Cognitive impairment and health-related quality of life following traumatic brain injury.

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Abstract

Background: Cognitive impairment is a common and disabling consequence of traumatic brain injury (TBI) but its impact on health-related quality of life is not well understood.

Objective: To investigate the relationship between cognitive impairment and health-related quality of life (HRQoL) after TBI.

Methods: Retrospective, cross-sectional study of a specialist TBI outpatient clinic patient sample. Outcome measures: Addenbrooke’s Cognitive Examination Tool - Revised (ACE-R), and SF-36 quality of life, Beck Depression Inventory II (BDI-II), Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) questionnaires.

Results: 240 adults were assessed: n=172 (71.7%) moderate-severe, 41 (23.8%) mild, 27 (11.3%) symptomatic TBI, 174 (72.5%) male, median age (range): 44 (22-91) years. TBI patients reported poorer scores on all domains of SF-36 compared to age-matched UK normative data. Cognitively impaired patients reported poorer HRQoL on the physical, social role and emotional role functioning, and mental health domains. Cognitive impairment predicted poorer HRQoL on the social and emotional role functioning domains, independently of depressive symptoms, sleep disturbance, daytime sleepiness and TBI severity. Mediation analysis revealed that the effect of depressive symptoms on the emotional role functioning domain of HRQoL was partially mediated by cognitive dysfunction.

Conclusion: Cognitive impairment is associated with worse health-related quality of life after TBI and partially mediates the effect of depressive symptoms on emotional role functioning.
Keywords: SF-36; cognition; depression; sleep disturbance; TBI.
Introduction
Traumatic brain injury (TBI) can have a detrimental impact on health-related quality of life (HRQoL) (Polinder, Haagsma, van Klaveren, Steyerberg, & van Beeck, 2015; Scholten et al., 2015). Improving patient HRQoL is a major goal of rehabilitative interventions and support structures aimed at TBI patients. However, efforts to improve HRQoL would benefit from a more accurate understanding of how the complex pattern of symptoms and impairments post-TBI, including its physical, cognitive and emotional effects, relate to the different facets of the patient’s physical, mental, emotional and social wellbeing.

Cognitive impairment, a common consequence of TBI, has major detrimental effects on functional ability, as demonstrated by its clear association with poor outcomes on a multitude of clinician- and carer-reported measures of disability in this patient population (Whitnall, McMillan, Murray, & Teasdale, 2006; Benedictus, Spikman, & van der Naalt, 2010; Ponsford, Olver, & Curran, 1995; Hoofien, Gilboa, Vakil, & Donovick, 2001). However, despite its known negative effects on functional outcome, it is not clear what impact post-TBI cognitive impairment has on HRQoL as perceived and reported by the patient. This relationship is not self-evident; for instance, severe cognitive impairment is commonly associated with impaired self-awareness of the effects of TBI (Sherer et al., 1998), which can lead to higher estimates of patients’ self-reported HRQoL (Sasse et al., 2013). It is therefore possible that cognitive impairment may be paradoxically associated with better self-reported HRQoL. Alternatively, the significant limitations that post-TBI cognitive impairment poses on everyday functioning may be associated with worse HRQoL as perceived by the patient.

In the present study, we addressed this question by examining the effect of cognitive impairment, as determined by the widely used Addenbrooke’s Cognitive Examination
Tool - Revised (ACE-R), on HRQoL, as measured by the Short Form-36 (SF-36) questionnaire in adult patients after TBI. ACE-R is a sensitive and easily administered test to identify cognitive impairment in TBI (Gaber, 2008). The SF-36 questionnaire has been extensively applied in TBI and has demonstrated high reliability and validity in this population, even in the presence of cognitive impairment (Findler, Cantor, Haddad, Gordon, & Ashman, 2001; Guilfoyle et al., 2010; Polinder et al., 2015; Riemersma, Forbes, Glanville, Eastwood, & Kleijnen, 2000). It consists of eight scaled scores, each of which summarizes a different aspect of the patient’s physical, mental, emotional and social wellbeing, therefore permitting a multidimensional examination of HRQoL (J. E. Ware, Kosinski, Dewey, & Gandek, 2000).

Cognitive impairment following TBI does not typically occur in isolation. Depression, sleep disturbance and daytime sleepiness are common consequences of TBI, which not only coexist with post-TBI cognitive impairment, but can also affect cognitive function in their own right (Silver, McAllister, & Arciniega, 2009; Marazziti, Consoli, Picchetti, Carlini, & Faravelli, 2010; Killgore, 2010; Ohayon & Vecchierini, 2002). Importantly, the presence of these symptoms is also related to poorer HRQoL following TBI (Grauwmeijer, Heijenbrok-Kal, & Ribbers, 2014; Englander, Bushnik, Oggins, & Katznelson, 2010; Cantor et al., 2008). Here we investigated whether cognitive impairment predicted health-related quality of life post-TBI independently of depressive symptoms, sleep disturbance and daytime sleepiness.

Depression has a known major detrimental effect on health-related quality of life following TBI (Bombardier et al., 2010), and also has a negative impact on cognitive function in this patient group (Chamelian & Feinstein, 2006). To further elucidate the role of cognitive impairment in TBI, we investigated whether the effect of depression on HRQoL may be partially mediated by cognitive impairment.
Methods

Study design
Case records were retrospectively reviewed from new patients attending the specialist multi-disciplinary adult TBI clinic at Charing Cross/St Mary’s Hospitals, Imperial College Healthcare NHS Trust (ICHNT), London, UK, to collate data from their first outpatient appointment. Adult patients (>18 years) with a history of at least one moderate-severe, mild (probable) or symptomatic (possible) TBI (Malec et al., 2007), who were able to complete the clinical questionnaires and cognitive assessment in clinic were included in the study. Data was anonymised prior to analysis. All data was collected as part of routine clinical care. Patients taking part in neuroimaging research and longitudinal assessment of cognitive function also gave written consent to allow records to be accessed (Research Ethics Committee West London 09/H0707/82).

Quality of life and clinical measures
Health-related quality of life (HRQoL) was assessed using the SF-36 questionnaire (Ware Jr., 1999). SF-36 was scored as per the published instructions (J. E. Ware et al., 2000). 35 of the items were grouped to form eight domain subscales: PF: physical functioning, RP: physical role functioning, BP: bodily pain, GH: general health perception, VT: vitality, SF: social role functioning, RE: emotional role functioning, MH: mental health.

Cognitive function was assessed using Addenbrooke’s Cognitive Examination – Revised (ACE-R) (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006). An upper cut-
off score of 88/100 on the ACE-R was selected to define cognitive impairment, which has been shown to maximize test sensitivity in the TBI population (Gaber, 2008).

Beck Depression Inventory-II (BDI-II) questionnaire was used as a measure of depressive symptoms (Beck, Steer, Brown, & others, 1996). To stratify patients into subgroups with and without depression, a lower cut-off score of 19 out of 63 on BDI-II was used for patients with mild (probable) and symptomatic (possible) TBI, and a lower cut-off score of 35/63 for those with moderate-severe TBI. These scores have been previously demonstrated to maximize sensitivity and specificity of BDI-II for the diagnosis of depression in TBI (Homaifar et al., 2009).

The Pittsburgh Sleep Quality Index (PSQI) questionnaire was used to quantify sleep disturbance (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). A cut-off score of >8 out of 21 for PSQI was used for group stratification as this has previously shown high sensitivity and specificity for insomnia following TBI (Fichtenberg, Putnam, Mann, Zafonte, & Millard, 2001). The Epworth Sleepiness Scale (ESS) was used to measure daytime sleepiness (Johns, 1991). Excessive daytime sleepiness (EDS) was defined by a score ≥10 out of 21 on the ESS. This cut-off can discriminate between patients with EDS and healthy controls (Johns, 1991), and has been used previously to stratify TBI patients with EDS (Baumann, Werth, Stocker, Ludwig, & Bassetti, 2007). TBI severity was categorized as moderate-severe, mild (probable) or symptomatic (possible) according to the Mayo classification system (Malec et al., 2007).

Statistical analysis
All statistical analyses were performed in the R software environment [www.r-project.org](http://www.r-project.org) (R Core Team & others, 2014). A standardized score (z-score) was derived for each SF-36 subscale using age- and gender-matched normative data for each patient. Normative data from the Omnibus Survey in Britain (Bowling, Bond, Jenkinson, & Lamping, 1999) were used, as this SF-36 normative sample was the most closely matched to our patient group in terms of demographic and socioeconomic factors. SF-36 scores deviated from normal distribution based on the Shapiro-Wilk test and Q-Q plots, therefore for these variables non-parametric tests were used for comparisons with the normative sample mean, and between subgroups as well as for correlations with other variables as specified in the Results. Two-tailed tests were used unless otherwise specified.

Multiple linear regression analysis was carried out with each standardized subscale of SF-36 as the dependent variable and presence of cognitive impairment, depression, sleep disturbance and excessive daytime sleepiness as well as TBI severity as categorical predictor variables. Assumptions of multiple linear regression analysis were tested as follows: analysis of standard residuals was carried out to identify outliers; variance inflation factor was used to test for multicollinearity; Durbin-Watson test was conducted to test for independence of errors; approximate normal distribution of errors, homoscedacity and linearity were assessed by plotting regression standardized residuals. These assumptions were met for all linear regression analyses presented in the Results.

Mediation analysis was carried out to examine whether the effect of depression on HRQoL was significantly mediated by cognitive impairment (Imai, Keele, Tingley, & Yamamoto, 2010). This analysis focused on depression as this variable (i) has a
known relationship with the mediator of interest, cognitive impairment (Chamelian & Feinstein, 2006), which was confirmed in our patient group, and (ii) is known to predict SF-36 scores, also confirmed in our patient sample (Bombardier et al., 2010). The analysis was carried out as follows: first, to establish the effect of depression on HRQoL, ordinary least squares regression was performed with SF-36 scores as the criterion variable and presence of depression as the regressor; second, the relationship between cognitive impairment (the mediator variable) and depression was tested by linear regression; third, the independent effect of the mediator variable was examined by entering both cognitive impairment and depression as predictors in a linear model with SF-36 as the dependent variable; fourth, the significance of the indirect (mediated) effect was calculated using bootstrapping, where indirect effects were computed for each of 10,000 bootstrapped samples.
Results

Patient demographics

240 patients [median age: 44 (range: 22 to 91 years); male: 174 (72.5%)] were recruited. 172 patients (71.7%) had moderate-severe, 41 (23.8%) mild (probable) and 27 (11.3%) symptomatic (possible) TBI. 79 patients (32.9%) had TBI from a fall, 74 (30.8%) road traffic accident, 37 (15.4%) assault, 25 (10.4%) blast injury in combat, 7 (2.9%) sport injury, 16 (6.7%) another mechanism, and 2 (0.01%) unknown mechanism. Median time since injury was 4.37 months (range: 18 days to 28 years). Patients’ mean scores (± SD) on clinical measures are presented in Table 1.

**Insert Table 1 here**

Health-related quality of life following TBI compared to normative data

SF-36 standardized scores (z-scores) were derived for each patient based on age- and gender-matched UK normative data (Bowling et al., 1999). As shown in Figure 1, TBI patients had significantly lower scores on all SF-36 domains when compared to the normative sample mean (z=0; Wilcoxon one-sample test, all P<0.001), indicating poorer health-related quality of life on every domain measured by SF-36 following TBI.

**Insert Figure 1 here**
Effect of cognitive impairment on health-related quality of life

Quality of life scores were compared between TBI patients with vs. those without cognitive impairment, based on their ACE-R scores. As shown in Figure 2, when comparing standardized SF-36 scores between these two groups, physical functioning (PF), social role functioning (SF), emotional role functioning (RE) and mental health (MH) domains were significantly lower in cognitively impaired patients when compared to those who were cognitively intact (Mann-Whitney-Wilcoxon test PF: \( W=1827, P=0.005 \); SF: \( W=1832, P=0.006 \); RE: \( W=1529, P<0.001 \); MH: \( W=2015, P=0.044 \)). There was no significant difference on the physical role functioning (RP), bodily pain (BP), general health perception (GH) or vitality (VT) domains between the two groups.

Insert Figure 2 here

Correlations with SF-36 standardized scores were also examined using ACE-R as a continuous measure of cognitive performance rather than as a binary cut-off defining cognitive impairment. ACE-R scores showed significant positive correlations with SF-36 scores on the physical functioning (PF: Spearman \( \rho=0.27, P=0.001 \)), general health (GH: \( \rho=0.21, P=0.013 \)), social role functioning (SF: \( \rho=0.24, P=0.004 \)), emotional role functioning (RE: \( \rho=0.35, P<0.001 \)) and mental health (MH: \( \rho=0.29, P<0.001 \)) domains, while there was no significant correlation between ACE-R and the physical role functioning (RP), bodily pain (BP), or vitality (VT) domains.

A previous study showed limited reliability and validity of SF-36 in older physically disabled individuals (Seymour et al., 2001). Therefore, we repeated the analyses,
restricting them to patients aged under 60 years. From 114 patients under 60 years, 49 were cognitively impaired and 65 were not. As shown across all ages, significantly poorer HRQoL was reported in cognitively impaired individuals on the physical functioning (PF: $W=1023$, $P=0.002$), social role functioning (SF: $W=1012.5$, $P=0.002$), emotional role functioning (RE: $W=832.5$, $P<0.001$) and mental health subscales (MH: $W=1089.5$, $P=0.006$). Additionally, cognitively impaired patients <60 years scored significantly lower on the general health subscale (GH: $W=1123$, $P=0.011$). As in the general group, there were no significant differences on the physical role functioning (RP), bodily pain (BP), or vitality (VT) subscales in patients <60 years with and without cognitive impairment. Correlations between ACE-R and SF-36 in the <60 years subgroup replicated the results shown above for the whole group.

**Effects of injury severity, depression, sleep disturbance and excessive daytime sleepiness on health-related quality of life**

SF-36 standardized scores were not significantly different when compared between different injury severities as defined by the Mayo classification [moderate-severe vs. mild (probable) vs. symptomatic (possible); Kruskal-Wallis $\chi^2<2.7$, $P>0.26$].

SF-36 scores were compared between TBI patients with vs. those without depression as determined by the BDI-II (Table 1). TBI patients with depression gave significantly lower standardized SF-36 scores on every HRQoL domain when compared to those without depression (Mann-Whitney-Wilcoxon test PF: $W=1982.5$, $P<0.001$; RP: $W=2341.5$, $P=0.001$; BP: $W=1648$, $P<0.001$; GH: $W=2058$, $P<0.001$; VT: $W=1357$, $P<0.001$; SF: $W=1555$, $P<0.001$; RE: $W=1526$, $P<0.001$; MH: $W=1141$, $P<0.001$).
SF-36 scores were also compared between TBI patients with and those without sleep disturbance as defined by their Pittsburgh Sleep Quality Index (PSQI) scores (Table 1). Patients with sleep disturbance gave significantly poorer HRQoL scores on every SF-36 domain when compared to those with no sleep disturbance (Mann-Whitney-Wilcoxon test PF: \( W = 1767, P < 0.001; \) RP: \( W = 1507, P = 0.001; \) BP: \( W = 1171.5, P < 0.001; \) GH: \( W = 1886, P < 0.001; \) VT: \( W = 1602.5, P < 0.001; \) SF: \( W = 1290.5, P < 0.001; \) RE: \( W = 1580.5, P < 0.001; \) MH: \( W = 1573, P < 0.001). The Epworth Sleepiness Scale (ESS) was used to quantify excessive daytime sleepiness (EDS) following TBI (Table 1). Patients with EDS had significantly lower HRQoL scores on every SF-36 domain except physical function (PF) when compared to those without EDS (Mann-Whitney-Wilcoxon test PF: \( W = 4489.5, P = 0.079; \) RP: \( W = 3899.5, P = 0.004; \) BP: \( W = 4113, P = 0.005; \) GH: \( W = 4241, P = 0.009; \) VT: \( W = 3404.5, P < 0.001; \) SF: \( W = 4347.5, P = 0.018; \) RE: \( W = 3668.5, P = 0.002; \) MH: \( W = 3709, P < 0.001).

**Effects of injury severity, depression, sleep disturbance and excessive daytime sleepiness on cognitive function**

ACE-R scores were significantly lower in patients with depression than in non-depressed patients \( (t=-2.42, P=0.022) \). There was no significant difference on cognitive performance as measured by ACE-R when comparing between different injury severities, between patients with sleep disturbance and those without, or between patients with excessive daytime sleepiness and those without. Correlations between ACE-R scores and BDI-II, PSQI and ESS scores were also examined. There was a significant correlation between ACE-R and BDI-II \( (Pearson r=-0.26, P=0.014) \), but there was no significant correlation between ACE-R and PSQI, or ACE-R and ESS scores.
Cognitive impairment, depression, sleep disturbance and daytime sleepiness are independent predictors of specific aspects of health-related quality of life

Next, multiple regression was performed for each SF-36 subscale, with presence or absence of cognitive impairment, depression, sleep disturbance and daytime sleepiness as well as injury severity as regressors (Table 2). Overall, this model explained a significant amount of the variance in all aspects of HRQoL. The presence of cognitive impairment significantly predicted the social and emotional role functioning domains of quality of life independently of injury severity, depression, sleep disturbance and daytime sleepiness (Table 2). Cognitive impairment did not significantly predict any of the other SF-36 sub-scale scores.

**Insert Table 2 here**

Depression was a significant independent predictor of poorer HRQoL on the bodily pain, general health, vitality, emotional role functioning domains and was the only independent predictor on the mental health domain. Sleep disturbance independently predicted all SF-36 scores except emotional role functioning and mental health. Excessive daytime sleepiness was a significant independent predictor of poorer HRQoL on the bodily pain, vitality and emotional role functioning domains. Finally, injury severity did not independently predict any aspect of HRQoL.

As reported in the previous section, there was a significant association between cognitive impairment and depression. However, variance inflation factors were <1.42 for all predictors, indicating acceptable levels of collinearity in the regression model above. Nevertheless, when the multiple regression analysis was repeated having
excluded depression as a predictor, presence of cognitive impairment significantly predicted the same two aspects of HRQoL, social and emotional role functioning (SF: $\beta=0.86, t=2.83, P=0.006$; RE: $\beta=0.98, t=3.24, P=0.002$), independently of injury severity, sleep disturbance and daytime sleepiness. In addition, the overall model still accounted for a significant amount of variance on all SF-36 domains.

**The effect of depression on emotional role functioning is partly mediated by cognitive impairment**

Next, we carried out a mediation analysis examining to what extent the effects of depression on the relevant aspects of HRQoL were mediated by cognitive impairment. This analysis focused on depression as this parameter significantly correlated with the mediator of interest, cognitive impairment. Sleep disturbance and excessive daytime sleepiness did not correlate with cognitive impairment therefore mediation analysis would not have been meaningful for these variables.

Mediation analysis was conducted as follows. First, it was established by regression that the causal variable, depression, significantly predicted all SF-36 scores (all $F>10.98$, all $P<0.001$). Second, we showed that depression significantly predicted the mediator variable, cognitive impairment ($F=5.8$, all $P=0.017$). Third, we performed multiple regression to examine the effect of cognitive impairment on HRQoL, controlling for the effect of depression. Fourth, the statistical significance of the indirect effect (i.e. the proportion of the effect of depression on HRQoL that was mediated by cognitive impairment) was tested by bootstrapping.

As shown in Figure 3, the effect of depression on the emotional role functioning (RE) domain of SF-36 was significantly mediated by the presence of cognitive impairment.
(bootstrapped indirect effect: 0.12, 95% CI: 0.02 to 0.31, P=0.02; standardized regression coefficients are shown in Figure 3). The indirect effect of cognitive impairment in mediating the relationship of physical functioning (PF) and depression was of borderline statistical significance (bootstrapped indirect effect: 0.01, 95% CI: 0 to 0.33, P=0.05). The effect of depression on the other subscales of SF-36 was not significantly mediated by cognitive impairment.

Insert Figure 3 here
Discussion

Health-related quality of life (HRQoL), of which SF-36 is the most widely used measure (Andresen & Meyers, 2000; Hays & Morales, 2001; J. E. J. Ware & Sherbourne, 1992), describes aspects of an individual’s experience relating both directly and indirectly to health, disease, disability, and impairment (Carr, Gibson, & Robinson, 2001; Moons, Budts, & De Geest, 2006). Quality of life (QoL) is a wider concept encompassing aspects of an individual’s wellbeing and life satisfaction not necessarily related to their health (Karimi & Brazier, 2016; Meeberg, 1993). HRQoL and QoL are therefore closely related but not interchangeable, and importantly, changes in HRQoL do not always correspond to changes in measures of general QoL (Carr et al., 2001).

Our results confirm the impact of traumatic brain injury (TBI) on HRQoL. HRQoL was poorer on all SF-36 scales in our TBI patient group than in a normative group matched for age, gender and geographical region. This is in keeping with multiple previous reports encompassing a variety of TBI patient groups (N. Andelic et al., 2009; Nada Andelic et al., 2010; Arango-Lasprilla, 2012; Beseoglu, Roussaint, Steiger, & Hänggi, 2013; Colantonio, Dawson, & McLellan, 1998; Tomberg, Toomela, Pulver, & Tikk, 2005; van Baalen et al., 2006), as well as with a recent meta-analysis in TBI which showed that the random effect weighted means of SF-36 scores across 17 studies were lower than USA norms on all domains, with lowest scores on the physical, social and emotional role functioning domains (Polinder et al., 2015).

The primary objective of our study was to examine the effect of cognitive impairment on the various aspects of HRQoL following TBI. We found that patients with cognitive impairment reported poorer HRQoL on the physical, social role and emotional role functioning and mental health domains. The social role and emotional role functioning aspects of quality of life pertain to difficulties at work, social activities and
other daily activities as a result of emotional problems (J. E. J. Ware & Sherbourne, 1992; J. E. Ware et al., 2000). Remarkably, we found that cognitive impairment was an independent predictor of poor scores on these aspects of HRQoL when depression, sleep disturbance, daytime sleepiness and injury severity were all taken into account. By contrast, limitation in physical activity was independently predicted by poor sleep quality rather than by cognitive impairment. Furthermore, the mental health domain, which quantifies the impact of irritability and depression on HRQoL (J. E. J. Ware & Sherbourne, 1992; J. E. Ware et al., 2000) was not independently associated with cognitive impairment but, as expected, it was significantly predicted by the presence of depressive symptoms.

A previous study in 275 TBI patients found no significant relationship between cognitive impairment and a self-reported one-item measure of general quality of life (Steadman-Pare, Colantonio, Ratcliff, Chase, & Vernich, 2001). This global measure encompassed all aspects of quality of life whereas the eight components of SF-36, more narrowly focused on HRQoL, described the multiple facets of health-related wellbeing that appear to be differentially affected by cognitive impairment after TBI.

Indeed, the independent association of cognitive impairment with social and emotional role functioning may highlight the effect of cognitive impairment on the ability to form and maintain interpersonal relationships and to function within work and the wider social environment. The impact of cognitive impairment on these particular HRQoL domains reinforces the need for additional social support for individuals with cognitive difficulties post-TBI. Furthermore, studies on pharmacological treatments and rehabilitative strategies targeting cognitive impairment in TBI (Dougall, Poole, & Agrawal, 2015; van Heugten, Gregório, & Wade, 2012) should assess the impact not only on cognitive tests and functional measures but also on the social and emotional aspects of HRQoL. Accordingly,
health economic evaluations of interventions targeting cognitive impairment following TBI would benefit from the inclusion of relevant HRQoL measures (Brazier, Deverill, & Green, 1999).

We found that TBI patients with depression scored lower on all SF-36 domains and that depression independently predicted multiple aspects of HRQoL. This result confirms previous findings indicating that depression is an independent predictor of poor HRQoL of life post-TBI (Bombardier et al., 2010). Moreover, depression after TBI is known to have a significant negative impact on cognitive function (Chamelian & Feinstein, 2006; Rapoport, McCullagh, Shammi, & Feinstein, 2005). We extended the understanding of this complex relationship using mediation analysis and found that cognitive impairment may be in part the mechanism by which depression causes emotional problems affecting patients’ HRQoL.

Successful treatment of depression in TBI may lead not only to improvement of HRQoL but also to amelioration of cognitive function (Silver et al., 2009). For example, treatment of post-TBI depression with Sertraline was associated with improved quality of life (Ashman et al., 2009) and in a different study, it was accompanied by improvements in processing speed, short-term memory and general cognitive performance (Fann, Uomoto, & Katon, 2001). Similar effects on cognitive performance were also seen after treatment of post-TBI depression with Fluoxetine (Horsfield et al., 2002). When these results are considered together with our findings, it may be inferred that the effect of successful treatment of depression on quality of life post-TBI may be partially mediated by improvements in cognition; future studies should examine this hypothesis directly.

Sleep disturbance following TBI is common, experienced between 25% and 60% of patients (Mathias & Alvaro, 2012). We found a strong relationship between sleep disturbance and poor HRQoL in TBI. This association is notable given that SF-36
does not contain items relating to sleep (J. E. Ware et al., 2000). Our finding corroborates previous results showing reduced satisfaction with quality of life in patients with ongoing sleep disturbance 1 year post-TBI (Fogelberg, Hoffman, Dikmen, Temkin, & Bell, 2012). Although sleep disturbance is known to adversely affect cognitive function in measures of information processing speed, working memory and attention (Mahmood, Rapport, Hanks, & Fichtenberg, 2004), we did not find an association with global cognitive function as measured by ACE-R.

Excessive daytime sleepiness in our data was associated with worse scores on every aspect of HRQoL and it independently predicted the bodily pain, vitality and emotional role functioning domains. In contrast to these results, and perhaps counterintuitively, a previous study found better quality of life in TBI patients with daytime sleepiness using the Functional Outcome of Sleep Questionnaire, a sleep-specific quality of life scale (Castriotta et al., 2007). These authors also found an association between excessive daytime sleepiness with performance on a vigilance task; we found no difference on cognitive performance between patients with vs. without excessive daytime sleepiness, but ACE-R does not include a measure of vigilance.

In keeping with several previous studies (Polinder et al., 2015), we found no association of injury severity with HRQoL. In contrast, a recent prospective study of all emergency department attendances at 1 year post-TBI found worse HRQoL in moderate-severe when compared with mild TBI (Scholten et al., 2015). We recruited from an outpatient clinic population who were, by definition, symptomatic, therefore the lack of association with injury severity in our sample may be due to the non-inclusion of mild TBI patients who were not symptomatic enough to seek medical attention post-TBI.
This study has several limitations. Patients were recruited from a single specialist outpatient clinic in the UK, therefore results may not necessarily generalize to the wider TBI patient population. The time elapsed since injury varied from days to several years in our group; it is therefore possible that factors other than TBI may have affected HRQoL, particularly in individuals who were assessed several years post-injury. Assessment of cognitive function was limited to ACE-R. Although this test is validated in TBI to screen for the presence of cognitive impairment (Gaber, 2008), which was the aim of our study, a more comprehensive cognitive assessment battery may have allowed a more detailed examination of the relationship between cognition and quality of life. Finally, inclusion of a disease-specific quality of life measure, such as Quolibri (von Steinbuechel, Petersen, Bullinger, group, & others, 2005) alongside SF-36, may have captured additional TBI-specific aspects of HRQoL (Bullinger & the TBI Consensus Group, 2002).

In conclusion, we show for the first time that cognitive impairment adversely affects health-related quality of life following TBI, it is an independent predictor of social and emotional role functioning when accounting for depression, sleep disturbance, daytime sleepiness and injury severity, and it partially mediates the effect of depression on emotional role functioning. These findings are of practical relevance to interventional trials and health economics evaluations.
References


Tables and Figures:

Table 1: Outcome measure scores

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean score (±SD)</th>
<th>N (%) abnormal</th>
</tr>
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<tbody>
<tr>
<td>ACE-R</td>
<td>86.8 (±11.6)</td>
<td>67 (47%)</td>
</tr>
<tr>
<td>BDI-II</td>
<td>15.9 (±13.3)</td>
<td>39 (17%)</td>
</tr>
<tr>
<td>PSQI</td>
<td>7.8 (±4.9)</td>
<td>59 (38%)</td>
</tr>
<tr>
<td>ESS</td>
<td>7.5 (±5.7)</td>
<td>74 (34%)</td>
</tr>
</tbody>
</table>

Table 1: Mean scores (±SD) and number of patients with abnormal scores on Addenbrooke’s Cognitive Examination – Revised (ACE-R), Beck Depression Inventory – II (BDI-II), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS).
Figure 1: SF-36 scores in TBI patients compared to normative data

All SF-36 standardized scores were significantly lower in TBI patients when compared to an age- and gender-matched UK normative sample. PF: physical functioning, RP: physical role functioning, BP: bodily pain, GH: general health perception, VT: vitality, SF: social role functioning, RE: emotional role functioning, MH: mental health; all P<0.001.
Cognitive impairment and quality of life following TBI. Physical functioning (PF), social role functioning (SF), emotional role functioning (RE) and mental health (MH) SF-36 standardized scores were lower in patients with cognitive impairment (ACE-R score ≤88, in dark grey) than in those without cognitive impairment (ACE-R score >88, in light grey). Group differences on physical role functioning (RP), bodily pain (BP), general health perception (GH) and vitality (VT), were not significant. * P<0.05, ** P<0.001.
Table 2: Multiple regression predicting SF-36 scores based on presence of cognitive impairment, sleep disturbance, daytime sleepiness and injury severity.

<table>
<thead>
<tr>
<th>SF36 scale</th>
<th>Cognitive β</th>
<th>Depression β</th>
<th>Sleep dist. β</th>
<th>Daytime somn. β</th>
<th>Injury severity β</th>
<th>Model F</th>
<th>Model R² Adj.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF</td>
<td>-0.47</td>
<td>-0.60</td>
<td>-1.69**</td>
<td>0.61</td>
<td>-0.46</td>
<td>3.96*</td>
<td>0.15</td>
</tr>
<tr>
<td>RP</td>
<td>-0.003</td>
<td>-0.06</td>
<td>-0.91*</td>
<td>-0.53</td>
<td>0.004</td>
<td>3.53*</td>
<td>0.13</td>
</tr>
<tr>
<td>BP</td>
<td>-0.13</td>
<td>-0.72*</td>
<td>-1.04**</td>
<td>-0.52*</td>
<td>-0.30</td>
<td>8.86**</td>
<td>0.31</td>
</tr>
<tr>
<td>GH</td>
<td>0.11</td>
<td>-0.88*</td>
<td>-0.67*</td>
<td>-0.06</td>
<td>-0.17</td>
<td>4.69**</td>
<td>0.18</td>
</tr>
<tr>
<td>VT</td>
<td>0.05</td>
<td>-0.91*</td>
<td>-0.60*</td>
<td>-0.52*</td>
<td>-0.07</td>
<td>8.29**</td>
<td>0.30</td>
</tr>
<tr>
<td>SF</td>
<td>-0.79*</td>
<td>-0.59</td>
<td>-1.22**</td>
<td>-0.22</td>
<td>-0.23</td>
<td>7.36**</td>
<td>0.27</td>
</tr>
<tr>
<td>RE</td>
<td>-0.86*</td>
<td>-1.04*</td>
<td>-0.38</td>
<td>-0.78*</td>
<td>-0.43</td>
<td>7.04**</td>
<td>0.27</td>
</tr>
<tr>
<td>MH</td>
<td>-0.13</td>
<td>-1.45**</td>
<td>-0.41</td>
<td>-0.35</td>
<td>-0.30</td>
<td>7.69**</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Table 2: Multiple regression predicting each SF-36 score based on presence of cognitive impairment, sleep disturbance, daytime sleepiness and injury severity. β values for each predictor and F and adjusted R² for each model are presented; * P<0.05, ** P<0.001. PF: physical functioning, RP: physical role functioning, BP: bodily pain, GH: general health perception, VT: vitality, SF: social role functioning, RE: emotional role functioning, MH: mental health.
Mediation analysis - standardized regression coefficients for direct and indirect effects (* P<0.05, ** P<0.001). The effect of depression on the emotional role functioning domain of quality of life is partially mediated by cognitive impairment (bootstrapped indirect effect: 0.12, 95% CI: 0.02 to 0.31, P=0.02).