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POST-TRAUMATIC STRESS DISORDER IN CIVILIANS WITH TRAUMATIC BRAIN INJURY: PREVALENCE OF PTSD AND ITS ASSOCIATIONS WITH RADIOLOGICAL MARKERS

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ABSTRACT

Objectives: To estimate the prevalence of post-traumatic stress disorder (PTSD) in a large civilian population with traumatic brain injury (TBI), and to assess whether brain injury severity is correlated with PTSD symptoms.

Design: Observational, cross-sectional study.

Setting and Participants: Outpatient clinic in a secondary care hospital which serves as a major trauma centre in the UK. Estimates of PTSD prevalence are based on a sample 171 individuals attending TBI clinic within an 18-month period. Analysis of the relationship between TBI severity and PTSD was performed on the subset of 127 patients for whom brain injury severity data were also available.

Methods: Civilian TBI clinic attendees completed validated self-report questionnaires assessing PTSD (PCL-C) and other psychiatric symptoms. Using these measures, the prevalence of PTSD was estimated. Post-resuscitation Glasgow Coma Score and Marshall grade on Computed Tomography brain scan were recorded as indicators of brain injury severity. A hierarchical regression performed to explore whether TBI severity may predict PTSD scores.

Results: A high prevalence of PTSD was estimated (21% with PCL-C score >50). Higher Marshall grading displayed a slight negative correlation with PTSD symptoms. This statistically significant relationship persisted after confounding factors such as depression and post-concussion symptoms were controlled for.

Conclusions: PTSD and TBI frequently co-exist, share antecedents and overlap in their resultant symptoms. This complex relationship has given rise to conflicting hypotheses about the relationship between the two. This research reveals that PTSD is common in civilians with TBI (adding to the substantial body of research in military populations). The analysis indicated that more severe brain injury may exert a slight protective influence against development of PTSD – potentially by disrupting implicit access to traumatic memories, or via overlapping neuropsychiatric symptoms that impede diagnosis. The association highlights the potential utility of routine neuroimaging in future research to predict psychiatric morbidity.

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References: 32

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study estimates the prevalence of PTSD using a large and diverse sample of civilians with TBI which is representative of the UK clinical population
- While analysing the link between brain injury and PTSD severity, this study controls for the potentially confounding effect of symptoms due to depression and concussion
- There is a strong emphasis on using data which can be readily collected in clinical practice (routinely-performed CT scans and standardised questionnaires)
- The sample is drawn from clinic attendees who self-report symptoms, so some individuals (such as those with less access to healthcare) may be under-represented
- The study is observational in nature rather than experimental. Conclusions can be drawn regarding brain injury predicting PTSD severity, but this does not necessarily imply a causal link

INTRODUCTION

The complex relationship between Post-Traumatic Stress Disorder (PTSD) and Traumatic Brain Injury (TBI) presents opportunities to further the understanding of both conditions individually as well as their interplay. PTSD is a common mental health condition with an estimated lifetime prevalence of 7.8%. Risk is increased by severely distressing experiences such as sexual assault, life-threatening injury, or emotional trauma during military service [1]. Its psychosocial impact is significant, with a high risk of suicidal behaviour in PTSD patients [2], impairments in social and occupational functioning, as well as increased utilisation of health services [3]. The purported aetiology of PTSD involves an antecedent psychologically

traumatic event which is deemed severely threatening. The presence of such a stressor is common to diagnostic criteria in the Diagnostic and Statistical Manual 5 [4] and the International Classification of Diseases 10 [5].

A psychologically traumatic event involving physical brain injury can potentially complicate the development of PTSD. Pre and post-event amnesia is often a feature of brain injury and concussion and yet the integrity of traumatic memories may also play an important role in the development of the disease. Where memory of an antecedent event is impaired due to traumatic amnesia, it has been proposed that this memory loss may have a potentially protective [6] or even preventative role [7] in PTSD development. The lack of intact recollection of a traumatic event may be associated with a failure to develop intrusive, distressing memories which are a hallmark of PTSD.

A varied range of cognitive deficits can result from TBI. This may in fact render patients more vulnerable to the development of PTSD as better pre-morbid function, with increased cognitive reserve, has been found to be a protective factor [8]. Further research in 2012 suggested severe TBI may predispose to PTSD even in the presence of amnesia and other cognitive abnormalities [12]. There are diverse mechanisms by which brain injury may produce cognitive deficits, for example diffuse axonal fragmentation can disrupt connections between key networks of cortical grey matter [9]. However the extent to which neuroimaging and gross structural changes can be linked to the development of PTSD in this patient group is poorly understood [12]. As a result, uncertainties remain about the neuropathological mechanisms by which TBI and PTSD may be linked, particularly outside of the military/blast injury context.

Large studies exploring the relationships between TBI and PTSD often involve military populations, typically those involved in wars in Afghanistan and Iraq [13]. Though pragmatic, an approach based on military cohorts is complicated by the potential exposure to multiple psychological stressors aside from the event responsible for TBI. Furthermore research in

this population is largely focused on damage attributable to blast-injuries or other mechanisms quite specific to military combat [13, 14]. In contrast, civilian TBI is most commonly due to falls, vehicle crashes and assaults (as well as a varied range of other mechanisms) [15]. These mechanisms may result in qualitatively differing patterns of brain damage and psychological trauma, limiting the extent to which findings from specific military studies can be generalised to the civilian populace.

The relationship between severity of brain injury and the development of PTSD remains controversial, with mixed findings in patients with mild versus severe injury [7, 8, 9]. As a result, some studies have focused on mild TBI (mTBI) in order to explore the effect on PTSD. A systematic review of such studies [16] has highlighted marked heterogeneity of study design which obscures the relationship between the conditions. Drawing a distinction between mTBI and more severe injury may introduce an artificial dichotomy onto the spectrum of brain injury, potentially limiting our understanding of the relationship with PTSD.

This study aimed to explore the relationship between brain injury factors and PTSD symptoms in a large civilian, outpatient population - while controlling for confounding variables. This has been conducted with the objectives of estimating the prevalence of PTSD, and assessing whether indicators of TBI severity predict PTSD symptom levels.

METHODS

Data were collected prospectively between December 2013 and June 2015 from patients attending an outpatient TBI clinic at the Queen Elizabeth Hospital in Birmingham – a large UK major trauma centre. Ethical approval was granted under NHS Research Ethics (HRA 17/LO/0153). Exclusion criteria were: attendance due to non-traumatic pathology; chronic subdural haematoma; or non-completion of self-report questionnaires.

Admission records were interrogated to record demographic details and best post-resuscitative Glasgow Coma Score. Patients completed a battery of self-report questionnaires, including: health-related quality of life (Quality of Life after Brain Injury – QOLIBRI [19]), post-concussion symptoms (Rivermead PCS questionnaire [20]), depression (Patient Health Questionnaire – PHQ9 [21]), and PTSD severity (PTSD checklist civilian version – PCL-C [22]).

PCL-C is a measure of PTSD symptoms adapted from the military questionnaire use in a civilian population [18, 22] and scores can range from 17 (minimal symptoms) to 85. Two cut-off levels are established to estimate PTSD prevalence using PCL-C scores: Scores <50 have been regarded as a suitable diagnostic estimate in the mTBI population, and scores <44 have been validated based on studies in populations in which PTSD symptoms are anticipated to be high [24]. Prevalence estimates were recorded at both thresholds in this study, as use of either can be justified based on the limited prior research in civilian populations.

Two relatively objective indicators brain-injury severity were also recorded: best Glasgow Coma Scale (GCS) following initial resuscitation, and classification of admission Computed Tomography (CT) brain scan using the Marshal injury burden stratification score [17]. Marshall grades are defined as: 1 - no visible pathology; 2 – cisterns present with midline shift <5mm and/or lesion densities present; 3 - cisterns compressed/absent with midline shift 0-5mm; 4 - diffuse injury with midline shift >5mm; 5 – any lesion evacuated surgically; and 6 – high or mixed-density lesions >25cm^3 not surgically evacuated. Grades 5 and 6 were grouped together for the purposes of this analysis, as the progression from one to the other does not necessarily represent an increase in severity. GCS was classified into 3 severity levels, mild (13-15), moderate (9-12) and severe (3-8).

A hierarchical multiple regression analysis was performed using Statistical Package for the Social Sciences, version 11 for Windows (SPSS, Chicago, Illinois, USA) to determine

whether brain injury features (GCS and Marshall grade) were statistically significant predictors of PTSD scores (dependent variable), even when controlling for age, sex, quality of life, concussion symptoms and depression as potential confounding factors.

RESULTS

For estimates of PTSD prevalence, 171 patients were included and 79% were male and the median age was 38. See *Table 1* for sample description.

Table 1. Demographic characteristics and PCL-C scores of overall clinic sample *n=171*

Variable	
Age	Range 16-82 years; Median 38; IQR 32
Sex	F: 37 (22%), M:134 (78%)
Ethnicity	White 131(77%), African Caribbean 6 (4%), Asian 18 (11%), Mixed 8 (5%), other 8 (5%)
PTSD (PCL-C score /84)	Range 5-84; Mean 34.46; SD 18.12

Using PCL-C cut-off score >50, the prevalence of PTSD was 20.6%; using the lower threshold (score >44), prevalence was 31.6%.

Hierarchical multiple regression was performed based on those 127 participants who completed questionnaires, had CT head scan results available and their admission GCS recorded (see *Table 2*). The 44 participants excluded (due to missing data) did not differ significantly in demographic or injury characteristics, nor in PTSD, depression or post-concussion symptom scores.

Table 2.
Proportion of patients with TBI of differing severities based on GCS and Marshall Grade
n=127

Post-resuscitation GCS	**61%** [Mild: 13-15]		**13%** [Moderate: 9-12]		**26%** [Severe: 3-8]
Marshall grade	**16%** [grade 1]	**56%** [grade 2]	**3%** [grade 3]	**1%** [grade 4]	**24%** [grade 5-6]

Uncorrected exploratory correlations conducted within the included group (*n=127*) suggested that post-concussion symptoms (r= 0.70) and depression (r= 0.76) were moderately positively correlated with PTSD severity (p <0.01).

Table 3. Descriptive Statistics of group included in Hierarchical Regression n=127

Variable	**Range**	**Median**	**IQR**
Quality of Life (QOLIBRI - %)	33-100	59	29
Concussion symptoms (Rivermead PCS)	0-60	24	26.25
Depression symptoms (PHQ9)	0-26	7	15.5
PTSD symptoms PCL-C	17-85	25	28

A two-level hierarchical regression was performed (see *Table 3*), with PTSD severity (PCL-C score) as the dependent variable. Model assumptions were tested and met. The first level of the regression consisted of potential predictors of PTSD score which may be confounding factors, specifically age, sex, depression scores (PHQ9), post-concussion symptoms (Rivermead) and quality of life (QOLIBRI). The second level contained GCS and Marshall grade. See *table 4*.

Table 4. Hierarchical Regression Models

Potential Predictor	**Coefficient Beta**	**Standard error**	**B (95% CI)**
Model One			
Sex	-0.10	2.90	-0.47 (-6.22 – 5.284)
Age	-0.03	0.06	-0.03 (-0.16 – 0.10)
QoL	0.13	0.11	0.15 (-0.07 – 0.36)
Concussion symptoms	0.23	0.17	0.28 (-0.06 – 0.62)
Depression symptoms	0.65	0.30	1.57 (0.97 – 2.173)*
Model Two			
Sex	-0.01	2.84	-0.51 (-6.13 – 5.11)
Age	-0.03	0.06	-0.03 (-0.16 – 0.09)
QoL	0.13	0.11	-0.15 (-0.07 – 0.36)
Concussion symptoms	0.18	0.17	0.22 (-0.12 – 0.56)
Depression symptoms	0.69	0.30	1.67 (1.08 – 2.26)*
Admission GCS[1] *(mild, moderate or severe)*	-0.08	1.42	-1.73 (-4.67 – 0.96)
Marshall grade[1]	-0.12	0.87	-1.86 (-0.01 – -0.21)*

[1] Second level of hierarchical regression (routinely-recorded brain injury factors)
*Statistically significant p<0.01

At the first level, depression and other potential confounders contribute significantly to the model, F (5,121) = 35.59, $p < 0.01$, accounting for 57.9% of the variance in PTSD severity, with depression the only individual significant factor. The second level including Marshall grade added a modest but statistically significant contribution to PTSD severity – F (7,119) = 28.06, $p < 0.05$.

DISCUSSION

These findings reveal a high level of PTSD symptoms in the civilian TBI clinic population. Dependant on diagnostic threshold used, estimated prevalence of PTSD is between 20.6% – 31.6%, which is in keeping with previous studies of smaller cohorts [9]. Furthermore, this is in keeping with findings from military populations showing a strong association between even mild TBI and PTSD [23] Depression is significantly correlated with PTSD severity. This is plausible given their symptomatic overlap, the tendency of stress to trigger both depressive episodes and PTSD, and it is in keeping with the high level of comorbidity between the two conditions [25]. Nonetheless, even when depression and other factors are controlled for, Marshall grade is a statistically significant predictor of the variance in PTSD scores. More severe radiological injury burden (based on higher Marshall grade) is associated with less severe PTSD scores. GCS was not a significant correlate of PTSD severity. This reflects the possibility that a conventional distinction between mild, moderate and severe brain injury based purely on post-resuscitative GCS, may not reflect the particular factors that predispose toward psychiatric morbidity. Further study is required to explore whether there is a relationship between altered GCS and PTSD in other settings.

The current results suggest that PTSD is common in this large cohort and that routinely-collected radiological data may be of use in identifying those at greatest risk of severe PTSD symptoms. The strengths of this study include a pragmatic emphasis on tools which can be employed in routine clinical practice- review of CT scans, GCS levels and self-report questionnaires. Different criteria for PTSD have been used in previous research (using the ICD-10, DSM 4, and DSM 5) each with subtly different emphases. The PCL-C is based on established diagnostic features and can be reliably administered in the clinic setting, thereby enabling comparisons in the wider literature.

This study has attempted to isolate the relationship between PTSD and TBI from confounding factors. Diagnostic confusion can arise when the damage associated with brain injury results in a neuropsychiatric syndrome which overlaps with PTSD even if the initial injury has not featured severe psychological trauma [12]. This post-concussion syndrome (PCS) and PTSD potentially both include features such as irritability, and both conditions can be associated depressed mood [10]. Such potential for overlap at the symptom-level introduces the possibility that the co-occurrence of PTSD, depression and PCS may be over-estimated. Furthermore, some mild cognitive deficits are associated with PCS which may increase vulnerability to PTSD as previously discussed. In this study, controlling for post-concussion symptoms within the regression analysis served to partially mitigate against this potential source of confusion.

Inevitably, certain limitations apply to the approach presented. A brief survey inevitably produces less precise estimates of prevalence of PTSD than a full psychiatric assessment. However since prior research suggests PTSD may be under-recognised in this group, relying on prior psychiatric diagnoses may not have been sufficient. Broader concerns about self-report measures may apply- whether this manifests as patients denying the severity of their symptoms, or over-stating them in the hope of receiving more support. In spite of this, the PCL-C has been found to be reliable across comparable populations [26].

The outpatient sample taking part in this study represents a large and well-categorised civilian group in a real-world hospital setting, however some factors may limit its generalisability to the wider TBI population. There is potential for selection bias in favour of patients with more persistent symptoms, as those attending the clinic are more likely to have enduring neuropsychiatric symptoms which justify their attendance. Conversely, patients with more severe injuries may have cognitive deficits that render them unable to complete the necessary questionnaires for inclusion, or they may be in inpatient settings that make clinic attendance less likely. In spite of the majority of the cohort consisting of mTBI, the sample contains a wide range of injury severity levels, which partially serves to mitigate against a systematic bias of this type. Finally, the majority male sample, may be typical of TBI sufferers, however this may be less representative of the wider civilian PTSD cohort. This study included TBI both with and without structural changes identified on CT. A full understanding of the links between acquired brain injury and psychiatric symptoms will require the location of any overt injury to be taken into account, although this was beyond the scope of the analysis presented.

The high prevalence of PTSD found in this study provides an important epidemiological estimate within the UK civilian population. These prevalence findings are in accordance with research in populations who have suffered general trauma (including extra-cranial injury) such as those involved in motor vehicle accidents [27] and assaults [28]. The novel finding of an independent negative correlation identified between Marshall grade and PTSD invites speculation that more severe structural brain damage may exert a modest protective effect against PTSD symptoms. This is borne out in previous literature suggesting severe TBI may prevent development of PTSD in some cases. For example it has been proposed that prolonged periods of unconsciousness may exert a protective influence [29]. This may be attributable to amnesia interfering with the process by which traumatic memories are formed. While intuitively plausible, the picture is complicated by findings in mTBI patients, in which a longer duration of post-traumatic amnesia was found to be protective against certain PTSD

symptoms in spite of the absence of overt structural brain injury [30]. Some have extended this line of reasoning further to suggest that mild TBI and PTSD are mutually exclusive regardless of amnesia [31].

In order to reconcile the findings of these potentially conflicting studies, three main mechanisms have been proposed to link TBI with PTSD via memory systems: unimpaired traumatic memories, traumatic amnesia with spared implicit memory of trauma, and 'islands of memory' within post-traumatic amnesia [32]. The findings of this study can be recognised within this framework, as more severe brain injury findings on CT are a significant predictor of milder PTSD symptoms. In more severe TBI, structural damage (and resultant neuronal loss) may produce functional impairment of implicit memory systems. Deficits in implicit memory are not easily recognised in routine clinical assessment of post-traumatic amnesia (which essentially test declarative, but not implicit, memory). Future research into these mechanisms may benefit from avoiding a potentially arbitrary dichotomy between mild and more severe TBI. Quantifying or systematically classifying brain injury severity on a continuous basis using more sophisticated imaging may enable measurable brain injury factors to be linked to different symptoms within PTSD. A refined method based on this principle may enable information from more detailed TBI imaging to predict psychiatric symptoms at a level of precision that is clinically meaningful. In cases where a focal traumatic lesion is identified, future research may benefit from also exploring the effect of the anatomical location of TBI and its relationship to symptoms.

In spite the limitations inherent in observational study of an outpatient clinic cohort, this research illustrates that PTSD represents a common condition among people with TBI. Furthermore, routinely-performed CT scans can be reviewed to identify features that relate to psychiatric morbidity in a real-world civilian population. Higher Marshall grades (e.g. 5-6) are modestly associated with lower PCL-C scores. The presence of a relationship between more severe brain injury and milder PTSD symptoms represents a novel finding, given that

depression and post-concussion symptoms have been controlled for in this design. The implications of this extend from the theoretical to the practical – inviting further exploration using more sophisticated imaging, as well as pointing toward pragmatic approaches to screen those TBI patients at highest risk of PTSD.

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FOOTNOTES

Contributors: KQ was involved in study design, reviewing collected data, performing the analyses and drafting the manuscript. RU was involved in study design, developing analytic strategy and also provided extensive commentary on the manuscript. ET was involved in data collection, assisted with study design and provided extensive commentary on the manuscript. DD, VS and AB were involved in development of the TBI database and edited the manuscript.

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Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data are available

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Addressed in
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	*Abstract (page 2)*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	*Abstract (page 2)*
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	*Pages 3-4*
Objectives	3	State specific objectives, including any prespecified hypotheses	*Page 4*
Methods			
Study design	4	Present key elements of study design early in the paper	*Page 5*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	*Page 5*
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	*Page 5*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	*Pages 5-6*
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Pages 5-6*
Bias	9	Describe any efforts to address potential sources of bias	*Pages 5-6*
Study size	10	Explain how the study size was arrived at	*Page 5*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	*Pages 5-6*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	*Page 6*
		(*b*) Describe any methods used to examine subgroups and interactions	*N/A*
		(*c*) Explain how missing data were addressed	*Page 5*
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	*N/A*
		(*e*) Describe any sensitivity analyses	*N/A*
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	*Pages 6-7*
		(b) Give reasons for non-participation at each stage	*N/A*
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	*Page 6*
		(b) Indicate number of participants with missing data for each variable of interest	*Pages 6-7*
Outcome data	15*	Report numbers of outcome events or summary measures	*Page 7*

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	*Pages 8-9*
		(*b*) Report category boundaries when continuous variables were categorized	*Pages 6-7*
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	*N/A*
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	*Page 7*
Discussion			
Key results	18	Summarise key results with reference to study objectives	*Page 10*
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	*Pages 11-12*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	*Pages 12-13*
Generalisability	21	Discuss the generalisability (external validity) of the study results	*Pages 11-12*
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	*N/A*

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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'Post-Traumatic Stress Disorder in UK civilians with Traumatic Brain Injury: An observational study of TBI clinic attendees to estimate PTSD prevalence and its relationship with radiological markers of brain injury severity'

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POST-TRAUMATIC STRESS DISORDER IN UK CIVILIANS WITH TRAUMATIC BRAIN INJURY:

AN OBSERVATIONAL STUDY IN TBI CLINIC ATTENDEES TO ESTIMATE PTSD PREVALENCE AND ITS RELATIONSHIP WITH RADIOLOGICAL MARKERS OF BRAIN INJURY SEVERITY

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ABSTRACT

Objectives: To estimate the prevalence of post-traumatic stress disorder (PTSD) in a large civilian population with traumatic brain injury (TBI), and to assess whether brain injury severity is correlated with PTSD symptoms.

Design: Observational, cross-sectional study.

Setting and Participants: Outpatient clinic in a major UK trauma centre and secondary care hospital. Estimates of PTSD prevalence are based on 171 sampled individuals attending TBI clinic within an 18-month period. Analysis of the relationship between TBI severity and PTSD was performed on the subset of 127 patients for whom injury severity data were also available.

Methods: Civilian TBI clinic attendees completed validated self-report questionnaires assessing PTSD (PCL-C) and other psychiatric symptoms. From this, the prevalence of PTSD was estimated in our cohort. Post-resuscitation Glasgow Coma Score and Marshall grade on Computed Tomography brain scan were recorded as indicators of brain injury severity. A hierarchical regression explored whether TBI severity may predict PTSD scores.

Results: A high prevalence of PTSD was estimated (21% with PCL-C score >50). Higher Marshall grading displayed a slight negative correlation with PTSD symptoms. This statistically significant relationship persisted after confounding factors such as depression and post-concussion symptoms were controlled for.

Conclusions: PTSD and TBI frequently co-exist, share antecedents and overlap in their resultant symptoms. This complexity has given rise to conflicting hypotheses about relationships between the two. This research reveals that PTSD is common in civilians with TBI (adding to evidence drawn from military populations). The analysis indicated that more severe brain injury may exert a slight protective influence against development of PTSD – potentially by disrupting implicit access to traumatic memories, or via overlapping neuropsychiatric symptoms that impede diagnosis. The association suggests that further research is warranted to explore the reuse of routine clinical and neuroimaging data – investigating its potential to predict risk of psychiatric morbidity.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study estimates the prevalence of PTSD using a large and diverse sample of civilians with TBI which is representative of the UK clinical population
- While analysing the link between brain injury and PTSD severity, this study controls for the potentially confounding effect of symptoms due to depression and concussion
- There is a strong emphasis on using data which can be readily collected in clinical practice (routinely-performed CT scans and standardised questionnaires)
- The sampled clinic attendees self-report symptoms at various times after injury. This prevents conclusions being drawn about the timing at which psychiatric symptoms develop, and those who do not access care may be under-represented
- The study is observational in nature rather than experimental. Conclusions can be drawn regarding brain injury predicting PTSD severity, but this does not necessarily imply a causal link

INTRODUCTION

The complex relationship between Post-Traumatic Stress Disorder (PTSD) and Traumatic Brain Injury (TBI) presents opportunities to further the understanding of both conditions individually as well as their interplay. PTSD is a common mental health condition with an estimated lifetime prevalence of 7.8%[1]. Risk is increased by severely distressing experiences such as sexual assault, life-threatening injury, or emotional trauma during military service[1]. Its psychosocial impact is significant, with a high risk of suicidal behaviour in PTSD patients[2], impairments in social and occupational functioning, as well as increased utilisation of health services[3]. The purported aetiology of PTSD involves an antecedent psychologically traumatic event which is deemed severely threatening. The presence of such

a stressor is common to diagnostic criteria in the Diagnostic and Statistical Manual 5[4] and the International Classification of Diseases 10[5].

A psychologically traumatic event involving physical brain injury can potentially complicate the development of PTSD. Pre and post-event amnesia is often a feature of brain injury and concussion and yet the integrity of traumatic memories may also play an important role in the development of the disease. Where memory of an antecedent event is impaired due to traumatic amnesia, it has been proposed that this memory loss may have a potentially protective[6] or even preventative role[7] in PTSD development. The lack of intact recollection of a traumatic event may be associated with a failure to develop intrusive, distressing memories which are a hallmark of PTSD.

A varied range of cognitive deficits can result from TBI. This may in fact render patients more vulnerable to the development of PTSD as better pre-morbid function, with increased cognitive reserve, has been found to be a protective factor[8]. Further research suggested both mild and severe TBI may predispose to PTSD even in the presence of amnesia and other cognitive abnormalities[9,10]. There are diverse mechanisms by which brain injury may produce cognitive deficits, for example diffuse axonal fragmentation can disrupt connections between key networks of cortical grey matter[11]. However the extent to which neuroimaging and gross structural changes can be linked to the development of PTSD in this patient group is poorly understood [12]. As a result, uncertainties remain about the neuropathological mechanisms by which TBI and PTSD may be linked, particularly outside of the military/blast injury context.

Large studies exploring the relationships between TBI and PTSD often involve military populations, typically those involved in wars in Afghanistan and Iraq[13]. Though pragmatic, an approach based on military cohorts is complicated by the potential exposure to multiple psychological stressors aside from the event responsible for TBI. Furthermore research in this population is largely focused on damage attributable to blast-injuries or other

mechanisms quite specific to military combat[13,14]. In contrast, civilian TBI is most commonly due to falls, vehicle crashes and assaults (as well as a varied range of other mechanisms)[15]. These mechanisms may result in qualitatively differing patterns of brain damage and psychological trauma, limiting the extent to which findings from specific military studies can be generalised to the civilian populace.

The relationship between severity of brain injury and the development of PTSD remains controversial, with mixed findings in patients with mild versus severe injury[7,8,9,10]. As a result, some studies have focused on mild TBI (mTBI) in order to explore the effect on PTSD. A systematic review of such studies[16] has highlighted marked heterogeneity of study design which obscures the relationship between the conditions. Drawing a distinction between mTBI and more severe injury may introduce an artificial dichotomy onto the spectrum of brain injury, potentially limiting our understanding of the relationship with PTSD.

This current study aimed to explore the relationship between brain injury factors and PTSD symptoms in a large civilian, outpatient population - while controlling for confounding variables. This has been conducted with the objectives of estimating the prevalence of PTSD, and assessing whether indicators of TBI severity predict PTSD symptom levels.

METHODS

Data were collected prospectively between December 2013 and June 2015 from patients attending an outpatient TBI clinic at the Queen Elizabeth Hospital in Birmingham – a large UK major trauma centre. Ethical approval was granted under NHS Research Ethics (HRA 17/LO/0153). This included processes to ensure participants provided informed consent for their clinical data to be stored in database form, and for anonymised information to be used for the purposes of research.

Patient and Public Involvement:

Patients and public were not directly involved in the development of this study.

Admission records were interrogated to record demographic details and best post-resuscitative Glasgow Coma Score[17]. Patients completed a battery of self-report questionnaires, including: health-related quality of life (Quality of Life after Brain Injury – QOLIBRI [18]), post-concussion symptoms (Rivermead PCS questionnaire [19]), depression (Patient Health Questionnaire – PHQ9 [20]), and PTSD severity (PTSD checklist civilian version – PCL-C [21]). Exclusion criteria were: attendance due to non-traumatic pathology, chronic subdural haematoma, or declining to provide informed consent. Additionally, participants could not be included if required data for the analysis were not available (as reported in the *Results* below).

PCL-C is a measure of PTSD symptoms adapted from the military questionnaire use in a civilian population[21,22] and scores can range from 17 (minimal symptoms) to 85. Two cut-off levels are established to estimate PTSD prevalence using PCL-C scores: Scores <50 have been regarded as a suitable diagnostic estimate in the mTBI population, and scores <44 have been validated based on studies in populations in which PTSD symptoms are anticipated to be high[23]. Prevalence estimates were recorded at both thresholds in this study, as use of either can be justified based on the limited prior research in civilian populations[24]. While estimating prevalence necessitates use of dichotomous cut-offs, the possible associations between PTSD symptom severity and TBI severity may occur below these thresholds. As such, PCL-C scores were treated as a continuous variable in the regression analysis described below. This also reduces the need for multiple comparisons at different cut-off thresholds.

Two relatively objective indicators brain-injury severity were also recorded: best Glasgow Coma Scale (GCS) following initial resuscitation, and classification of admission Computed Tomography (CT) brain scan using the Marshal injury burden stratification score[17]. Rather

than basing the analysis on immediate GCS on admission (which can also indicate TBI severity), using the best GCS rating has been found to be a better predictor of long term functional and cognitive outcomes[25,26] and this is likely to be relevant to long-term mental health. Marshall grades are defined as: 1 - no visible pathology; 2 – cisterns present with midline shift <5mm and/or lesion densities present; 3 - cisterns compressed/absent with midline shift 0-5mm; 4 - diffuse injury with midline shift >5mm; 5 – any lesion evacuated surgically; and 6 – high or mixed-density lesions >25cm^3 not surgically evacuated. Grades 5 and 6 were grouped together for the purposes of this analysis, as the progression from one to the other does not necessarily represent an increase in severity. GCS was classified into 3 severity levels, mild (13-15), moderate (9-12) and severe (3-8). Marshall Grade and GCS were assessed by the Neurosurgery team involved in the participants' care. As GCS was recorded as part of routine practice by the attending team, it was not within the scope of this research to formally audit this or to assess inter-rater reliability.

A hierarchical multiple regression analysis was performed using Statistical Package for the Social Sciences, version 11 for Windows (SPSS, Chicago, Illinois, USA) to determine whether brain injury features (GCS and Marshall grade) were statistically significant predictors of PTSD scores (dependent variable), even when controlling for age, sex, quality of life, concussion symptoms and depression as potential confounding factors. This type of analysis was utilised due to the *a priori* hypothesis that brain injury severity may predict some risk of psychiatric morbidity. This thereby justified a qualitative distinction to be drawn between the confounding variables (first stage of the regression analysis) and the potential predictors (second stage).

RESULTS

To produce estimates of PTSD prevalence in this cohort, 171 participants were included (as their full PCL-C scores were available), 79% were male and the median age was 38. See *Table 1* for sample description.

Table 1. Demographic characteristics and PCL-C scores of overall clinic sample *n=171*

Variable	
Age	Range 16-82 years; Median 38; IQR 32
Sex	F: 37 (22%), M:134 (78%)
Ethnicity	White 131(77%), African Caribbean 6 (4%), Asian 18 (11%), Mixed 8 (5%), other 8 (5%)
PTSD (PCL-C score /84)	Range 5-84; Mean 34.46; SD 18.12

Using PCL-C cut-off score >50, the prevalence of PTSD was 20.6%; using the lower threshold (score >44), prevalence was 31.6%.

Brain injury severity data was not available for all of the participants described above, due to incomplete records. Hierarchical multiple regression was performed based on those 127 participants who completed questionnaires, had CT head scan results available and their admission GCS recorded (see *Table 2*). The 44 participants excluded (due to missing data) did not differ significantly in demographic or injury characteristics, nor in PTSD, depression or post-concussion symptom scores.

Table 2. Proportion of patients with TBI of differing severities based on best post-resuscitation GCS and Marshall Grade *n=127*

GCS	**61%** [Mild: 13-15]		**13%** [Moderate: 9-12]		**26%** [Severe: 3-8]
Marshall grade	**16%** [grade 1]	**56%** [grade 2]	**3%** [grade 3]	**1%** [grade 4]	**24%** [grade 5-6]

Uncorrected exploratory correlations conducted within the regression group (*n=127*) suggested that post-concussion symptoms (r= 0.70) and depression (r= 0.76) were moderately positively correlated with PTSD severity (p <0.01).

Table 3. Descriptive Statistics of group included in Hierarchical Regression n=127

Variable	**Range**	**Median**	**IQR**
Quality of Life (QOLIBRI - %)	33-100	59	29
Concussion symptoms (Rivermead PCS)	0-60	24	26.25
Depression symptoms (PHQ9)	0-26	7	15.5
PTSD symptoms (PCL-C)	17-85	25	28

A two-level hierarchical regression analysis was performed (see *Table 3*), with PTSD severity (PCL-C score) as the dependent variable. Model assumptions were tested and met. The first level of the regression consisted of potential predictors of PTSD score which may be confounding factors, specifically age, sex, depression scores (PHQ9), post-concussion symptoms (Rivermead) and quality of life (QOLIBRI). The second level contained GCS and Marshall grade (see *Table 4)*.

Table 4. Hierarchical Regression Models

Potential Predictor	Coefficient Beta	B (95% CI)	B Standard Error
Model One			
Sex	-0.10	-0.47 (-6.22, 5.28)	2.90
Age	-0.03	-0.03 (-0.16, 0.10)	0.06
QoL	0.13	0.15 (-0.07, 0.36)	0.11
Concussion symptoms	0.23	0.28 (-0.06, 0.62)	0.17
Depression symptoms	0.65	1.57 (0.97, 2.17)*	0.30
Model Two			
Sex	-0.01	-0.51 (-6.13, 5.11)	2.84
Age	-0.03	-0.03 (-0.16, 0.09)	0.06
QoL	0.13	-0.15 (-0.07, 0.36)	0.11
Concussion symptoms	0.18	0.22 (-0.12, 0.56)	0.17
Depression symptoms	0.69	1.67 (1.08, 2.26)*	0.30
GCS[1] *(mild/moderate/severe)*	-0.08	-1.86 (-4.67, 0.96)	1.42
Marshall grade[1]	-0.12	-1.73 (-3.45, -0.01)*	0.87

[1] Second level of hierarchical regression (routinely-recorded brain injury factors)

*Statistically significant p<0.05

At the first level, depression and other potential confounders contribute significantly to the model, F (5,121) = 35.59, $p < 0.01$, accounting for 57.9% of the variance in PTSD severity, with depression the only individual significant factor. The second level including Marshall grade added a modest but statistically significant contribution to PTSD severity – F (7,119) = 28.06, $p < 0.05$.In contrast, GCS was not a statistically significant predictor of PTSD severity when other potential confounders were controlled for.

DISCUSSION

These findings reveal a high level of PTSD symptoms in the civilian TBI clinic population. Dependant on diagnostic threshold used, estimated prevalence of PTSD is between 20.6% – 31.6%, which is in keeping with previous studies of smaller cohorts[9]. Furthermore, this is in keeping with findings from military populations showing associations between even mild TBI and PTSD[16,23]. Depression is significantly correlated with PTSD severity. This is plausible given their symptomatic overlap, the tendency of stress to trigger both depressive episodes and PTSD, and it is in keeping with the high level of comorbidity between the two conditions[27]. Nonetheless, even when depression and other factors are controlled for, Marshall grade is a statistically significant predictor of the variance in PTSD scores. More severe radiological injury burden (based on higher Marshall grade) is associated with less severe PTSD scores. GCS was not a significant correlate of PTSD severity. This reflects the possibility that a conventional distinction between mild, moderate and severe brain injury based purely on post-resuscitative GCS, may not reflect the particular factors that predispose toward psychiatric morbidity. Further study is required to explore whether there is a relationship between altered GCS and PTSD in other settings.

The current results suggest that PTSD is common in this large cohort and that routinely-collected radiological data may be of use in identifying those at greatest risk of severe PTSD

symptoms. The strengths of this study include a pragmatic emphasis on tools which can be employed in routine clinical practice- review of CT scans, GCS levels and self-report questionnaires. Different criteria for PTSD have been used in previous research (using the ICD-10, DSM 4, and DSM 5) each with subtly different emphases. The PCL-C is based on established diagnostic features and can be reliably administered in the clinic setting, thereby enabling comparisons in the wider literature[28].

This study has attempted to isolate the relationship between PTSD and TBI from confounding factors. Diagnostic confusion can arise when the damage associated with brain injury results in a neuropsychiatric syndrome which overlaps with PTSD even if the initial injury has not featured severe psychological trauma[8]. This post-concussion syndrome (PCS) and PTSD potentially both include features such as irritability, and both conditions can be associated depressed mood[10]. Such potential for overlap at the symptom-level introduces the possibility that the co-occurrence of PTSD, depression and PCS may be over-estimated. Furthermore, some mild cognitive deficits are associated with PCS which may increase vulnerability to PTSD as previously discussed. In this study, controlling for post-concussion symptoms within the regression analysis served to partially mitigate against this potential source of confusion.

Inevitably, certain limitations apply to the approach presented. A brief survey inevitably produces less precise estimates of prevalence of PTSD than a full psychiatric assessment. However prior research suggests a high rate of psychiatricsymptoms and that PTSD may be under-diagnosed in this group [29], so measuring symptom severity may highlight those for whom psychiatric review would be beneficial and could lead to diagnosis. Broader concerns about self-report measures may apply- whether this manifests as patients denying the severity of their symptoms, or over-stating them in the hope of receiving more support. In spite of this, the PCL-C has been found to be reliable across comparable populations[28].

The outpatient sample taking part in this study represents a large and well-categorised civilian group in a real-world hospital setting, however some factors may limit its generalisability to the wider TBI population. There is potential for selection bias in favour of patients with more persistent symptoms, as those attending the clinic are more likely to have enduring neuropsychiatric symptoms which justify their attendance. Conversely, patients with more severe injuries may have cognitive deficits that render them unable to complete the necessary questionnaires for inclusion, or they may be in inpatient settings that make clinic attendance less likely. The potential also exists for the severity of TBI to be underestimated through use of best GCS score after resuscitation, rather than use of initial GCS on admission. However this compromise improves the ability of GCS to predict long-term outcomes[25,30]. In spite of the majority of the cohort consisting of mild TBI, the sample contains a wide range of injury severity levels, which partially serves to mitigate against a systematic bias of this type. The use of routinely collected clinical brain injury data (GCS, CT-scan findings) is advantageous in that it is readily available and quite objective in nature, but the fact that such data are may be recorded by different clinical teams(without specific training for the purpose of this study) has the potential to reduce inter-rater reliability.

This study sought to characterise this particular civilian TBI cohort, as data from similar large populations is relatively limited. However the absence of a control group does limit the extent to which one can meaningfully speculate about the neural mechanisms by which TBI and PTSD may be linked. To elucidate this in future, studies including a control group of participants with extra-cranial trauma may be valuable to isolate the effect of brain damage from other aspects of psychological trauma associated with injury and hospitalisation. Finally, the majority male sample, may be typical of TBI sufferers, however this may be less representative of the wider civilian PTSD cohort. This study included TBI both with and without structural changes identified on CT. A full understanding of the links between acquired brain injury and psychiatric symptoms will require the location of any overt injury to be taken into account, although this was beyond the scope of the analysis presented.

The high prevalence of PTSD found in this study provides an important epidemiological estimate within the UK civilian population. These prevalence findings are in accordance with research in populations who have suffered general trauma (including extra-cranial injury) such as those involved in motor vehicle accidents[31] and assaults[32]. The novel finding of an independent negative correlation identified between Marshall grade and PTSD invites speculation that more severe structural brain damage may exert a modest protective effect against PTSD symptoms. This is borne out in previous literature suggesting severe TBI may prevent development of PTSD in some cases. For example it has been proposed that prolonged periods of unconsciousness may exert a protective influence[33]. This may be attributable to amnesia interfering with the process by which traumatic memories are formed. While intuitively plausible, the picture is complicated by findings in mTBI patients, in which a longer duration of post-traumatic amnesia was found to be protective against certain PTSD symptoms in spite of the absence of overt structural brain injury[34]. Some have extended this line of reasoning further to suggest that mild TBI and PTSD are mutually exclusive regardless of amnesia[35].

In order to reconcile the findings of these potentially conflicting studies, three main mechanisms have been proposed to link TBI with PTSD via memory systems: unimpaired traumatic memories, traumatic amnesia with spared implicit memory of trauma, and 'islands of memory' within post-traumatic amnesia[36]. The findings of this study can be recognised within this framework, as more severe brain injury findings on CT are a significant predictor of milder PTSD symptoms. In more severe TBI, structural damage (and resultant neuronal loss) may produce functional impairment of implicit memory systems. Deficits in implicit memory are not easily recognised in routine clinical assessment of post-traumatic amnesia (which essentially test declarative, but not implicit, memory). Future research into these mechanisms may benefit from avoiding a potentially arbitrary dichotomy between mild and more severe TBI. Quantifying or systematically classifying brain injury severity on a continuous basis using more sophisticated imaging may enable measurable brain injury

factors to be linked to different symptoms within PTSD. A refined method based on this principle may enable information from more detailed radiological modalities (such as magnetic resonance imaging) to predict psychiatric symptoms at a level of precision that could become clinically meaningful. In future, this may require the specific use of appropriate imaging (such as MRI)to search for relevant markers of poor long-term outcome, rather than repurposing existing scans in an opportunistic manner. In cases where a focal traumatic lesion is identified, future research may benefit from also exploring the effect of the anatomical location of TBI and its relationship to psychiatric symptoms. Such precision may in future enable a meaningful taxonomy of the specific psychiatric sequelae that may arise, depending on the nature of their brain injury[37], with interventions targeted accordingly.

In spite of the limitations inherent in observational study of an outpatient clinic cohort, this research illustrates that PTSD represents a common condition among people with TBI. Furthermore, routinely-performed CT scans can be reviewed to identify features that relate to psychiatric morbidity in a real-world civilian population. Higher Marshall grades (e.g. 5-6) are modestly associated with lower PCL-C scores. The presence of a relationship between more severe brain injury and milder PTSD symptoms represents a novel finding, given that depression and post-concussion symptoms have been controlled for in this design. The implications of this extend from the theoretical to the practical – inviting further exploration using more sophisticated imaging, as well as pointing toward pragmatic approaches to screen those TBI patients at highest risk of PTSD.

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FOOTNOTES

Contributors: KQ was involved in study design, reviewing collected data, performing the analyses and drafting the manuscript. RU was involved in study design, developing analytic strategy and also provided extensive commentary on the manuscript. ET was involved in data collection, assisted with study design and provided extensive commentary on the manuscript. DD, VS and AB were involved in development of the TBI database and edited the manuscript.

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Data sharing statement: Data underlying results can be applied for via the corresponding author after de-identification. Full access to the patient database will not be available.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Addressed in
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	*Abstract (page 2)*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	*Abstract (page 2)*
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	*Pages 3-5*
Objectives	3	State specific objectives, including any prespecified hypotheses	*Page 5*
Methods			
Study design	4	Present key elements of study design early in the paper	*Page 5-6*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	*Pages 2,6*
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	*Pages 5-6*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	*Pages 5-6*
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Pages 5-6*
Bias	9	Describe any efforts to address potential sources of bias	*Pages 5-6*
Study size	10	Explain how the study size was arrived at	*Page 5-6*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	*Pages 6-7*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	*Page 6-7*
		(*b*) Describe any methods used to examine subgroups and interactions	*N/A*
		(*c*) Explain how missing data were addressed	*Page 6-7*
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	*N/A*
		(*e*) Describe any sensitivity analyses	*N/A*
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	*Pages 7-8*
		(b) Give reasons for non-participation at each stage	*N/A*
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	*Pages 7-8*
		(b) Indicate number of participants with missing data for each variable of interest	*Pages 7-8*
Outcome data	15*	Report numbers of outcome events or summary measures	*Page 8*

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	*Pages 9-10*
		(*b*) Report category boundaries when continuous variables were categorized	*Pages 7-8*
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	*N/A*
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	*Page 9*
Discussion			
Key results	18	Summarise key results with reference to study objectives	*Page 11*
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	*Pages 12-13*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	*Pages 12-14*
Generalisability	21	Discuss the generalisability (external validity) of the study results	*Pages 13-14*
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	*N/A*

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.