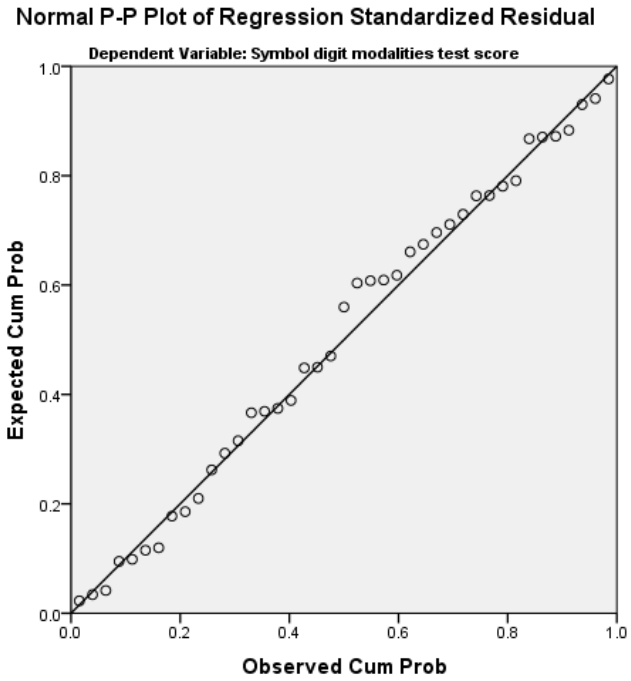


Figure 20 - Normal P-P plot of regression standardized residual

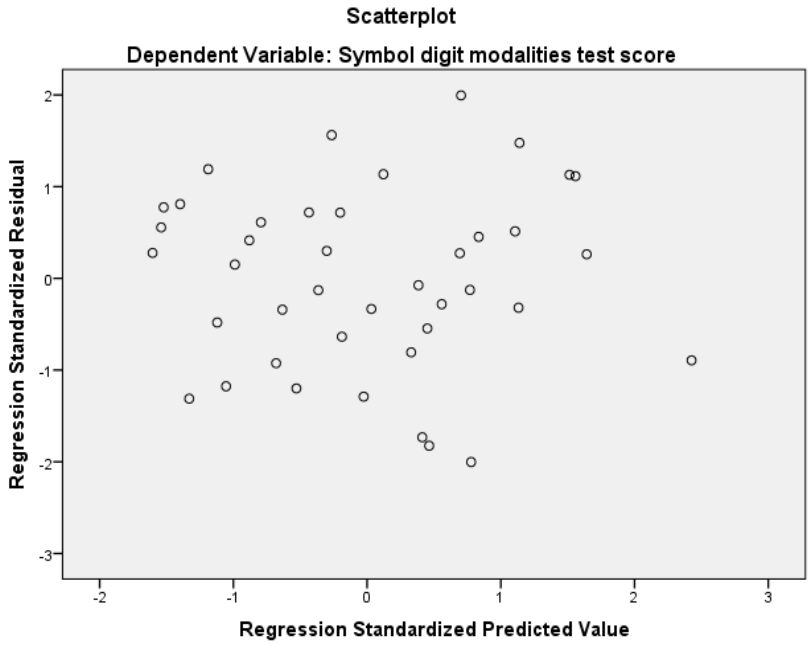


Figure 21 - Scatterplot of the regression standardized residual and regression standardized predicted value

1.10: Chapter 7, Hypothesis 3

The assumptions of a hierarchical regression for the association between AL score and immediate verbal memory for paired associates score, adjusting for age:

The analysis of standard residuals showed that the data contained no outliers (minimum standard residual = -1.89, maximum standard residual = 1.50). Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.98, VIF = 1.02; AL score, tolerance = 0.98, VIF = 1.02). The data met the assumption of independent errors (Durbin-Watson value = 2.04). The histogram of standardised residuals indicated that the data contained normally distributed errors (Figure 22), as did the normal P-P plot of standardised residuals, which showed points that were close to the line (Figure 23). The scatterplot of standardised predicted values showed that the data met the assumptions of homogeneity of variance and linearity (Figure 24). The data also met the assumption of non-zero variances (immediate verbal memory for paired

associated score, variance = 18.16; age, variance = 138.80; AL score, variance = 6.10).

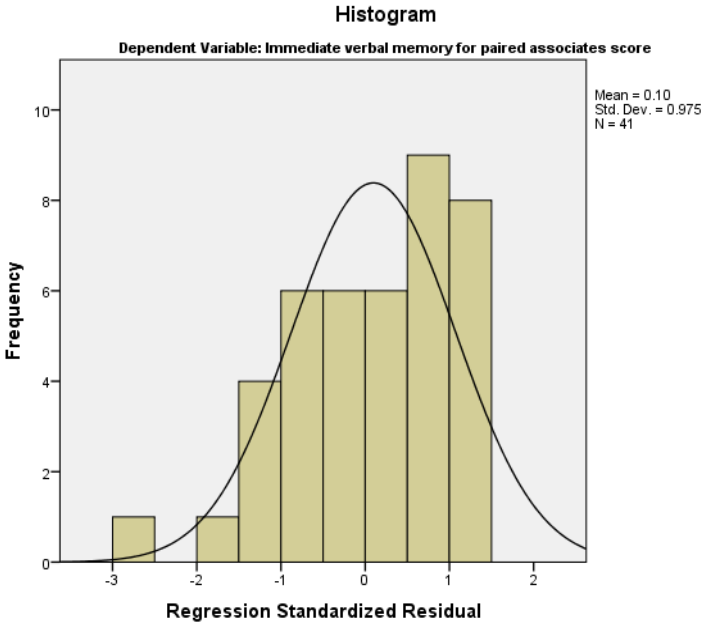


Figure 22 - Histogram of the regression standardised residual

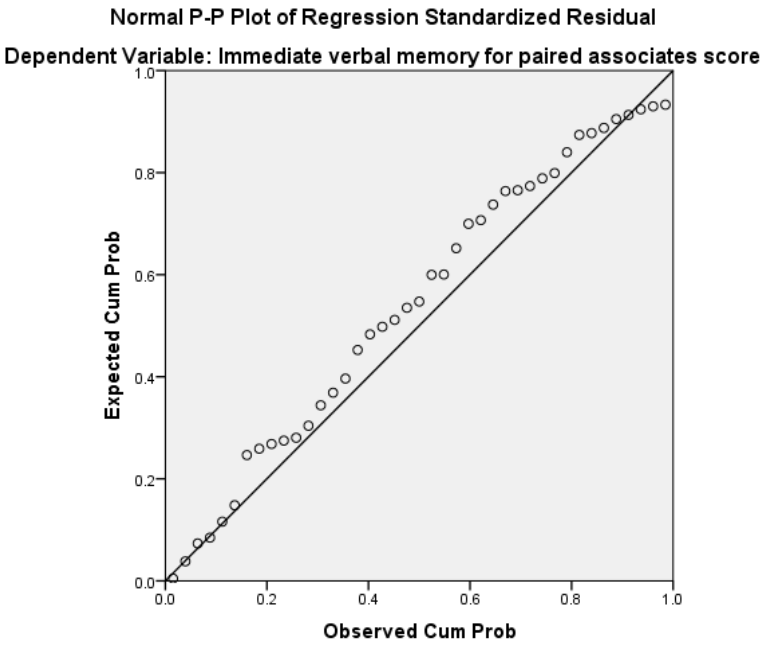


Figure 23 - Normal P-P plot of regression standardized residual

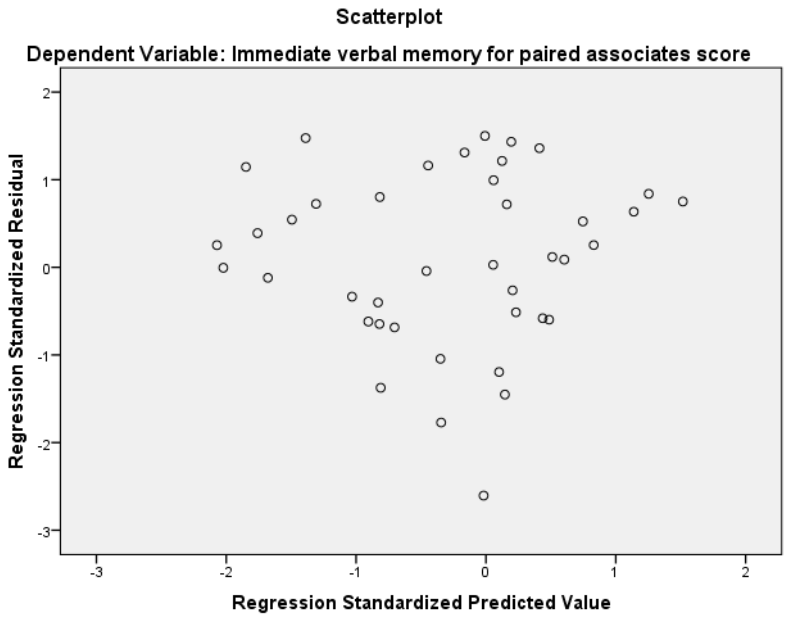


Figure 24 - Scatterplot of the regression standardized residual and regression standardized predicted value

1.11: Chapter 7, Hypothesis 4

The assumption of proportional odds for the association between change in GOS ratings between 6 months post-head injury and late outcome and AL component scores late after head injury:

Allostatic load component	X^2	*p*
Cardiovascular	2.04	0.565
Neuroendocrine	5.46	0.681
Anthropometric	2.86	0.413

Table 22- Ordinal logistic regression analysis of the relationship between change in GOS ratings between 6 months post-head injury and late outcome and allostatic load component scores late after head injury in Study 3 (Chapter 7)

1.12: Chapter 8, Hypothesis 1

The assumptions of a hierarchical regression for the association between participant group and cardiovascular component score, adjusting for age:

The analysis of standard residuals showed that the data contained outliers (minimum standard residual = -1.98, maximum standard residual = 3.32). One comparison participant had a standardised residual value of 3.32, which is defined as an outlier as it is above the value of 3.00, although only just

(Tabachnick & Fidell, 2007). The data was checked and the participant had a high but correct cardiovascular component score, therefore it was left in the analysis. Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 1.00, VIF = 1.00; concussion group, tolerance = 1.00, VIF = 1.00). The data met the assumption of independent errors (Durbin-Watson value = 1.90). The histogram of standardised residuals indicated that the data contained normally distributed errors (Figure 25), as did the normal P-P plot of standardised residuals, which showed points that were close to the line (Figure 26). The scatterplot of standardised predicted values showed that the data met the assumptions of homogeneity of variance and linearity (Figure 27). The data also met the assumption of non-zero variances (cardiovascular component scores, variance = 0.87; age, variance = 131.50, retired player/ comparison group, variance = 0.24).

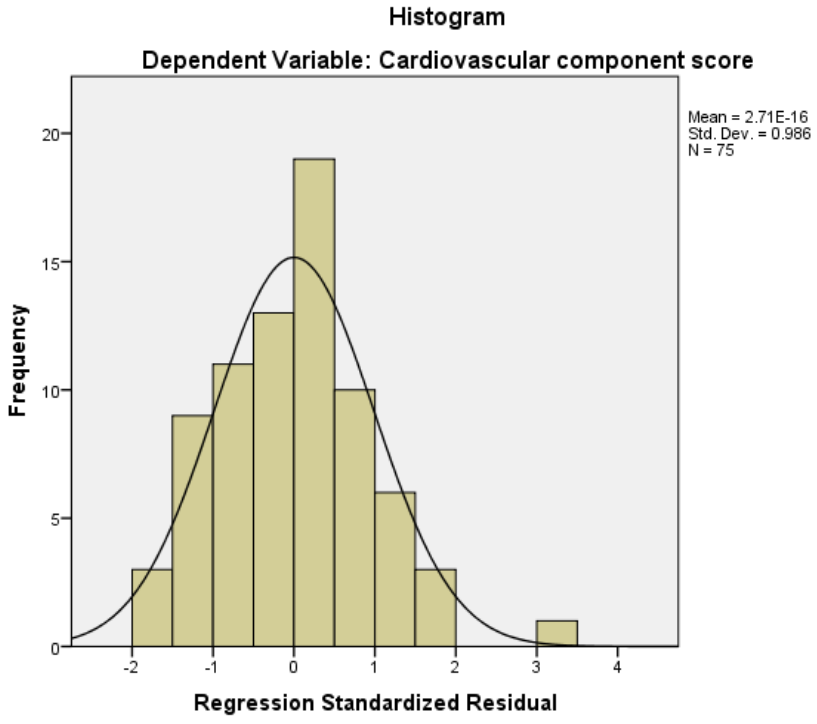


Figure 25 - Histogram of the regression standardised residual

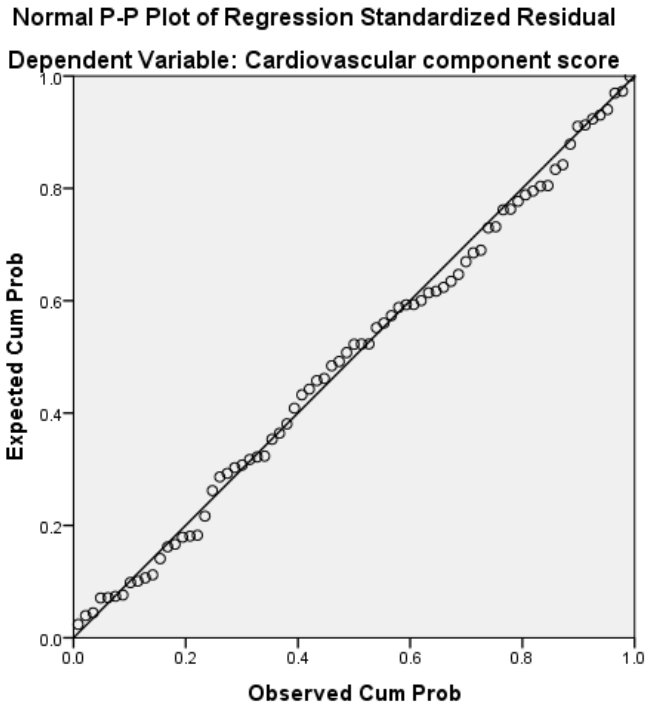


Figure 26 - Normal P-P plot of regression standardized residual

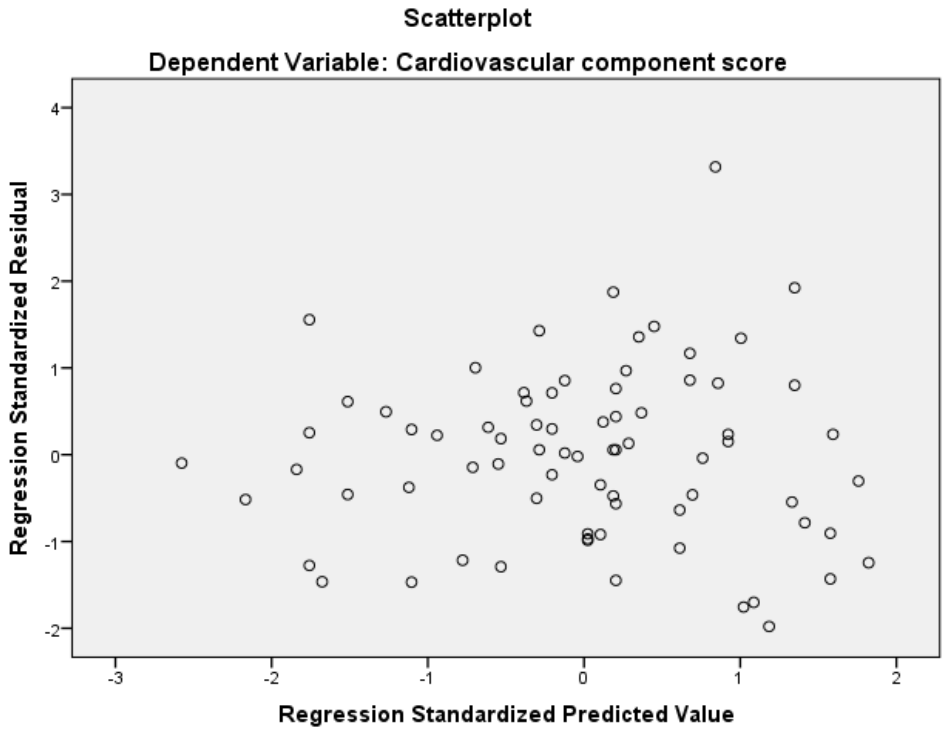


Figure 27 - Scatterplot of the regression standardized residual and regression standardized predicted value

1.13: Chapter 8, Hypothesis 1

The assumptions of a hierarchical regression for the association between participant group (retired international rugby players or comparison participant) and neuroendocrine component score, adjusting for age:

The analysis of standard residuals showed that the data contained outliers (minimum standard residual = -1.94, maximum standard residual = 3.46). One comparison participant had a standardised residual value of 3.46, which is defined as an outlier as it is above the value of 3.00 (Tabachnick & Fidell, 2007). The data was checked and the participant had a high but correct neuroendocrine component score (driven by very low DHEAS), therefore it was left in the analysis. Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 1.00, VIF = 1.00; concussion group, tolerance = 1.00, VIF = 1.00). The data met the assumption of independent errors (Durbin-Watson value = 1.76). The histogram of standardised residuals indicated that the data contained normally distributed errors (Figure 28), as did the normal P-P plot of standardised residuals, which showed points that were close to the line (Figure 29). The scatterplot of standardised predicted values showed that the data met the assumptions of homogeneity of variance and linearity (Figure 30). The data also met the assumption of non-zero variances (neuroendocrine component scores, variance = 0.79; age, variance = 131.50, retired player/ comparison group, variance = 0.24).

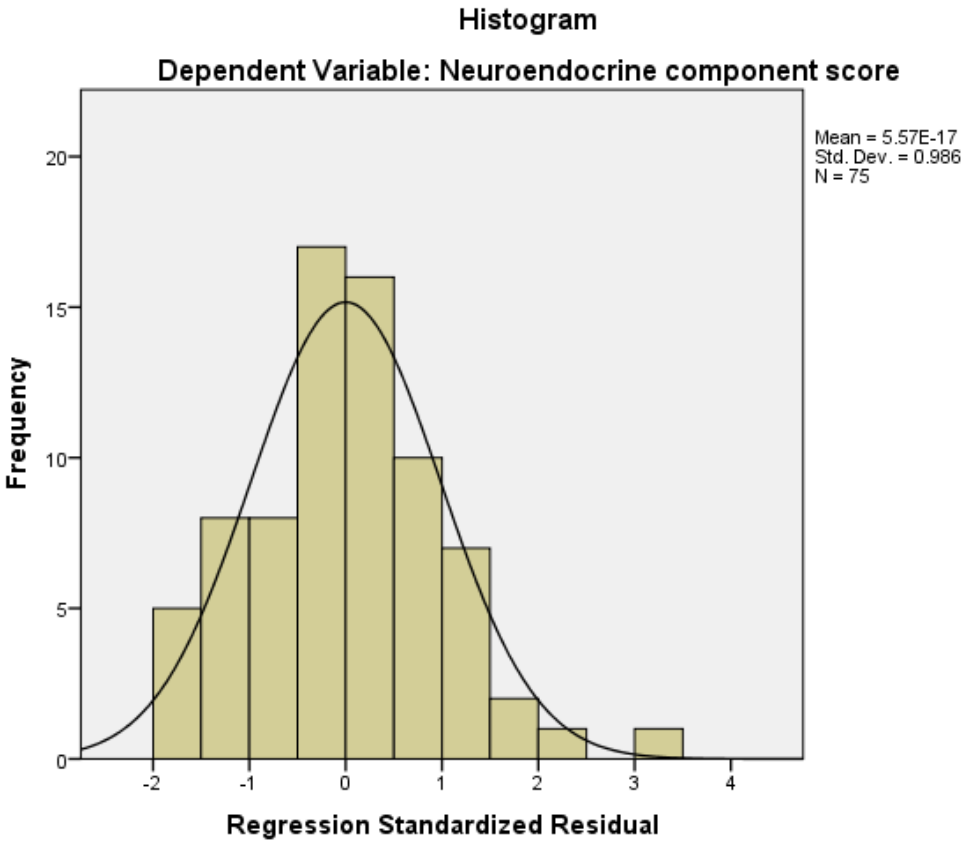


Figure 28 - Histogram of the regression standardised residual

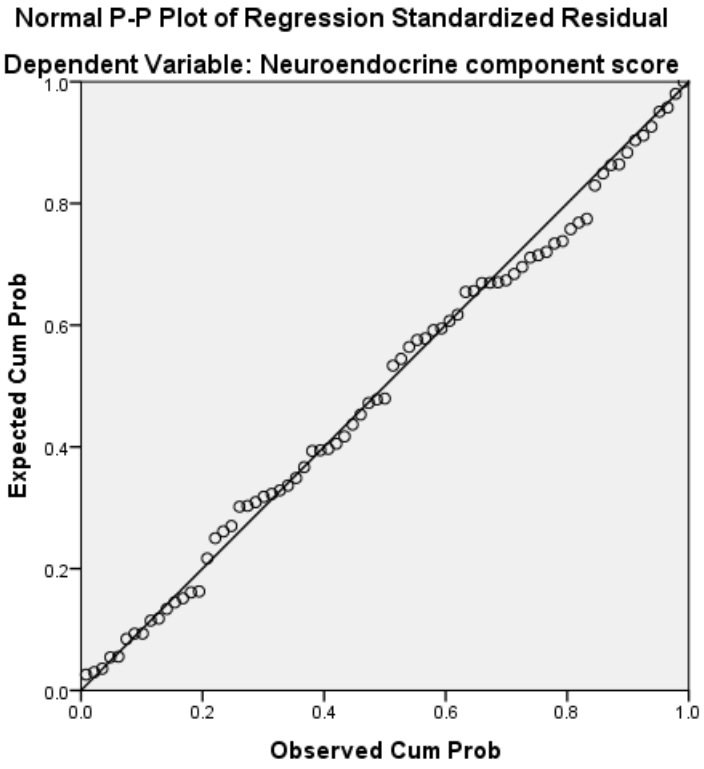


Figure 29 - Normal P-P plot of regression standardized residual

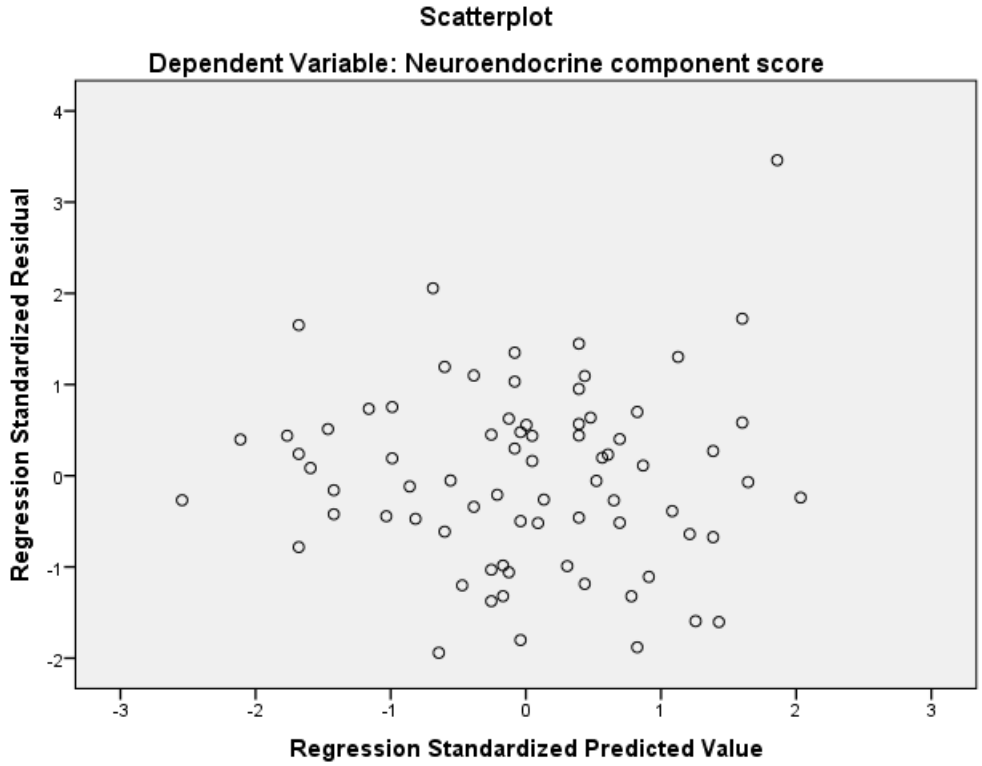


Figure 30 - Scatterplot of the regression standardized residual and regression standardized predicted value

1.14: Chapter 8, Hypothesis 1

The assumptions of a hierarchical regression for the association between participant group and metabolic component score, adjusting for age:

The analysis of standard residuals showed that the data contained no outliers (minimum standard residual = -1.88, maximum standard residual = 2.90). Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 1.00, VIF = 1.00; retired rugby player/ comparison group, tolerance = 1.00, VIF = 1.00). The data met the assumption of independent errors (Durbin-Watson value = 1.62). The histogram of standardised residuals indicated that the data contained errors that may have a small positive skew, (Figure 31), however with a small sample size of residuals the normal P-P plot of standardised residuals is a better indicator of normality, and this showed points that were close to the line (Figure 32). The scatterplot of standardised predicted values showed that although the data were not normally distributed (Figure 33). The data also

met the assumption of non-zero variances (metabolic component scores, variance = 0.85; age, variance = 131.50, retired player/ comparison group, variance = 0.24).

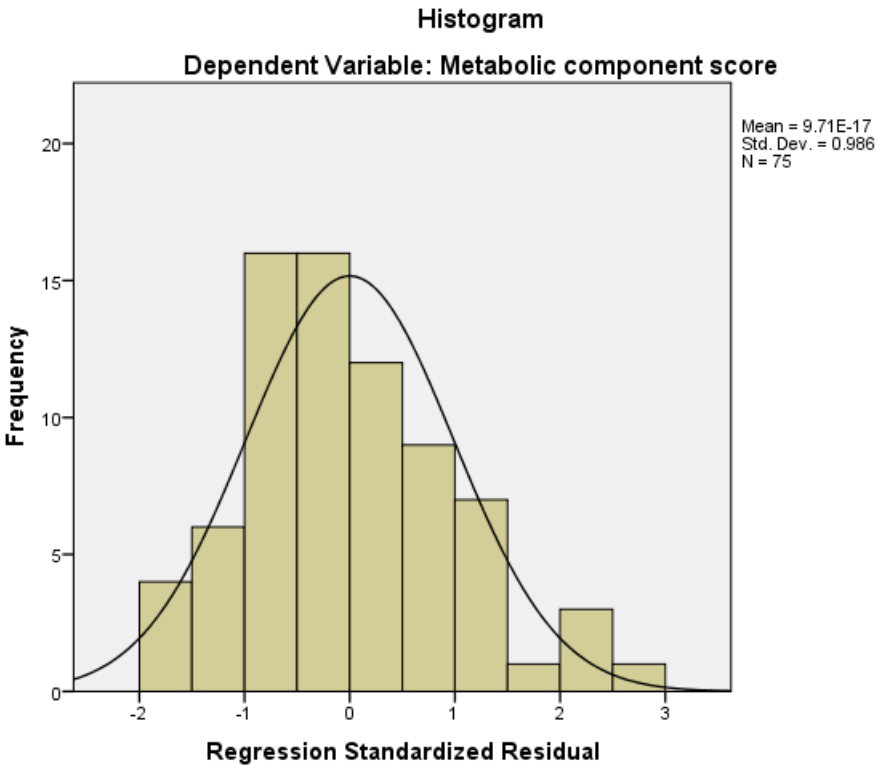


Figure 31 - Histogram of the regression standardised residual

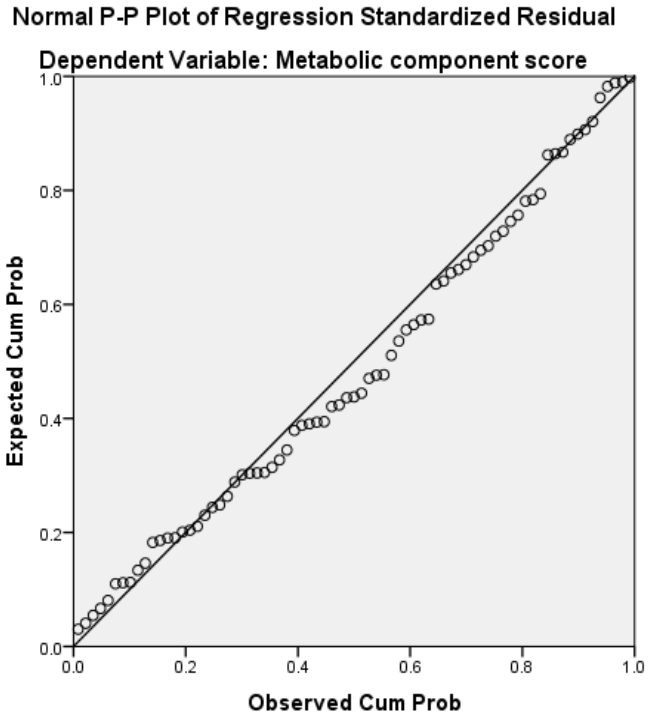


Figure 32 - Normal P-P plot of regression standardized residual

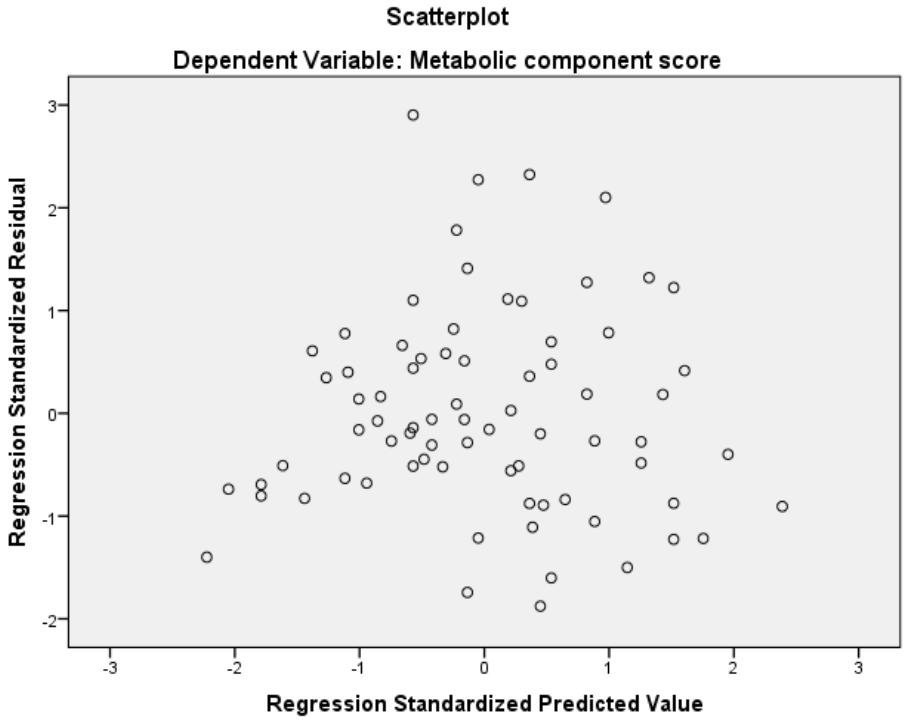


Figure 33 - Scatterplot of the regression standardized residual and regression standardized predicted value

1.15: Chapter 8, Hypothesis 3

The assumption of proportional odds for the association between GOS-E ratings and AL component scores late in retired international rugby players:

Allostatic load component	X^2	*p*
Cardiovascular	0.02	0.895
Neuroendocrine	1.59	0.208
Immune	0.38	0.537
Metabolic	0.19	0.661
Anthropometric	0.02	0.894

Table 23- Ordinal logistic regression analysis of the relationship between GOS-E ratings and allostatic load component scores in 46 retired international rugby players in Study 4 (Chapter 8)

1.16: Chapter 8, Hypothesis 5

The assumptions of a hierarchical regression for the association between AL and symbol digit modalities test score in 46 retired international rugby players, adjusting for age and number of years in education:

The analysis of standard residuals showed that the data contained outliers (minimum standard residual = -3.02, maximum standard residual = 1.86). One retired international rugby player had a standardised residual value of -3.02, which is defined as an outlier as it is below the value of -3.00, although only just (Tabachnick & Fidell, 2007). The data was checked and the participant had a low but correct symbol digit modalities test score, therefore it was left in the analysis. Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.97, VIF = 1.03; number of years in education, tolerance = 1.00, VIF = 1.00; AL scores, tolerance = 0.97, VIF = 1.03). The data met the assumption of independent errors (Durbin-Watson value = 2.16). The histogram of standardised residuals indicated that the data contained normally distributed errors (Figure 34), as did the normal P-P plot of standardised residuals, which showed points that were close to the line (Figure 35). The scatterplot of standardised predicted values showed that the data met the assumptions of homogeneity of variance and linearity (Figure 36). The data also met the assumption of non-zero variances (Symbol Digit Modalities scores, variance = 117.57; AL score, variance = 7.26; age, variance = 164.96).

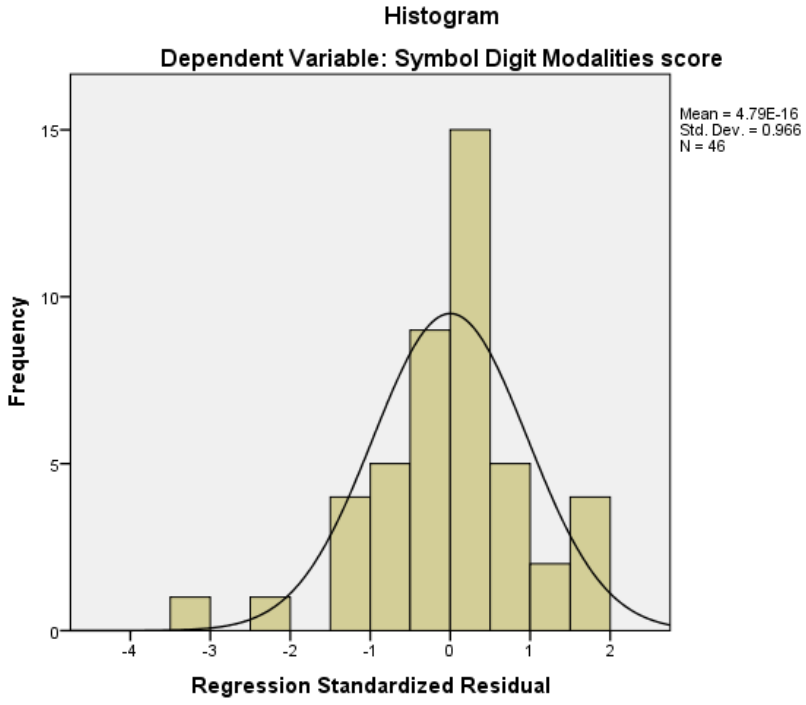


Figure 34 - Histogram of the regression standardised residual

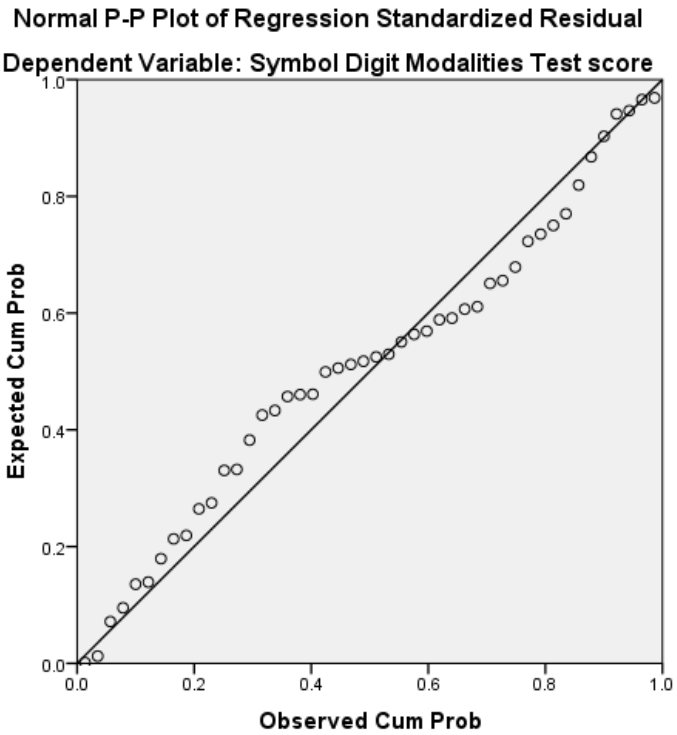


Figure 35 - Normal P-P plot of regression standardized residual

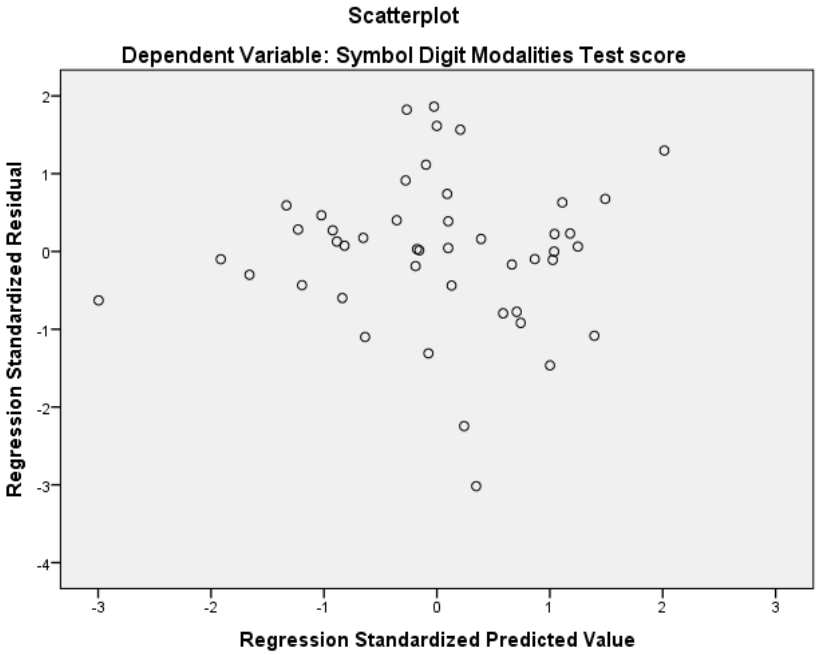


Figure 36 - Scatterplot of the regression standardized residual and regression standardized predicted value

1.17: Chapter 8, Hypothesis 5

The assumptions of a hierarchical regression: association between AL and time (seconds) to complete Form B of the Trails Making Test in 46 retired

international rugby players, adjusting for age, number of years in education and number of concussions:

The analysis of standard residuals showed that the data contained outliers (minimum standard residual = -1.55, maximum standard residual = 3.41). One retired international rugby player had a standardised residual value of -3.41, which is defined as an outlier as it is above the value of 3.00 (Tabachnick & Fidell, 2007). The data was checked and the participant had taken a long time to complete the task (1 minute 38 seconds). Despite being an outlier, this score was correct; therefore it was left in the analysis. Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.76, VIF = 1.31; number of years in education, tolerance = 0.99, VIF = 1.01; number of concussions tolerance = 0.74, VIF = 1.35; AL scores, tolerance = 0.94, VIF = 1.06). The data met the assumption of independent errors (Durbin-Watson value = 1.79). The histogram of standardised residuals indicated that the distribution of the data was slightly skewed (Figure 37), however the normal P-P plot of standardised residuals showed points that were close to the line, indicating a normal distribution (Figure 38). The scatterplot of standardised predicted values showed that the data met the assumptions of homogeneity of variance and linearity (Figure 39). The data also met the assumption of non-zero variances (time (seconds) to complete the Form B Trail Making Test, variance = 321.04.57; AL score, variance = 7.26; age, variance = 164.96; number of years in education, variance = 6.45, total number of concussions, variance = 184.21).

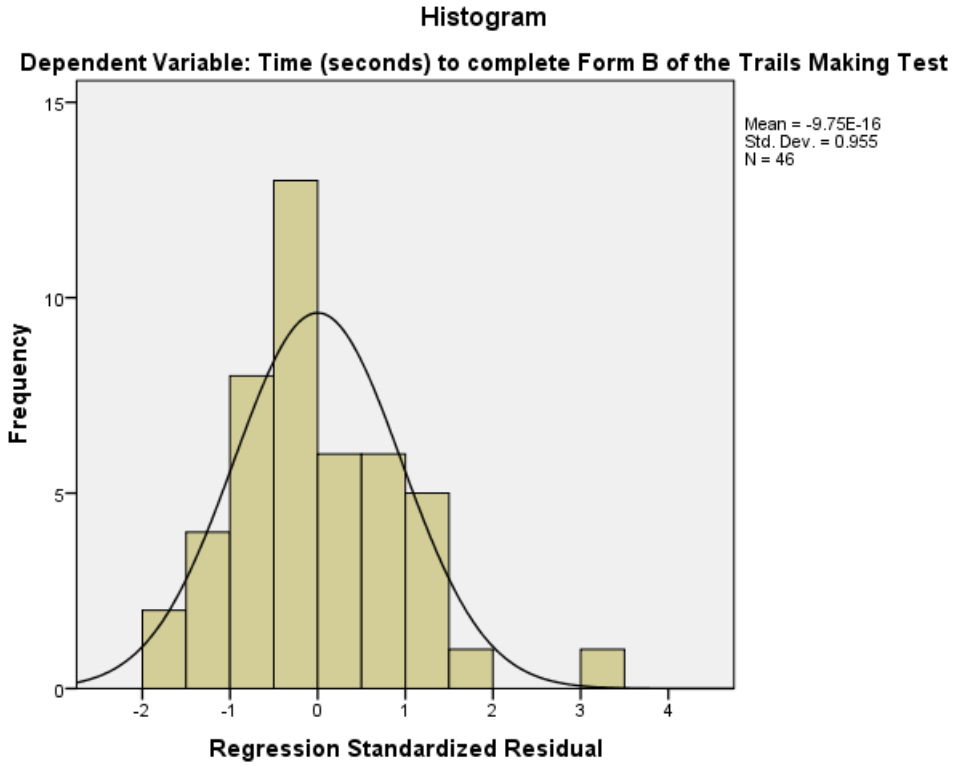


Figure 37 - Histogram of the regression standardised residual

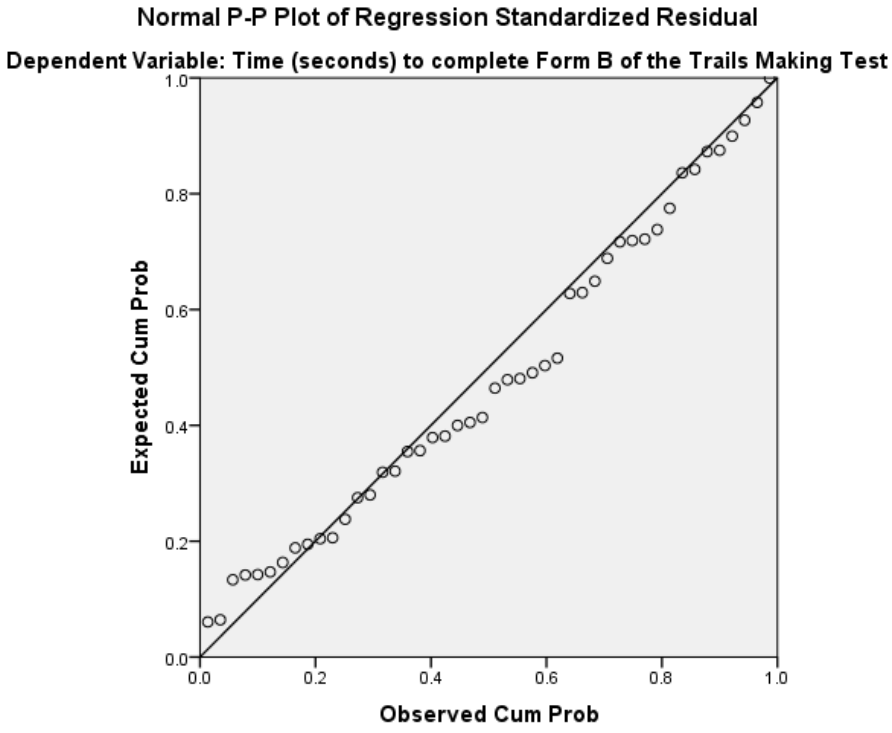


Figure 38 - Normal P-P plot of regression standardized residual

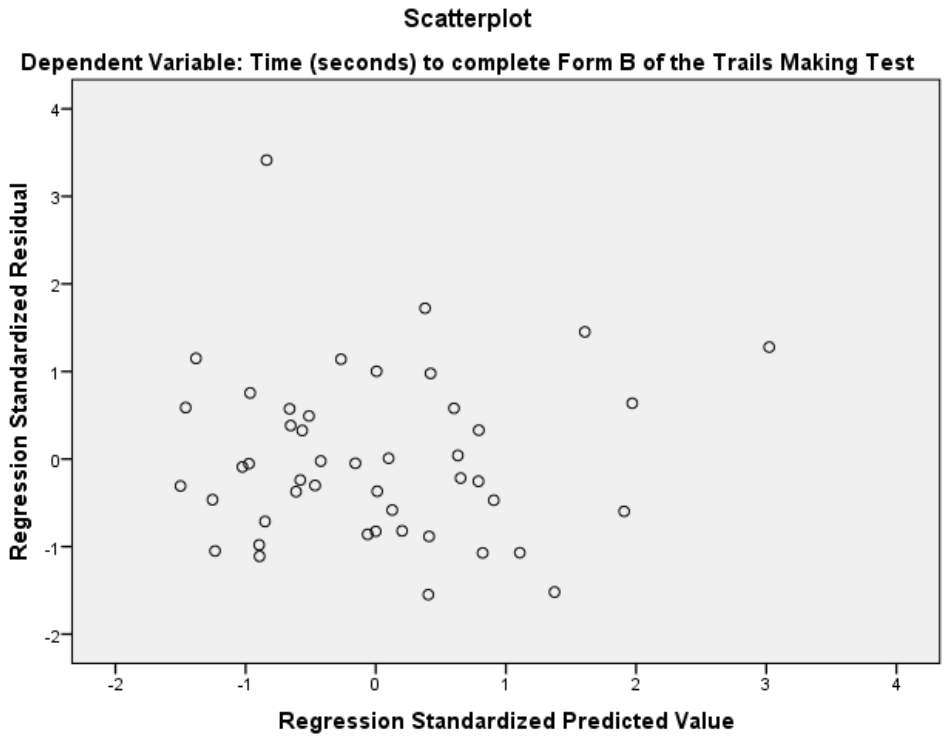


Figure 39 - Scatterplot of the regression standardized residual and regression standardized predicted value

1.18: Chapter 8, Hypothesis 5

The assumptions of a hierarchical regression for the association between AL scores and immediate recall scores for auditory verbal learning in 46 retired international rugby players, adjusting for age and number of concussions:

The analysis of standard residuals showed that the data contained no outliers (minimum standard residual = -2.17, maximum standard residual = 1.99). Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.77, VIF = 1.31; number of concussions, tolerance = 0.74, VIF = 1.34; AL scores, tolerance = 0.94, VIF = 1.06). The data met the assumption of independent errors (Durbin-Watson value = 1.83). The histogram of standardised residuals indicated that the data contained normally distributed errors (Figure 40), as did the normal P-P plot of standardised residuals, which showed points that were close to the line (Figure 41). The scatterplot of standardised predicted values showed that the data met the assumptions of homogeneity of variance and linearity (Figure 42). The data also met the assumption of non-zero variances (immediate

recall scores for auditory verbal learning, variance = 120.82; AL score, variance = 7.26; age, variance = 164.96; total number of concussions, variance = 184.21).

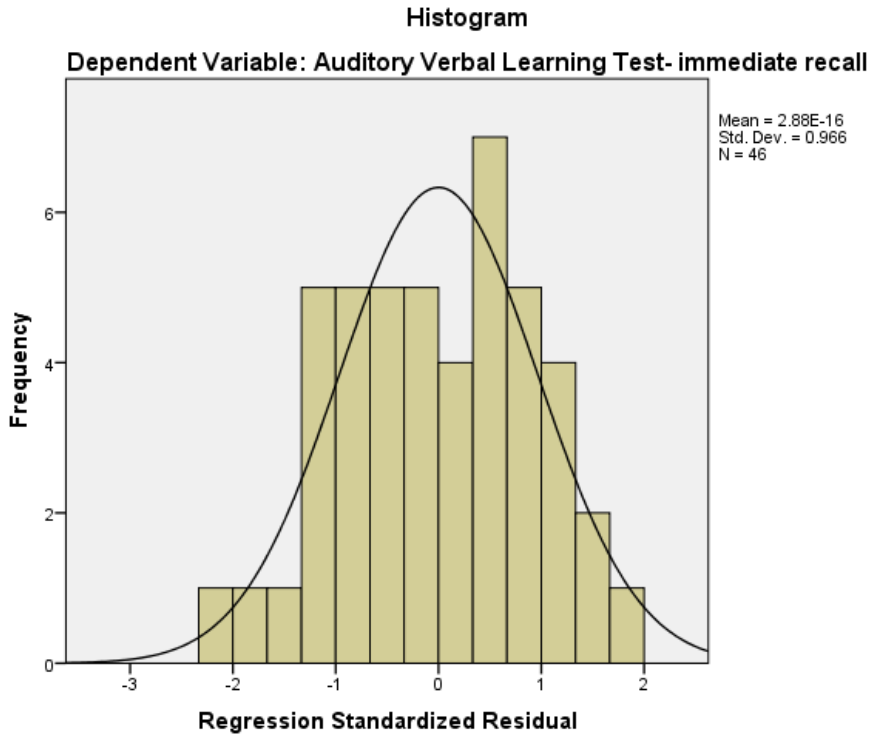


Figure 40 - Histogram of the regression standardised residual

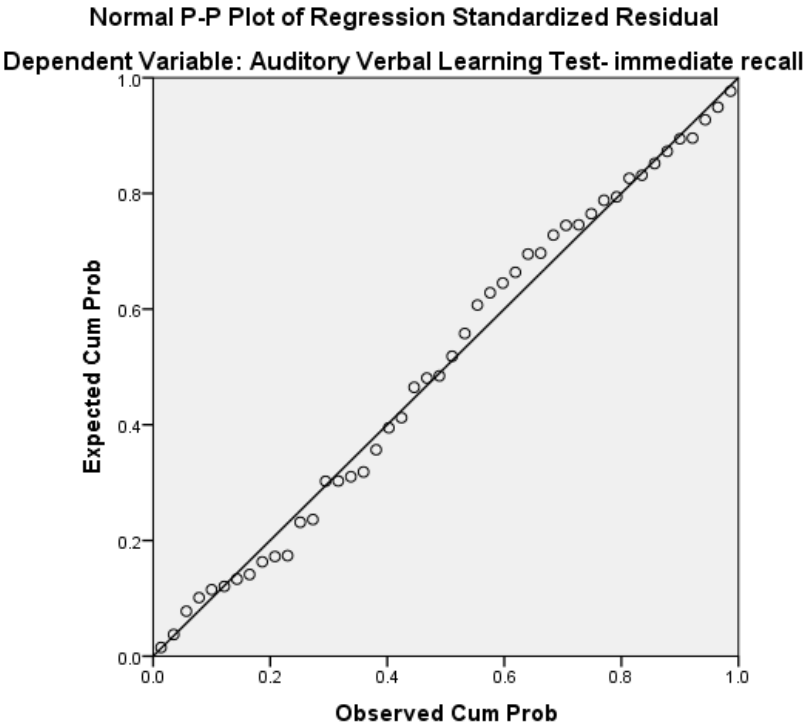


Figure 41 - Normal P-P plot of regression standardized residual

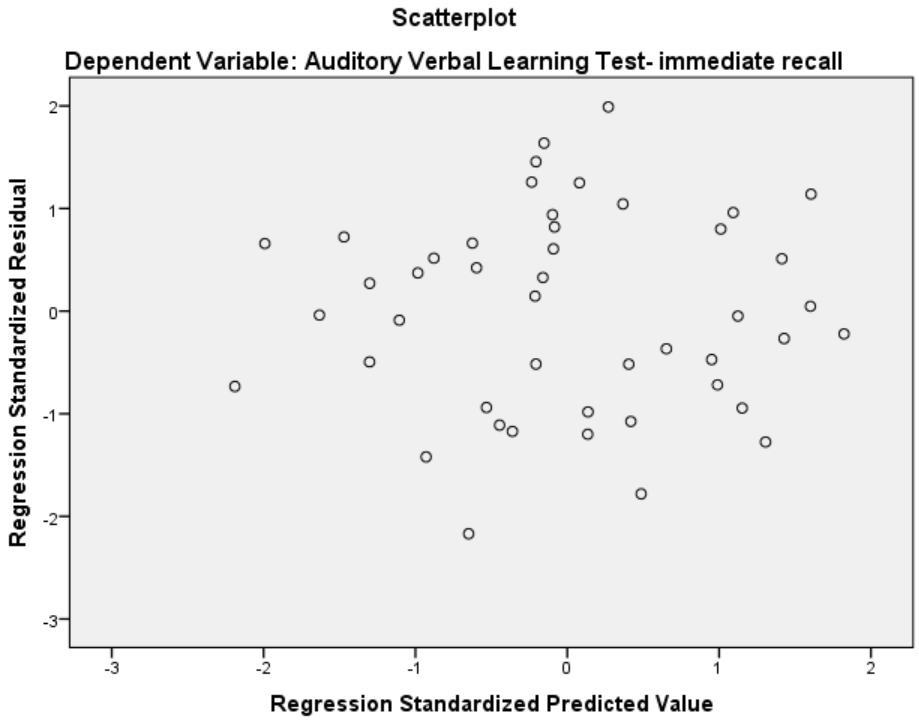


Figure 42 - Scatterplot of the regression standardized residual and regression standardized predicted value

1.19: Chapter 8, Hypothesis 5

The assumptions of a hierarchical regression for the association between AL scores and delayed recall of auditory verbal learning in 46 retired international rugby players, adjusting for age:

The analysis of standard residuals showed that the data contained no outliers (minimum standard residual = -2.27, maximum standard residual = 1.84). Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.97, VIF = 1.03; AL scores, tolerance = 0.97, VIF = 1.03). The data met the assumption of independent errors (Durbin-Watson value = 2.07). The histogram of standardised residuals indicated that the data contained roughly normally distributed errors (Figure 43), as did the normal P-P plot of standardised residuals, which showed points that were close to the line (Figure 44). The scatterplot of standardised predicted values showed that the data met the assumptions of homogeneity of variance and linearity (Figure 45). The data also met the assumption of non-zero variances (delayed recall scores for

auditory verbal learning, variance = 11.81; AL score, variance = 7.26; age, variance = 164.96).

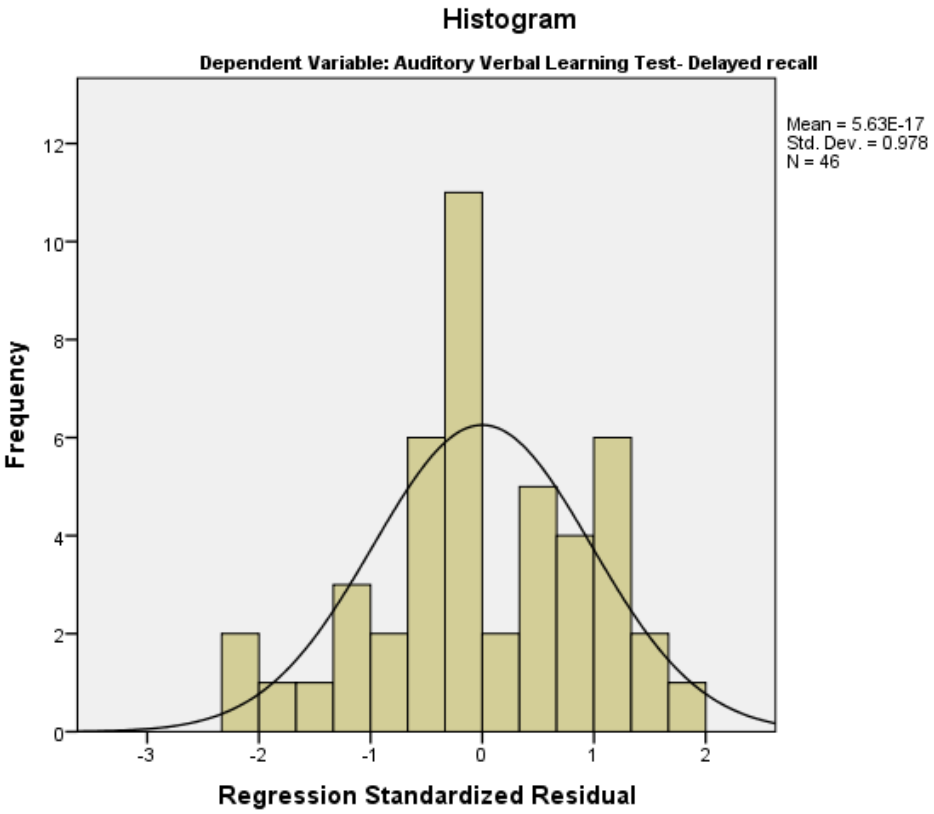


Figure 43 - Histogram of the regression standardised residual

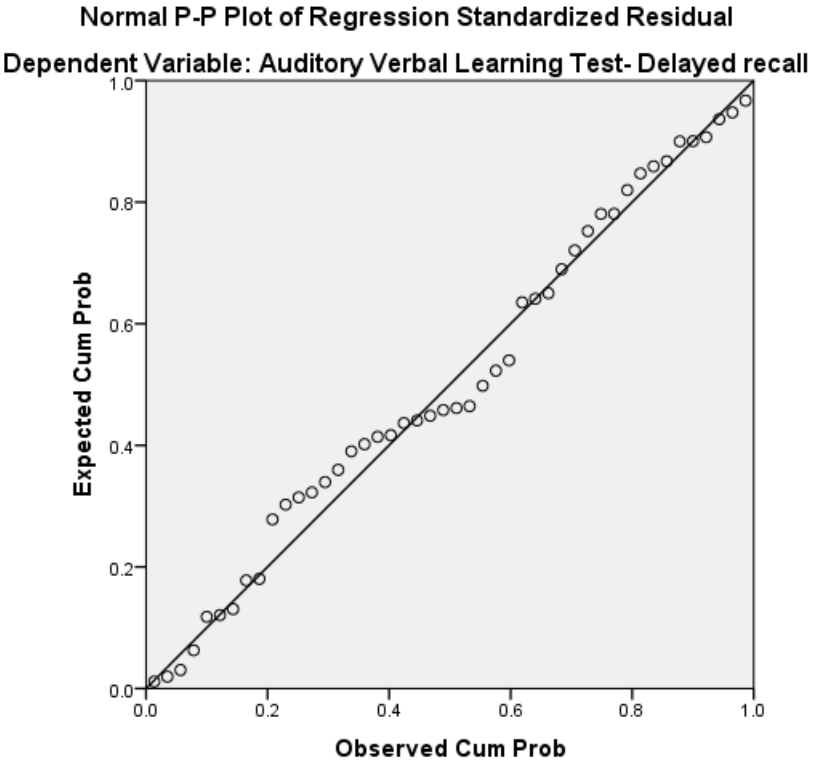


Figure 44 - Normal P-P plot of regression standardized residual

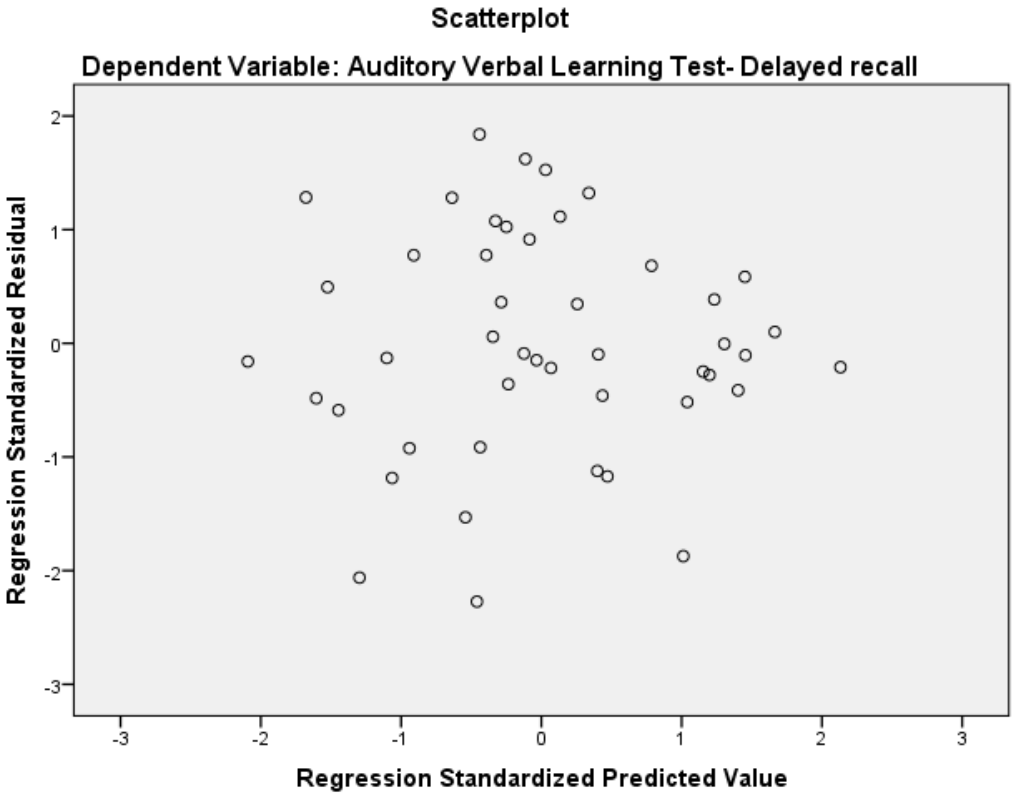


Figure 45 - Scatterplot of the regression standardized residual and regression standardized predicted value

1.20: Chapter 8, Hypothesis 5

The assumptions of a hierarchical regression for the association between AL and time (seconds) to complete the Grooved Pegboard with the dominant hand in 46 retired international rugby players, adjusting for age:

The analysis of standard residuals showed the data contained no outliers (minimum standard residual = -2.53, maximum standard residual = 1.93). Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.97, VIF = 1.03; AL scores, tolerance = 0.97, VIF = 1.03). The data met the assumption of independent errors (Durbin-Watson value = 1.94). The histogram of standardised residuals indicated that the data contained normally distributed errors (Figure 46), as did the normal P-P plot of standardised residuals, which showed points that were close to the line (Figure 47). The scatterplot of standardised predicted values showed that the data met the assumptions of homogeneity of variance and linearity (Figure 48). The data also met the assumption of non-zero variances (time (seconds) to complete the Grooved Pegboard with dominant hand, variance = 154.41; AL score, variance = 7.26; age, variance = 164.96; total number of concussions, variance = 184.21).

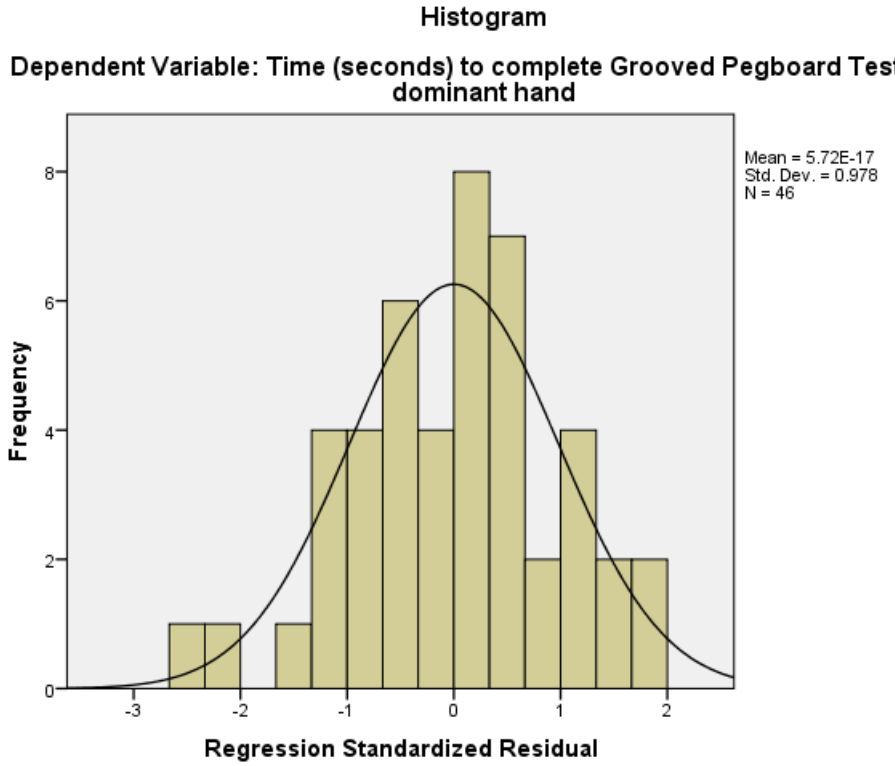


Figure 46 - Histogram of the regression standardised residual

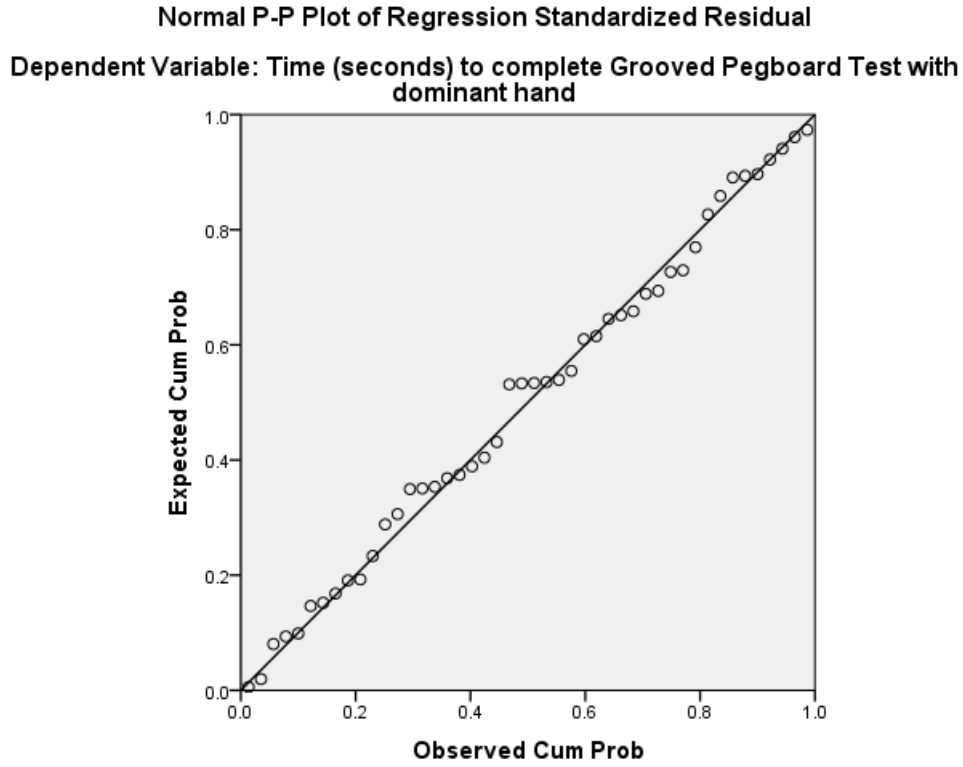


Figure 47 - Normal P-P plot of regression standardized residual

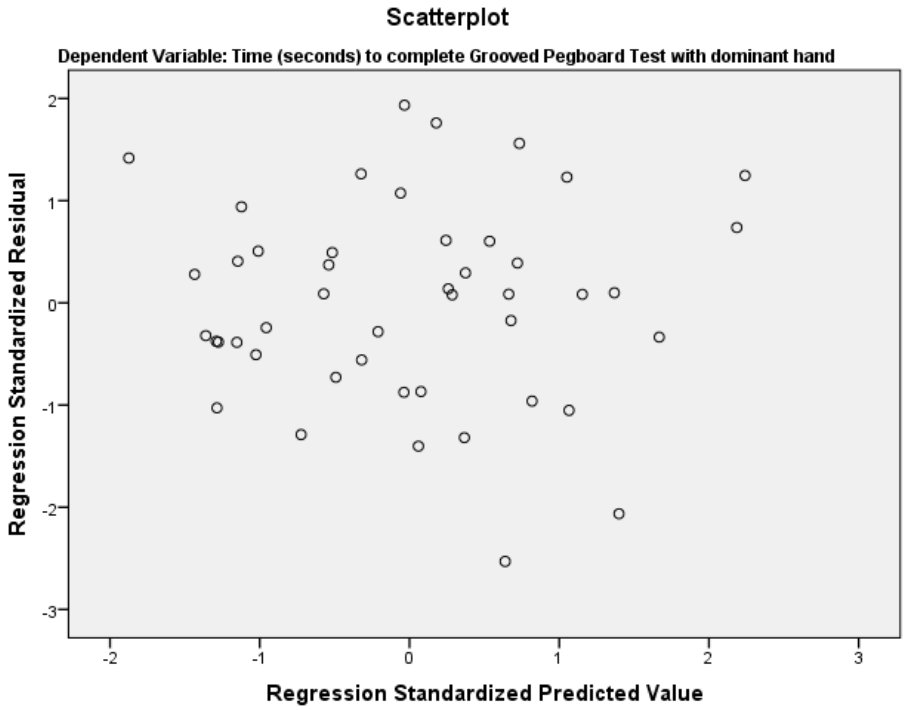


Figure 48 - Scatterplot of the regression standardized residual and regression standardized predicted value

1.21: Chapter 8, Hypothesis 5

The assumptions of a hierarchical regression for the association between AL and time (seconds) to complete the Grooved Peg Board with the non-dominant hand in 46 retired international rugby players, adjusting for age:

The analysis of standard residuals showed the data contained no outliers (minimum standard residual = -2.18, maximum standard residual = 2.19). Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (age, tolerance = 0.97, VIF = 1.03; AL scores, tolerance = 0.97, VIF = 1.03). The data met the assumption of independent errors (Durbin-Watson value = 1.80). The histogram of standardised residuals indicated that the data contained normally distributed errors (Figure 49), as did the normal P-P plot of standardised residuals, which showed points that were close to the line (Figure 50). The scatterplot of standardised predicted values showed that the data met the assumptions of homogeneity of variance and linearity (Figure 51). The data also met the assumption of non-zero variances (time (seconds) to complete the Grooved

Pegboard with the non-dominant hand, variance = 255.59; AL score, variance = 7.26; age, variance = 164.96; total number of concussions, variance = 184.21).

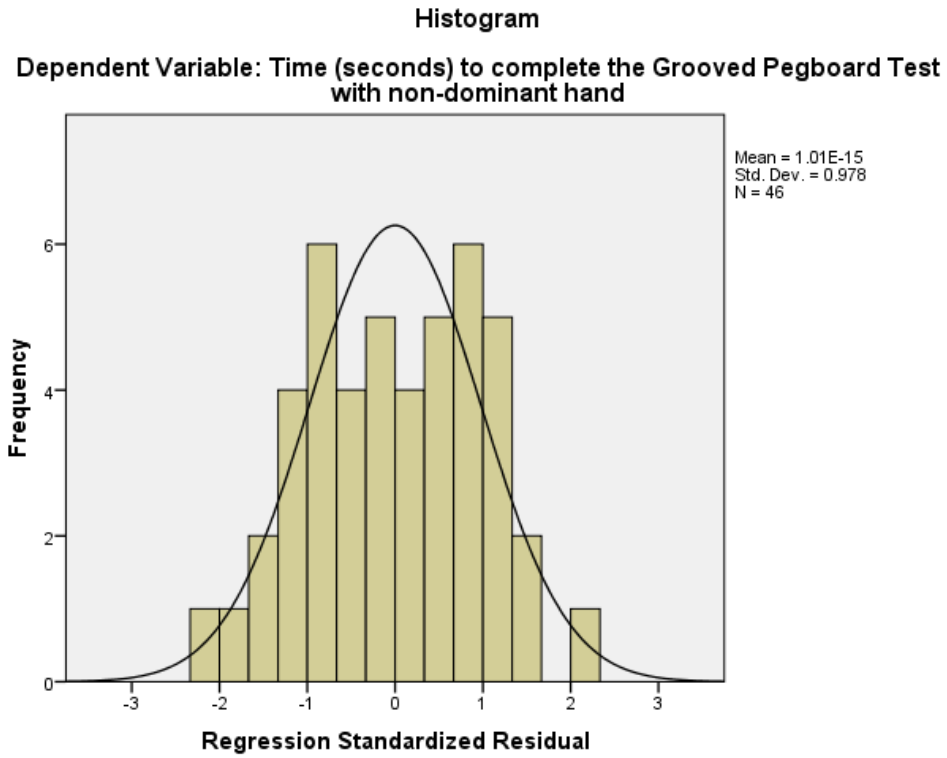


Figure 49 - Histogram of the regression standardised residual

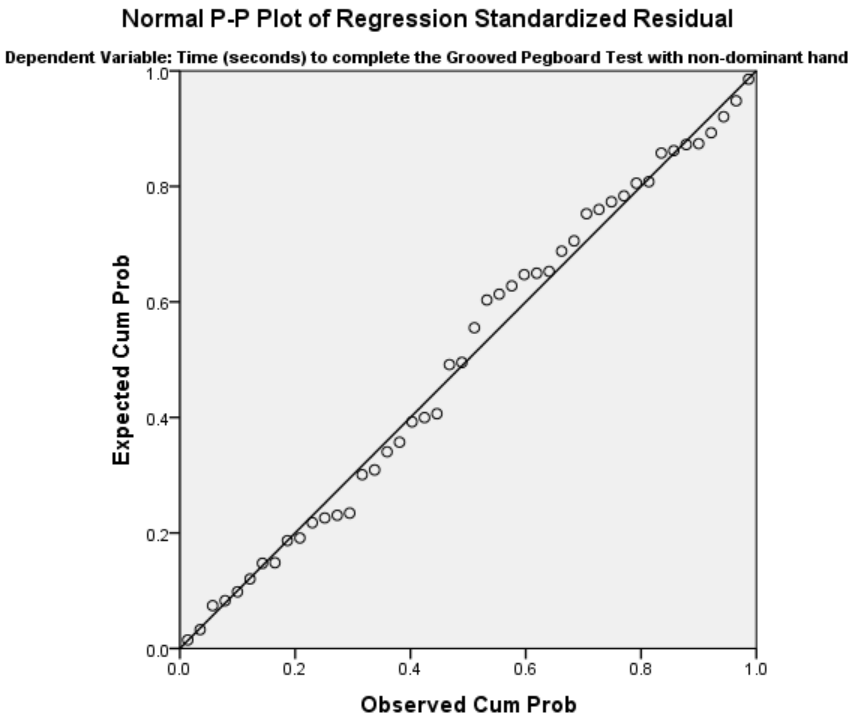


Figure 50 - Normal P-P plot of regression standardized residual

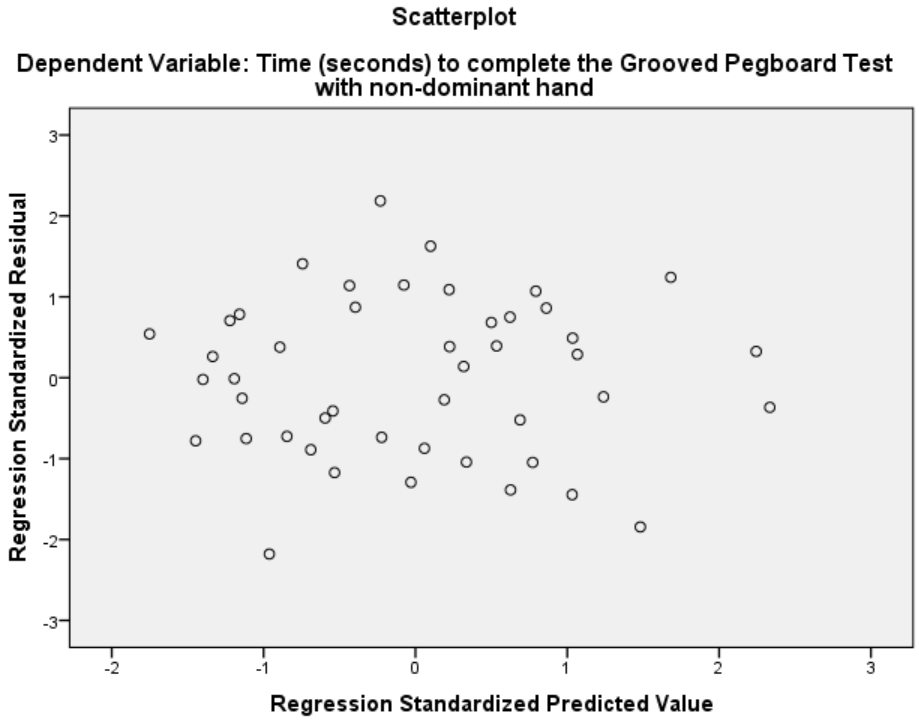


Figure 51 - Scatterplot of the regression standardized residual and regression standardized predicted values