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Longitudinal changes in oculomotor function in young adults with mild traumatic brain injury (mTBI) - a prospective, controlled observational study

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3 **Longitudinal changes in oculomotor function in young adults with**
4 **mild traumatic brain injury (mTBI) – a prospective, controlled**
5 **observational study**
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ABSTRACT

Objectives: to assess 1) whether objectively measurable visual disturbances are observed more often in patients with mTBI compared to controls and if these disturbances change over time, and 2) whether self-reported visual symptoms after mTBI correlate with objectively detectable changes in visuomotor performance.

Design: A prospective, controlled observational study.

Setting: Emergency department of a general hospital in Stockholm, Sweden.

Participants: Fifteen patients with mTBI, 15 patients with minor musculoskeletal injury but no head trauma and 15 non-injured controls, all aged 18-40 years.

Outcome measures: Symptom assessment using Convergence Insufficiency Symptoms Survey (CISS) and Rivermead Post-concussion Symptoms Questionnaire (RPQ). Visual examination included assessment of visual acuity, accommodation, eye alignment and saccades. Assessments were performed at two time points – baseline (7-10 days) and follow up (75-100 days) after injury.

Results: Near point of convergence (NPC) in mTBI group was receded at baseline and improved significantly at follow up ($p = 0.015$). A significant difference was found between the mTBI group and non-injured controls in accommodative amplitude at baseline ($p = 0.001$). Six out of 13 mTBI patients still had accommodative insufficiency at follow up. At baseline, mTBI patients reported significantly more symptoms according to CISS compared to orthopaedic controls ($p = 0.012$) and non-injured controls ($p = 0.02$). For mTBI patients the CISS score correlated with fusional vergence. No significant difference was found between the groups regarding pro-saccades, anti-saccades and self-paced saccades at any time point.

Conclusion: There are some transient measurable visual changes regarding convergence in mTBI patients during the subacute period after the injury. Our findings of remaining accommodative insufficiency in a considerable proportion of mTBI patients suggest that this visual function should not be overlooked in clinical assessment.

Key words: neurology, mild traumatic brain injury, visual dysfunction, near point of convergence, accommodation, posttraumatic symptoms.

ARTICLE SUMMARY

Strengths and limitations of this study

- Prospective longitudinal design with measurement at two time points.
- Strict inclusion criteria for mTBI according to American Congress of Rehabilitation Medicine.
- Inclusion of both an uninjured control group and also a group with minor non-head trauma to control for non-specific effects of injury such as pain and distress.
- Study methods include several easily replicable objective optometric measurements.
- The limitation of this study is a small sample of patients with mTBI aged 18-40 years, which limits the generalisability.

INTRODUCTION

Monitoring recovery after mild traumatic brain injury (mTBI) is mostly based on reported symptoms. Outcome assessment, if this relies on symptoms, might be affected by biopsychosocial factors that might hamper recovery and sustain complaints. There is a need for objective methods to assess and monitor recovery after mTBI as a base for developing evidence based clinical follow up guidelines for patients sustaining mTBI. Oculomotor changes affecting accommodation, eye alignment and eye movements have been highlighted recently as a possible objective correlate of mTBI-related symptoms.

Visual networks are widely spread throughout the brain including cortical and subcortical areas, and several cranial nerves have a role in vision.(1) Traumatic impact to the head, as in mTBI, affects these networks(1, 2) and may result in visual disturbances. Vision is one of the most important senses and as such even a mild impairment may interfere with daily activities. Specific visual symptoms such as blurred vision and double vision are reported only with low frequency in some studies of mTBI.(3, 4) However, there are other complaints experienced by injured individuals, e.g. reading problems, dizziness in visually crowded environments, and issues with near work, where visual disturbance could act as an aggravating factor. Ability to appropriately alter focus, align the eyes and make gaze changes, can be measured objectively, and have been the focus of several recent studies of mTBI.(5-8) Convergence, that is the ability to move both eyes inwards to maintain a single retinal image of objects at different viewing distances,(9) is one of the most frequently described changes in oculomotor measurements after head injury.(10) Symptoms after mTBI, both direct visual symptoms (double vision, blurred vision), and indirect symptoms (increased effort at near work), might be attributed to impaired convergence. Convergence insufficiency (CI) was found in 42-48% of mTBI patients in retrospective studies,(11, 12) and controlled studies of military personnel who have suffered blast-induced mTBI have shown a significant difference in near point of convergence (NPC).(12, 13)

Fusional vergence maintains eye alignment and thereby provides for clear single vision. Impaired fusional vergence causes unstable binocular vision, which may present as losing one's place when reading, blurred or even double vision. Fusion vergence disorders may occur in about 3-6% of an otherwise healthy population with

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3 vision based symptoms(14, 15) but may be significantly more frequent in TBI
4 patients.(16)
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7 Accommodation provides a clear optical image of an object at different distances
8 through the altering of refractive power in the crystalline lens. Symptoms of
9 accommodative disorders include blurred vision and impaired flexibility to alter focus
10 between near and far. A physiological deterioration of accommodative ability,
11 presbyopia, is to be expected with age. The current study therefore included pre-
12 presbyopic subjects of age 40 or younger. In an otherwise healthy pre-presbyopic
13 population, accommodative changes may be present in up to about 10 % of
14 individuals with vision complaints.(15, 17) Significantly more prevalent
15 accommodative disorders have been found in mTBI patients in the sub-acute
16 stage(13) and also as part of persisting issues.(18, 19)
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24 Saccades are group of rapid eye movements that shift the gaze to areas of interest in
25 the visual field. They are necessary because only a small part of the central retina is
26 capable of high resolution vision. Through purposeful and accurate saccades, initiated
27 without delay, the environment can be scanned and the functional visual field is
28 increased. Thus, an efficient saccade performance is an important base for efficient
29 and safe interactions with the environment and for detailed work such as reading.(20)
30 The initiation and programming of saccades involves cognitive functions that are
31 subserved by complex neuronal networks involving different parts of the brain.
32 Various parameters of saccades have been shown to be affected after mTBI such as
33 latency and accuracy.(21-24)
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41 A recent systematic review of oculomotor-based vision assessment to monitor
42 changes after mTBI found promising, yet preliminary evidence.(25) It was concluded
43 that measurement of oculomotor functions appear useful in detecting changes after
44 mTBI but the strength of evidence in currently available research is not yet sufficient
45 enough to inform clinical guidelines. Some of the limitations addressed were lack of
46 well-defined study populations, description of baseline data and detailed study
47 protocols. Prospective studies with early assessment and follow up of vision related
48 oculomotor changes after mTBI are scarce.(21, 24) In this study we aim to assess
49 oculomotor and visual changes after mTBI prospectively, and compare these to a
50 control group unexposed to head injury but with minor musculoskeletal injury, and a
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3 non-injured control group. The study objectives are to assess: 1) whether objectively
4 measurable visual disturbances are observed more often in mTBI patients compared
5 to controls and if these disturbances change over time, and 2) whether self-reported
6 visual symptoms after mTBI correlate with objectively detectable changes in
7 visuomotor performance.
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10 11 **METHODS**

12 This work is a part of a prospective controlled observational study on mTBI. The
13 setting was a large emergency department of a general hospital serving the north-east
14 of Stockholm. Fifteen patients with mTBI and a control group of 15 patients with
15 minor trauma to extremities with no head trauma and not requiring surgical
16 intervention were included in to the study between January 2015 and April 2016. A
17 second control group without any traumatic injury included staff from Department of
18 Rehabilitation Medicine, their friends and family members. All study participants
19 were 18-40 years of age. Groups were matched for age. For demographic information
20 see table 1.
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23 The mTBI patients met criteria described in the guidelines of Mild Traumatic Brain
24 Injury Committee of American Congress of Rehabilitation Medicine (ACRM):(26)
25 acute brain injury resulting from mechanical energy to the head from external
26 physical forces: (i) 1 or more of the following: confusion or disorientation, loss of
27 consciousness (LOC) for 30 minutes or less, post-traumatic amnesia (PTA) for less
28 than 24 hours, and/or other transient neurological abnormalities such as focal signs,
29 seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale
30 (GCS)(27) score of 13–15 after 30 minutes post-injury or later upon presentation for
31 healthcare. These manifestations of mTBI must not be due to drugs, alcohol,
32 medications, caused by other injuries or treatment for other injuries (e.g. systemic
33 injuries, facial injuries or intubation), caused by other problems (e.g. psychological
34 trauma, language barrier or coexisting medical conditions) or caused by penetrating
35 craniocerebral injury.
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50 **Exclusion criteria**

51 The following patients were excluded: patients with traumatic brain injury and GCS
52 <13, those in need of neurosurgery, previous moderate or severe traumatic brain
53 injury, any head injury in the previous year requiring medical attention,
54 contraindications for MRI, progressive neurological disease or other medical
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conditions with expected short survival, severe visual impairment or manifest strabismus, need for personal help in activities of daily living before the current injury, intoxication with alcohol at the time of the injury, not fluent in Swedish.

Table 1 Demographic data

	mTBI patients	Orthopaedic controls	Non-injured controls
Age, median (range)	25.0.(18 – 39)	27.0 (18 – 40)	26.0 (19 – 36)
Men, n (%)	7 (47)	11(73)	9 (60)
Women, n (%)	8 (53)	4 (27)	6 (40)
GCS 15 (ER)	14	N/A	N/A
GCS 14 (ER)	1	N/A	N/A
Type of trauma: n (%)	Fall: 7 (47 %) Bicycle: 2 (13 %) Horse back riding: 2 (13 %) Other: 4 (27 %)	Sports: 9 (60 %) Other: 6 (40 %)	

N/A – not applicable

Inclusion procedure

Patients attending the Emergency Department (ED) at Danderyd hospital with mTBI or minor musculoskeletal injury but no head trauma who fulfilled inclusion and exclusion criteria were recruited at ED or if discharged contacted by phone within 1-3 days after the injury. Study participants received written information about the study and gave informed consent.

Data collection

All data related to the injury, GCS on arrival at the ED, results of CT-scan were collected from the medical records. Demographic data were collected by interview at the baseline examination.

All study participants were assessed twice: at baseline, in the subacute phase, (trauma patients 7-10 days after the trauma), and at follow up - 75-100 days after first assessment. Neuropsychological testing and visual assessment were performed at different time points on the same day or on adjacent days.

Assessments

The mTBI and patients with minor musculoskeletal injury underwent examination with structural magnetic resonance imaging (MRI) and resting state functional magnetic resonance imaging (rsfMRI) of the brain at baseline and at follow up (imaging results will be presented separately). At baseline and follow up all study participants self-rated their symptoms using Rivermead Post-concussion Symptoms Questionnaire (RPQ)(28) and Convergence Insufficiency Symptom Survey (CISS).(29, 30) The RPQ is based on a Likert scale and includes 16 items with ratings: 0 "no symptoms", 1 "no more of a problem or transient symptoms", 2-4 "mild to severe" symptoms. A total sum of all symptom scores ("mild to severe", excluding ratings of 1) is calculated, max 64. Three or more symptoms after mTBI describes "postconcussional syndrome" in the International Classification of Diseases (ICD-10).(31) The CISS is a valid and reliable instrument,(29) which evaluates near work related visual symptoms. It includes assessment of direct symptoms, such as blur and double vision, as well as indirect symptoms e.g. difficulty maintaining concentration, sleepiness while reading, headache and ocular discomfort. The survey includes 15 questions with ratings from 0 "never" to 4 "always" for assessment of visual symptoms. The total score is 60 and the cut-off score for abnormal levels of symptoms is 21 (this value giving good sensitivity (97,8 %) and specificity (87 %) in otherwise healthy young adults who have presented to optometrists with visual symptoms).(30)

The visual examination was performed by qualified optometrists using standard optometric clinical methods. It included assessment of visual acuity at far and near, refractive error, stereo acuity, near point of accommodation, facility (flexibility) of accommodation, near point of convergence with an accommodative target, non-strabismic eye-turn (heterophoria), eye motility and fusional vergence. Diagnosis of visual dysfunctions were based on established diagnostic criteria(32). The expected accommodative amplitude was defined according to the Hofstetter formula ($18.5 - 1/3$ age).(32) Diagnosis of accommodative insufficiency required amplitude less than minimum expected according to the Hofstetter formula ($15 - 1/4$ age). Diagnosis of convergence insufficiency required near point of convergence ≥ 6 cm plus at least one of the following; reduced positive fusional vergence at near (< 20 prism diopters) or divergent heterophoria at least four prism diopters greater at near than at distance.(32)

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3 Saccadic eye movements were recorded using an eye tracker (Tobii TX300, Tobii
4 Corp., Stockholm, Sweden, www.tobii.com). The participant was positioned 60 cm
5 directly in front of the eye tracker display. Three test paradigms were applied to test
6 (1) visually induced pro-saccades; mean latency and gain, (2) self-paced saccades;
7 number of saccades performed in 30 seconds and mean intersaccadic interval (ms),
8 (3) anti-saccades, latency and proportion of erroneous saccades. The stimuli consisted
9 of a dot, diameter 5 mm. In the pro-saccade paradigm the participant fixated a
10 centered cross and then re-fixated to a dot that appeared at 2, 4, 6, or 8 degrees to the
11 left or right of the cross. In the self-paced saccade paradigm two dots were
12 simultaneously presented for 30 seconds at 8 degrees to the left and right of center.
13 The participant was instructed to move the gaze rapidly, as many times as possible,
14 between the dots. In the anti-saccade paradigm the participant viewed a centered cross
15 and then rapidly looked in the opposite direction to that of a dot presented 8 degrees
16 to the left or right of the centre.

26 **Data analyses**

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28 All data were analysed using SPSS 23. Due to the relatively small sample size and
29 skewed distribution of data, the nonparametric Kruskal-Wallis (three groups), Mann-
30 Whitney U (two groups), Wilcoxon sign rank tests and Spearman's rank correlation
31 were used for comparison between patients and controls. Two-tailed p-values were
32 used with a critical significance level of $p < 0.05$. Parametric statistics were used for
33 oculomotor measures.

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38 Statistical power calculation: With an expected incidence of visual disturbances in 70
39 % of mTBI group and 10 % in the control group, 10 individuals per group were
40 needed to detect visual disturbances(10) with 80 % power at alpha 0.05. With an
41 expected drop out rate of 30 %, 15 persons were included in each group.

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46 All participants also rated anxiety, depression and fatigue using Hospital Anxiety and
47 Depression Scale (HADS)(33) and Fatigue Severity Scale (FSS)(34) and underwent
48 neuropsychological testing. These data will be reported separately.

51 **RESULTS**

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53 A total of 15 mTBI patients, 15 patients with minor musculoskeletal injuries
54 unexposed to head injury (orthopaedic controls) and 15 non-injured controls were
55 included in the study (table 1). One mTBI patient was excluded due to not completing
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3 the assessments and two controls were excluded due to manifest strabismus. Two
4 mTBI patients had pathological findings on computer tomography brain: one had a
5 small subdural haemorrhage and the other one a small subarachnoid haemorrhage.
6 Neither required surgery. The median time between injury and baseline assessment
7 was 6.0 days (range 4-12 days) for mTBI, and 8.0 days, range (2-9 days) for
8 orthopaedic controls. The median time between baseline and follow up was 95 days
9 (range 81-225) for mTBI, and 108 days (range 87-324) for orthopaedic controls. No
10 significant difference was found between mTBI and orthopaedic control group
11 regarding time between the injury and assessments (baseline and follow up). Among
12 the consecutive patients who were invited to participate in the study a total of ninety-
13 nine declined; 17 mTBI and 82 orthopaedic controls. Of those who declined, 88 % of
14 mTBI patients and 64 % of minor trauma patients were men, and there was no
15 difference regarding age between participating and non-participating individuals. The
16 reasons stated for not participating were lack of time and inconvenience.
17 Two individuals in mTBI group and two individuals in orthopaedic control group
18 were lost to follow up despite several reminding phone calls and letters. One person in
19 orthopaedic group did not complete the visual examination.

31 **Symptoms measured by RPQ**

32 There was a significantly higher sum of symptom scores at baseline according to RPQ
33 in mTBI group compared to orthopaedic controls ($p = 0.002$) and to non-injured
34 controls ($p = 0.0005$). Significant difference was found in sum of symptom scores at
35 follow up between mTBI group and orthopaedic controls ($p = 0.003$) and between
36 mTBI group and non-injured controls ($p = 0.0005$) (Mann-Whitney U test). No
37 difference was found between control groups at any time. Sum of symptom scores
38 decreased in mTBI group over time but the difference did not reach statistical
39 significance ($p = 0.092$) (Wilcoxon signed rank test).

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42 There was a significant difference regarding number of symptoms in RPQ (rated 2-4,
43 “minor to severe”) between mTBI group and orthopaedic control group at baseline (p
44 = 0.003), and at follow up ($p = 0.0005$), and between mTBI group and non-injured
45 control group at baseline ($p = 0.002$) and at follow up ($p = 0.0004$).

53 **Visual examination**

54 No cranial nerve palsies or direct trauma related pathology were found. Insufficient
55 accommodation (AI) and convergence (CI) were identified. At baseline three mTBI
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3 patients had combined CI/AI and nine had AI. At follow up one mTBI patient still
4 had CI and six had AI. Five orthopaedic controls had AI at baseline and six at follow
5 up. Two non-injured controls with CI and two with AI were found at baseline and at
6 follow up.
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10 The near point of convergence (NPC) changed significantly in the mTBI group
11 between the baseline and follow up ($p = 0.015$) (figure 1). There was no significant
12 difference in NPC between mTBI group and each of the control groups at any time.
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15 (Insert Figure 1 here)
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18 Figure 1 Near point of convergence in mTBI group at baseline and at follow up
19 measured in cm. The lower the value, the better convergence performance. The box
20 indicates median, upper and lower quartile. The whiskers indicate min and max
21 excluding outliers. The x's indicate outliers and miniature squares indicate mean
22 values.
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27 A significant difference was found at baseline in the magnitude of deviation from
28 expected accommodative amplitude in mTBI group compare to non-injured controls
29 ($p = 0.001$) (figure 2). At follow up six out of 13 mTBI patients still presented with
30 reduced accommodative amplitude which met diagnostic criteria for accommodative
31 insufficiency.
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36 Performance in accommodative facility in mTBI group improved marginally from
37 baseline to follow up but this did not reach statistical significance.
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40 (Insert Figure 2 here)
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43 Figure 2 Deviation from expected accommodative amplitude. The higher the negative
44 value, the greater the deviation (insufficiency). Closer to zero is better. The box
45 indicates median, upper and lower quartile. The whiskers indicate min and max
46 excluding outliers. The x's indicate outliers and miniature squares indicate mean
47 values.
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51 The analysis of fusional vergences did not show any significant differences at the
52 group level. At baseline, reduced positive fusional vergences (< 20 prism diopters) at
53 near point of focus were found in four mTBI patients, four orthopaedic controls and
54 marginally reduced in two non-injured controls.
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Saccade performance

In the pro-saccade task no significant differences in latency or gain were found between the groups or test occasions. That is, performance in terms of reaction time and accuracy was not different at the group level. One mTBI patient and one non-injured control exhibited a markedly prolonged latency both at baseline and follow up.

In the self-paced saccade task the mTBI group performed slightly fewer saccades on average at both baseline and follow up compared to controls but the difference was not statistically significant. The mTBI group also showed a slightly elevated intersaccadic interval at baseline but this was not statistically significant.

In the anti-saccade task all groups performed equally well at both test occasions with no statistically significant differences in latency or proportion of erroneous saccades. The mTBI group showed an apparent greater variability in latency with three subjects exhibiting prolonged latency.

Assessment of visual symptoms

Patients with mTBI had more visual symptoms with near work compared to the two control groups as measured by the CISS score at baseline: mTBI vs. orthopaedic controls ($p = 0.012$) and mTBI vs. non-injured controls ($p = 0.02$) (Mann-Whitney U test). The median value of CISS score in mTBI group at baseline was 24. It then decreased to 19 at follow up but the change did not reach statistical significance. The CISS score was below cut-off level at both time points in control groups. A CISS score of 21 or higher was applied as the cut-off for abnormal visual symptoms. The association with convergence and/or accommodative insufficiency was analysed (table 2). No significant associations between symptoms and objective findings were found using the Fisher's exact test. At baseline nine out of 12 mTBI patients with a vision diagnosis were identified using CISS. Of these 12 patients five had scored two or higher on one or both of the RPQ items concerning blurred or double vision. At follow up seven mTBI patients still had a vision diagnosis; one with convergence- and six with accommodative insufficiency. Three of these patients scored as symptomatic on CISS. Three of these patients also scored two or greater on RPQ items concerning blurred or double vision however there was only an overlap for two patients.

Table 2 Vision diagnoses (accommodative– and/or convergence insufficiency) versus CISS symptom score.

Subjects	Examination	Vision diagnosis	CISS < 21	CISS ≥ 21	Score ≥ 2 on RPQ blurred or double vision
mTBI patients	Baseline	No diagnosis	2	1	-
		Diagnosis	3	9	5
	Follow up	No diagnosis	4	2	1
		Diagnosis	4	3	3
Orthopaedic controls	Baseline	No diagnosis	8	1	-
		Diagnosis	5	-	-
	Follow up	No diagnosis	5	1	-
		Diagnosis	6	-	-
Non-injured controls	Baseline	No diagnosis	11	-	1
		Diagnosis	4	-	1
	Follow up	No diagnosis	10	1	-
		Diagnosis	3	1	-

In mTBI group CISS score at baseline correlated with reduced positive fusional vergence measured at near, i.e. the capacity to maintain clear single vision while performing near work ($r = -0.6$; $p = 0.02$) (figure 3).

(Insert Figure 3 here)

Figure 3 CISS score versus positive fusional vergence in mTBI patients. Higher positive fusion value corresponds to better function.

DISCUSSION

We have found transient objectively measured visual disturbances in a well-defined mTBI group. We also observed differences in visual measurements between mTBI group and two control groups.

As expected, mTBI patients reported significantly more symptoms on the RPQ compared to controls at baseline. Symptoms after mTBI, such as fatigue, headache and cognitive problems are not specific to the head injury, and therefore referred to as posttraumatic symptoms as it was concluded in the systematic review on prognosis after mTBI.⁽³⁵⁾ Previous studies have demonstrated that similar symptoms are

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3 present after any trauma because of emotional distress and pain related to the
4 injury.(36) However, patients with mTBI report more symptoms than individuals
5 without injury to the head.(37)
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8 We found a significant change in NPC in the mTBI group between the baseline and
9 follow up. Receded NPC has previously been suggested as a potential sensitive vision
10 based biomarker after mTBI(8) and our findings support this. Similar findings in NPC
11 performance were made by Capo-Aponte and co-workers when comparing mTBI
12 patients and controls.(13) However, the median NPC at baseline was within 10 cm,
13 which may be clinically considered as within the tolerance limit,(9) and therefore not
14 pose a clinical sign for further examination regarding suspected convergence
15 insufficiency. On the other hand, according to established diagnostic criteria for
16 convergence insufficiency, any NPC greater than six cm is considered
17 insufficient.(32)
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20 The mechanism behind the spontaneous recovery of NPC in the present patient
21 sample remains to be understood. The convergence responses are based on visual
22 processing of binocular disparity and correct ocular motor alignment through vergence
23 eye movements. Given the recovery of NPC any manifest structural injury affecting
24 motor function (vergence eye movements) can probably be ruled out. Some of the
25 remaining aspects to consider are the sensory-motor integration and the ability to
26 respond appropriately to the stimulus. Certain tasks, including the actual test
27 condition for NPC, means that the subject must exert maximal convergence effort to
28 maintain single vision of a very near target. This most likely involves voluntary effort.
29 A question for further discussion is how the constellation of somatic symptoms,
30 cognitive impairments and fatigue, known to be associated with mTBI, may affect the
31 capacity to perform maximally. Our clinical observations during this study, along
32 with previous research, may suggest that these factors can have aggravating
33 effects.(16)
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49 In accordance to previous studies,(13) a significant difference in accommodation
50 between mTBI and each of the control groups at the baseline was found in our study.
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52 The accommodative amplitude was significantly lower in mTBI compared to controls
53 at baseline. It then recovered to a certain degree at follow up but six mTBI patients
54 still presented with deviations meeting the diagnostic criteria for accommodative
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3 insufficiency. This corresponds to almost half of the mTBI patients (n=13) who were
4 examined at the follow up around three months after the injury. To our knowledge
5 there is quite limited research available regarding the expected course of spontaneous
6 improvement. Capo Aponte et al. found significantly reduced accommodative
7 amplitude 15-45 days after injury.(13) There are some indications that spontaneous
8 recovery may occur up to a year after the injury(32) but also that it may be part of
9 persisting issues even long time after the injury.(18, 19) Mechanisms contributing to
10 slow or incomplete spontaneous recovery of accommodation are unclear. Our
11 findings, along with previous observations,(18) indicate the importance of being
12 aware of possible accommodative disorders and its effects on the patients capacity to
13 perform daily activities.
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21 We found that mTBI patients had significantly more visual symptoms as measured by
22 CISS score than minor trauma- and non-injured controls. CISS score decreased from
23 baseline to follow up without the difference reaching significance. CISS scores never
24 reached the cut-off point 21 in either control groups. Our findings about reporting
25 visual disturbances at near work after mTBI are consistent with previous studies
26 study.(13)
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32 We were not able to replicate the findings of previous studies that found differences
33 in several measures of saccadic eye movements between mTBI patients and controls.
34 An explanation could be that changes in saccadic reaction time/latency are subtle,
35 transient, and possibly only to be demonstrated directly after a minor trauma to the
36 head. In our study, baseline optical examination took place a few days after mTBI.
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42 Our findings are in line with a study of amateur boxers where saccadic latency was
43 expressed as latency distribution and was measured at several time points, with the
44 baseline before the boxing match (pre-fight) and at 3 days, 7 days and 12 days after-
45 fight, after blows to the head.(24) Results in this study showed increased mean
46 saccadic latency distribution directly after the fight, however 12 days later the mean
47 latency had returned to baseline. The small number of participants and lack of the
48 description of mTBI criteria limit interpretation of findings in that study.
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54 The strength of our study is two control groups. Traumatic injury generally can
55 impact on reporting of various symptoms related to acute posttraumatic stress and
56 pain. Therefore, to avoid confounding, we included group of patients with minor
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3 musculoskeletal injuries without trauma to the head, presenting at the same
4 emergency department.
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6 7 **Study limitations**

8 When the study population is small, there is always a risk for type II error, that is the
9 risk of not revealing a true difference in the studied population. The differences found
10 between mTBI patients and controls regarding oculomotor measures were few and the
11 within group variations were large. The degree of overlap between groups and
12 incomplete correlation between visual symptoms and objective measurements,
13 suggest that caution is appropriate when interpreting findings in an individual patient,
14 based on the current state of knowledge. However several aspects merit further
15 investigation.
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21 Study participants were 18-40 years old making the mTBI patient group in this
22 explorative study highly selected. This age limitation was chosen to minimize the
23 effect of presbyopia on study results. Our findings will have relevance regarding the
24 large number of young adults suffering head trauma, but will not be directly
25 applicable to older patients, which limits the generalisability.
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31 **Future recommendations**

32 Larger confirmatory studies are needed to clarify the clinical role the transient visual
33 disturbances observed in this study. The role of vergence and accommodation as
34 potential biomarkers for mTBI and their interplay with persisting symptoms such as
35 fatigue also needs further elucidation.
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39 Furthermore, investigations of visual disturbances after mTBI should aim to
40 determine if visual testing in subacute stage after mTBI could help to predict long
41 lasting symptoms and be a target for intervention to promote recovery.
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45 **CONCLUSIONS**

46 Some transient measurable visual changes regarding convergence were noted in
47 mTBI patients during the subacute period after injury. The finding of persistent
48 accommodative insufficiency in a substantial proportion of mTBI patients requires
49 further evaluation; this could be either a biomarker for persistent functional
50 impairment in neural networks, or a target for intervention to promote recovery, or
51 possibly both.
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Data sharing statement: No additional data are available.

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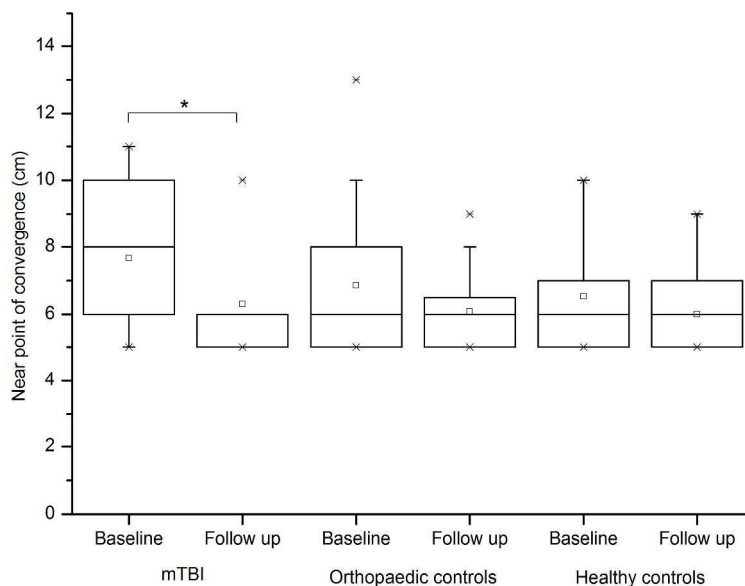


Figure 1 Near point of convergence in mTBI group at baseline and at follow up measured in cm. The lower the value, the better convergence performance. The box indicates median, upper and lower quartile. The whiskers indicate min and max excluding outliers. The x's indicate outliers and miniature squares indicate mean values.

288x201mm (300 x 300 DPI)

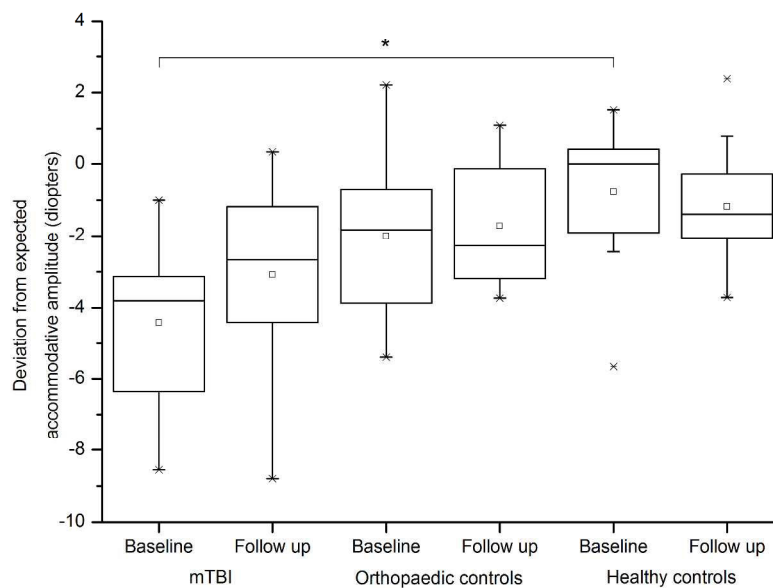


Figure 2 Deviation from expected accommodative amplitude. The higher the negative value, the greater the deviation (insufficiency). Closer to zero is better. The box indicates median, upper and lower quartile. The whiskers indicate min and max excluding outliers. The x's indicate outliers and miniature squares indicate mean values.

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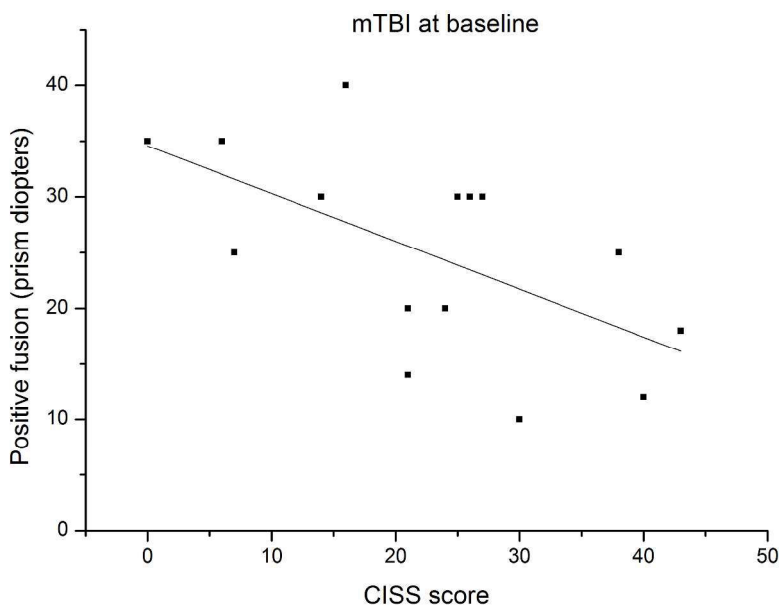


Figure 3 CISS score versus positive fusional vergence in mTBI patients. Higher positive fusion value corresponds to better function.

288x201mm (300 x 300 DPI)

Table 1. Demographic data

	mTBI patients	Orthopaedic controls	Non-injured controls
Age, median (range)	25.0.(18 – 39)	27.0 (18 – 40)	26.0 (19 – 36)
Men, n (%)	7 (47)	11(73)	9 (60)
Women, n (%)	8 (53)	4 (27)	6 (40)
GCS 15 (ER)	14	N/A	N/A
GCS 14 (ER)	1	N/A	N/A
Type of trauma: n (%)	Fall: 7 (47 %) Bicycle: 2 (13 %) Horse back riding: 2 (13 %) Other: 4 (27 %)	Sports: 9 (60 %) Other: 6 (40 %)	
N/A – not applicable			

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Table 2. Vision diagnoses (accommodative– and/or convergence insufficiency) versus CISS symptom score.

Subjects	Examination	Vision diagnosis	CISS < 21	CISS ≥ 21	Score ≥ 2 on RPQ blurred or double vision
mTBI patients	Baseline	No diagnosis	2	1	-
	n=15	Diagnosis	3	9	5
	Follow up	No diagnosis	4	2	1
	n=13	Diagnosis	4	3	3
Orthopaedic controls	Baseline	No diagnosis	8	1	-
	n=14	Diagnosis	5	-	-
	Follow up	No diagnosis	5	1	-
	n=12	Diagnosis	6	-	-
Non-injured controls	Baseline	No diagnosis	11	-	1
	n=15	Diagnosis	4	-	1
	Follow up	No diagnosis	10	1	-
	n=15	Diagnosis	3	1	-

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Research checklist

STROBE Statement - checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
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	8-9
Bias	9	Describe any efforts to address potential sources of bias	3
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	-
		(d) If applicable, explain how loss to follow-up was addressed	-
		(e) Describe any sensitivity analyses	-
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	10
		(b) Give reasons for non-participation at each stage	10
		(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	7
		(b) Indicate number of participants with missing data for each variable	11-13

		of interest	
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13
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	10-13
		(b) Report category boundaries when continuous variables were categorized	-
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
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	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
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	17

*Give information separately for exposed and unexposed groups.

NA – not applicable

BMJ Open

Longitudinal changes in oculomotor function in young adults with mild traumatic brain injury (mTBI) - an exploratory Swedish prospective observational study

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Neurology
Keywords:	mild traumatic brain injury, visual dysfunction, near point of convergence, accommodation, posttraumatic symptoms, NEUROLOGY

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Manuscripts

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3 **Longitudinal changes in oculomotor function in young adults with**
4 **mild traumatic brain injury (mTBI) – an exploratory Swedish**
5 **prospective observational study**
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8 Giedre Matuseviciene¹, Jan Johansson², Marika Möller¹, Alison K Godbolt¹, Tony
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37 Word count: 4595 words (including acknowledgements, contributors, competing
38 interests, patient consent, ethics approval, provenance and peer review, data sharing
39 statement)
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ABSTRACT

Objectives: To assess 1) whether visual disturbances can be demonstrated with objective measures more often in patients with mild traumatic brain injury (mTBI) compared to controls and if these disturbances change over time, and 2) whether self-reported visual symptoms after mTBI correlate with objectively measurable changes in visuomotor performance.

Design: A prospective, controlled observational study.

Setting: Emergency department of a general hospital in Stockholm, Sweden.

Participants: Fifteen patients with mTBI, 15 patients with minor orthopaedic injury but no head trauma, and 15 non-injured controls, aged 18-40 years.

Outcome measures: Visual examination included assessment of visual acuity, accommodation, eye alignment and saccades. Assessments were performed at two time points – baseline (7-10 days) and follow-up (75-100 days) after injury. Symptom assessment using Convergence Insufficiency Symptoms Survey (CISS) and Rivermead Post-concussion Symptoms Questionnaire.

Results: Near point of convergence in the mTBI group was receded at baseline and improved significantly at follow-up ($p=0.015$). The accommodative amplitude was significantly lower in the mTBI group compare to non-injured controls at baseline ($p=0.001$). Six out of 13 mTBI patients who were followed up had accommodative insufficiency. At baseline, mTBI patients reported significantly more symptoms according to CISS compared to orthopaedic controls ($p=0.012$) and non-injured controls ($p=0.02$). For mTBI patients the CISS score correlated with fusional vergence. No significant difference was found between the mTBI and control groups regarding pro-saccades, anti-saccades and self-paced saccades at any time point.

Conclusion: There are some transient measurable visual changes regarding convergence in mTBI patients during the subacute period after the injury. Our findings of persistence of accommodative insufficiency in a considerable proportion of mTBI patients suggest that this visual function should not be overlooked in clinical assessment.

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Key words: neurology, mild traumatic brain injury, visual dysfunction, near point of convergence, accommodation, posttraumatic symptoms.

For peer review only

ARTICLE SUMMARY

Strengths and limitations of this study

- Prospective longitudinal design with measurement at two time points.
- Strict inclusion criteria for mTBI according to American Congress of Rehabilitation Medicine.
- Inclusion of both an uninjured control group and a group with minor orthopaedic injuries without trauma to the head to control for non-specific effects of injury such as pain and distress.
- Study methods include several easily replicable optometric measurements.
- The generalisability of this study is limited because the sample of patients with mTBI was small in size and restricted in age range.

INTRODUCTION

There is a need for objective methods to assess and monitor recovery after mTBI, as a base for developing evidence based clinical follow-up guidelines. Oculomotor changes affecting accommodation, eye alignment and eye movements have been highlighted recently as a possible measurable correlate of symptoms related to a mild traumatic brain injury.(1-4) A recent systematic review of oculomotor-based vision assessment to monitor changes after mTBI found promising, yet preliminary evidence.(5) It was concluded that measurement of oculomotor functions appeared useful in detecting changes after mTBI, but the strength of evidence in currently available research is not yet sufficient enough to inform clinical guidelines.

Traumatic impact to the head, as in mTBI, may affect visual networks that are widely spread throughout the brain,(1, 6) and thus result in visual disturbances. Visual impairments of different kinds have been found in several studies with prevalence up to 70 percent in a cohort of patients with long lasting problems after mTBI.(4, 7, 8) However, these studies have several limitations such as retrospective design, selection bias, heterogeneity regarding severity of injury, and lack of appropriate control groups. Prospective studies with early assessment and follow- up of vision related oculomotor changes after mTBI are scarce.(9, 10)

Ability to appropriately alter focus, align the eyes and make gaze changes, can be measured, and has been the focus of several recent studies of mTBI.(11-14) Convergence, that is the ability to move both eyes inwards to maintain a single retinal image of objects at different viewing distances,(15) is one of the most frequently described oculomotor measurements where changes after head injury have been reported.(16) Symptoms after mTBI, both direct visual symptoms (double vision, blurred vision), and indirect symptoms (increased effort at near work

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3 might be attributed to impaired convergence. Recent test protocols using eye tracking
4 have added knowledge about the physiology of convergence eye movements in those
5 mTBI patients with convergence related symptoms.(17) These methods appear
6 promising in that they can provide additional information about subtle changes
7 affecting oculomotor efficiency and subsequent symptoms. Convergence
8 insufficiency (CI) was found in 42-48% of mTBI patients in retrospective studies,(4,
9 7) and controlled studies of military personnel who have suffered blast-induced mTBI
10 have shown a significant difference in near point of convergence (NPC).(3,7)

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13 Fusional vergence aligns the two eyes and thereby provides for clear single vision.
14 Impaired fusional vergence causes unstable binocular vision, which may present as
15 losing one's place when reading, blurred or even double vision. Fusion vergence
16 disorders may occur in about 3-6% of an otherwise healthy population with vision
17 based symptoms,(18, 19) but may be significantly more frequent in TBI patients.(20)

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20 Accommodation provides a clear optical image of an object at different distances
21 through the altering of refractive power in the crystalline lens. Symptoms of
22 accommodative disorders include blurred vision and impaired flexibility to alter focus
23 between near and far. A physiological deterioration of accommodative ability,
24 presbyopia, is to be expected with age. The current study therefore included pre-
25 presbyopic subjects of age 40 or younger. In an otherwise healthy pre-presbyopic
26 population, accommodative changes may be present in up to about 10 % of
27 individuals with vision complaints.(19, 21) Significantly more prevalent
28 accommodative disorders have been found in mTBI patients in the sub-acute stage,(3)
29 and also as part of persisting issues.(22, 23)

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32 Saccades are a group of rapid eye movements that shift the gaze to areas of interest in
33 the visual field. Through purposeful and accurate saccades, executed in quick
34 succession, the environment can be scanned and functional visual field is increased.
35 Thus, an efficient saccadic performance is an important base for efficient and safe
36 interaction with the environment, and for detailed work such as reading.(24) The
37 initiation and programming of saccades involves cognitive functions that are
38 subserved by complex neuronal networks involving different parts of the brain.
39 Parameters of saccades, such as latency and accuracy, have been shown to be affected
40 after mTBI.(2, 9, 10, 25)

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3 In this study we aim to assess oculomotor and visual changes after mTBI
4 prospectively, and compare these to a control group unexposed to head injury but
5 with minor orthopaedic injury, and to a non-injured control group. The orthopaedic
6 control group is important to control for non-specific effects of pain and distress after
7 trauma, and allow evaluation of brain injury specific effects.
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11 The study objectives are to assess: 1) whether visual disturbances can be
12 demonstrated with objective measures more often in mTBI patients compared to
13 controls and if these disturbances change over time, and 2) whether self-reported
14 visual symptoms after mTBI correlate with objectively measurable changes in
15 visuomotor performance.
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20 21 **METHODS**

22 This work is a part of a prospective controlled observational study on mTBI. The
23 setting was a large emergency department (ED) of a general hospital serving the
24 north-east of Stockholm. Patients with mTBI and a control group of patients with
25 minor orthopaedic trauma to extremities, but no head trauma and not requiring
26 surgical intervention, were included to the study. A second control group without
27 traumatic injury included staff from Department of Rehabilitation Medicine, their
28 friends and family members. All study participants were 18-40 years of age. Groups
29 were matched for age. For demographic information, see Table 1.
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36 Inclusion was conducted between January 2015 and January 2016, and was stopped
37 when 15 persons were included in each group, in accordance with the power
38 calculation below.
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42 A power calculation was conducted: with an expected incidence of visual
43 disturbances in 70 % in the mTBI group,(4, 7, 8) and 10 % in the control group(19,
44 21), 10 individuals per group were needed to detect visual disturbances with 80 %
45 power at alpha 0.05. With an expected drop out rate of 30 %, 15 persons would be
46 needed in each group.
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51 The mTBI patients met criteria described in the guidelines of Mild Traumatic Brain
52 Injury Committee of American Congress of Rehabilitation Medicine:(26) acute brain
53 injury resulting from mechanical energy to the head from external physical forces: (i)
54 1 or more of the following: confusion or disorientation, loss of consciousness for 30
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minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale (GCS)(27) score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations of mTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury.

Exclusion criteria

The following patients were excluded: patients with traumatic brain injury and GCS <13, those in need of neurosurgery, previous moderate or severe traumatic brain injury, any head injury in the previous year requiring medical attention, contraindications for MRI (magnetic resonance imaging), progressive neurological disease or other medical conditions with expected short survival, severe visual impairment or manifest strabismus, need for personal help in activities of daily living before the current injury, intoxication with alcohol at the time of the injury, not fluent in Swedish.

Table 1 Demographic data

	mTBI patients	Orthopaedic controls	Non-injured controls
Age, median (range)	25.0 (18 – 39)	27.0 (18 – 40)	26.0 (19 – 36)
Men, n (%)	7 (47)	11(73)	9 (60)
Women, n (%)	8 (53)	4 (27)	6 (40)
GCS 15 (ED)	14	N/A	N/A
GCS 14 (ED)	1	N/A	N/A
Type of trauma: n (%)	Fall: 7 (47 %) Bicycle: 2 (13 %) Horse back riding: 2 (13 %) Other: 4 (27 %)	Sports: 9 (60 %) Other: 6 (40 %)	

N/A – not applicable

Inclusion procedure

Patients attending the ED at Danderyd hospital with mTBI or with minor orthopaedic injury but no head trauma who fulfilled inclusion and exclusion criteria were recruited at ED or if discharged contacted by phone within 1-3 days after the injury. Study participants received written information about the study and gave informed consent.

Data collection

All data related to the injury, GCS on arrival at the ED, and results of computerised tomography scan (CT-scan), were collected from the medical records. Demographic data were collected by interview at the baseline examination.

All study participants were assessed twice: at baseline, in the subacute phase, (trauma patients 7-10 days after the trauma), and at follow-up - 75-100 days after first assessment. Neuropsychological testing and visual assessment were performed at different time points on the same day or on an adjacent day.

Assessments

The mTBI and patients with minor orthopaedic injury underwent examination with structural MRI and resting state functional MRI of the brain at baseline and at follow-up (imaging results will be presented separately). At baseline and follow-up all study participants self-rated their symptoms using Rivermead Post-concussion Symptoms Questionnaire (RPQ),(28) and Convergence Insufficiency Symptom Survey (CISS).(29, 30) The RPQ is based on a Likert scale and includes 16 items with ratings: 0 "no symptoms", 1 "no more of a problem or transient symptoms", 2-4 "mild to severe" symptoms. A total sum of all symptom scores ("mild to severe", excluding ratings of 1) is calculated, with a maximum score of 64. Three or more symptoms after mTBI describes "postconcussional syndrome" in the International Classification of Diseases, 10th revision.(31) The CISS is a valid and reliable instrument,(29) which evaluates near work-related visual symptoms. It includes assessment of direct symptoms, such as blur and double vision, as well as indirect symptoms (e.g., difficulty maintaining concentration, sleepiness while reading, headache and ocular discomfort). The survey includes 15 questions with ratings from 0 "never" to 4 "always" for assessment of visual symptoms. The total score is 60 and the cut-off score for abnormal levels of symptoms is 21. This value giving good sensitivity (97.8 %) and specificity (87 %) in otherwise healthy young adults who have presented to optometrists with visual symptoms.(30)

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3 The visual examination was performed by licensed optometrists, using standard
4 optometric clinical methods. It included assessment of visual acuity at far and near,
5 refractive error, stereo acuity, near point of accommodation, facility (flexibility) of
6 accommodation, near point of convergence with an accommodative target, non-
7 strabismic eye-turn (heterophoria), eye motility and fusional vergence. Diagnosis of
8 visual dysfunctions were based on established diagnostic criteria.⁽³²⁾ NPC was
9 measured using the push-up method (RAF rule). Positive fusional vergence (PFV)
10 was measured with a prism bar. In both cases the patient is instructed to try as hard as
11 possible to maintain single vision and to report when perceiving double vision.
12 Meanwhile, the examiner carefully observes eye alignment in order to verify the
13 patient's response. The expected accommodative amplitude was defined according to
14 the Hofstetter formula ($18.5 - 1/3$ age).⁽³²⁾ Diagnosis of accommodative insufficiency
15 (AI) required amplitude less than minimum expected according to the Hofstetter
16 formula ($15 - 1/4$ age). Diagnosis of CI required near point of convergence ≥ 6 cm plus
17 at least one of the following; reduced PVF at near (< 20 prism diopters) or divergent
18 heterophoria at least four prism diopters greater at near than at distance.⁽³²⁾ Saccadic
19 eye movements were recorded (spatial res 0.15 degrees; temporal res 300 Hz) using
20 an eye tracker (Tobii TX300, Tobii Corp., Stockholm, Sweden, www.tobii.com). The
21 participant was positioned 60 cm directly in front of the eye tracker display. Three test
22 paradigms were applied to test (1) visually induced pro-saccades; mean latency and
23 gain, 2) anti-saccades; latency of correctly performed saccades and proportion of
24 erroneous saccades, (3) self-paced saccades; number of saccades performed in 30
25 seconds and mean intersaccadic interval (ms). The stimuli consisted of a dot with a
26 diameter of 5 mm. In the pro-saccade paradigm the participant fixated a centered
27 cross and then re-fixated to a dot that appeared at 2, 4, 6, or 8 degrees to the left or
28 right of the cross. In the anti-saccade paradigm the participant viewed a centered cross
29 and then rapidly looked in the opposite direction to that of a dot presented 8 degrees
30 to the left or right of the centre. In the self-paced saccade paradigm two dots were
31 simultaneously presented for 30 seconds at 8 degrees to the left and right of centre.
32 The participant was instructed to move the gaze rapidly, as many times as possible,
33 between the dots.
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Data analyses

All data were analysed using SPSS 23. Due to the relatively small sample size and skewed distribution of data, the nonparametric Kruskal-Wallis (three groups), Mann-Whitney U (two groups), Wilcoxon sign rank tests and Spearman's rank correlation were used for comparison between patients and controls. Two-tailed p-values were used with a critical significance level of $p < 0.05$. Parametric statistics (a two-way repeated measures ANOVA and t-test) were used for oculomotor measures. Fischer's exact test was applied for analysis of the categorical data and small sample size.

All participants also rated anxiety, depression and fatigue using Hospital Anxiety and Depression Scale (HADS)(33) and Fatigue Severity Scale (FSS),(34) and underwent neuropsychological testing. These data will be reported separately.

RESULTS

A total of 15 mTBI patients, 15 orthopaedic controls, and 15 non-injured controls were included in the study (Table 1). Two of the 15 mTBI patients had pathological findings on CT-scan of the brain: one had a small subdural haemorrhage and the other a small subarachnoid haemorrhage. Neither required surgery. The median time between injury and baseline assessment was 6.0 days (range 4-12 days) for mTBI, and 8.0 days, (range 2-9 days) for orthopaedic controls. In order to minimize dropouts, we extended the planned follow-up time. The median time between baseline and follow-up was 95 days (range 81-225) for mTBI, and 108 days (range 87-324) for orthopaedic controls. No significant difference was found between mTBI subjects and the orthopaedic control group regarding time between the injury and assessments (baseline and follow-up). Among the consecutive patients who were invited to participate in the study a total of ninety-nine declined; 17 mTBI and 82 orthopaedic controls. Of those who declined, 88 % of mTBI patients and 64 % of orthopaedic controls were men, and there was no difference regarding age between participating and non-participating individuals. The reasons stated for not participating were lack of time and inconvenience. Two individuals in the mTBI group and two individuals in the orthopaedic control group were lost to follow-up despite several follow-up phone calls and letters.

Symptoms measured by RPQ

There was a significant difference, regarding the sum of symptom scores on the RPQ, between the three groups at baseline ($df=2$, $p=0.0004$) and at follow-up ($df=2$, $p=0.001$) (Kruskal-Wallis test). At baseline, the RPQ sum of symptom scores was significantly greater in the mTBI group compared to the orthopaedic control group ($z=-3.03$, $p=0.002$) and to non-injured controls ($z=-3.5$, $p=0.0005$) (Mann-Whitney U test). A significant difference was found in the sum of symptom scores at follow-up, between the mTBI group and the orthopaedic control group ($z=-2.99$, $p=0.003$), and between the mTBI group and non-injured controls ($z=-3.48$, $p=0.0005$) (Mann-Whitney U test). No difference was found between control groups at any time (Mann-Whitney U test). Sum of symptom scores decreased in the mTBI group over time but the difference did not reach statistical significance ($z=-1.7$, $p=0.092$) (Wilcoxon signed rank test).

Visual examination

No cranial nerve palsies or direct trauma related eye pathology was found. AI and CI were identified. At baseline, three mTBI patients had combined CI and AI, and nine had AI. At follow-up, one mTBI patient still had CI, and six had AI; five orthopaedic controls had AI at baseline, and six at follow-up. Two non-injured controls with CI and two with AI were found at baseline and at follow-up.

The NPC improved in the mTBI group between baseline and follow-up. Statistical analysis showed a significant interaction effect ($df=2$, $F=3.793$, $p=0.042$) and the ensuing pairwise analysis showed a significant difference for the mTBI group ($p=0.015$) (Figure 1). There were no significant differences between or within the control groups.

(Insert Figure 1 here)

A significant interaction effect was found for the deviation from expected accommodative amplitude ($df=2$, $F=4.406$, $p=0.028$). The ensuing pairwise analysis showed a significantly greater deviation in mTBI compared to non-injured controls at baseline ($p=0.001$) (Figure 2). At follow-up six out of 13 mTBI patients still presented with reduced accommodative amplitude, which met the diagnostic criteria for AI. No significant differences in accommodative facility were found within or between groups or test occasions.

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3 (Insert Figure 2 here)
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5 The analysis of fusional vergence did not show any significant differences at the
6 group level. At baseline, reduced positive fusional vergence (< 20 prism diopters) at
7 near point of focus was found in four mTBI patients, four orthopaedic controls and
8 marginally reduced in two non-injured controls.
9

10 11 12 **Saccade performance**

13 In the pro-saccade task, no significant difference in latency or gain was found
14 between groups or test occasions. No significant differences within or between groups
15 were found in the self-paced saccade task. In the anti-saccade task all groups
16 performed well at both test occasions with no statistically significant differences in
17 latency or proportion of erroneous saccades.
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20 21 22 **Stereo acuity**

23 All non-injured controls performed 60 seconds of arc or better at both test occasions.
24 In the orthopaedic group three subjects performed 120-240 at baseline and two of these
25 performed similarly at follow-up (one missing). A contrasting finding was that one
26 third (n=5) of the mTBI patients showed crude level of stereo acuity at baseline (120-
27 240) whilst at follow-up, all but one (subject 14, TNO 120), performed 60 or better.
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30 31 32 **Assessment of visual symptoms**

33 There was a significant difference between the three groups regarding CISS score at
34 the baseline (df=2, p=0.003) (Kruskal-Wallis test). Patients with mTBI had more
35 visual symptoms with near work, compared to the two control groups, as measured by
36 the CISS score at baseline: mTBI vs. orthopaedic controls (z=-2.512, p=0.012) and
37 mTBI vs. non-injured controls (z=-3.092, p=0.02) (Mann-Whitney U test). The
38 median value of the CISS score in the mTBI group at baseline was 24. It then
39 decreased to 19 at follow-up but the change did not reach statistical significance. The
40 CISS score was below cut-off level at both time points in control groups. Vision
41 diagnoses based on optometric assessment of CI or AI were compared with CISS
42 symptoms scores (Table 2). No significant association was found, based on Fisher's
43 exact test. At baseline nine out of 12 mTBI patients with a vision diagnosis were
44 identified using the CISS. Of these 12 patients five had scored two or higher on one or
45 both of the RPQ items concerning blurred or double vision. At follow-up, seven
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mTBI patients still had a vision diagnosis; one with CI and six with AI. Three of these patients scored as symptomatic on CISS. Three of these patients also scored two or greater on RPQ items concerning blurred or double vision, however there was only an overlap for two patients.

Table 2 Vision diagnoses (accommodative– and/or convergence insufficiency) versus CISS and RPQ scores.

Subjects	Examination	Vision diagnosis	CISS < 21	CISS ≥ 21	Score ≥ 2 on RPQ blurred or double vision
mTBI patients	Baseline n=15	No	2	1	-
		Yes	3	9	5
	Follow-up n=13	No	4	2	1
		Yes	4	3	3
Orthopaedic controls	Baseline n=14	No	8	1	-
		Yes	5	-	-
	Follow-up n=12	No	5	1	-
		Yes	6	-	-
Non-injured controls	Baseline n=15	No	11	-	1
		Yes	4	-	1
	Follow-up n=15	No	10	1	-
		Yes	3	1	-

In the mTBI group, CISS scores at baseline correlated with reduced positive fusional vergence measured at near, i.e. the capacity to maintain clear single vision while performing near work ($r=-0.6$; $p=0.02$) (Figure 3).

(Insert Figure 3 here)

DISCUSSION

We objectively measured transient visual disturbances in a well-defined mTBI group. We also observed differences in visual measurements between the mTBI group and two control groups.

The patients sustaining a trauma to the head in this study reported significantly more symptoms on the RPQ and CISS compared to both controls groups at baseline. The symptoms decreased at follow-up, but the change was not statistically significant.

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3 However, the role of brain-injury for these symptoms, especially for patients with
4 long-term problems after mTBI, has been questioned.(35) Several biases have been
5 suggested to affect symptom reporting after mTBI, e.g., recall bias, biopsychosocial
6 factors. Previous studies have demonstrated that similar symptoms also are present
7 after any trauma, presumably due to emotional distress and pain related to the
8 injury.(35, 36) Therefore the scope for this study was on potential objective measures
9 after an mTBI, rather than symptom report. One of the reasons for improvement of
10 self-rated symptom scores might be lack of interest or habituation in filling out a
11 questionnaire.
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14 We found a significant change in NPC in the mTBI group between the baseline and
15 follow-up. Receded NPC has previously been proposed as a potentially sensitive
16 vision-based biomarker after mTBI(14) and our findings tentatively support this.
17 Similar findings in NPC performance were made by Capo-Aponte and co-workers
18 when comparing mTBI patients and controls.(3) However, the median NPC at
19 baseline of these mTBI patients was just within 10 cm, which may or may not be
20 considered clinically meaningful,(15, 32) and therefore not pose a clinical sign for
21 further examination of CI. On the other hand, according to established diagnostic
22 criteria for CI, any NPC greater than six cm is considered insufficient.(32)
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24
25 The mechanism behind the spontaneous recovery of NPC in the present patient
26 sample remains to be understood. The convergence responses are based on visual
27 processing of binocular disparity and correct ocular motor alignment through
28 vergence eye movements. Given the recovery of NPC, any manifest structural injury
29 affecting motor function (vergence eye movements) can probably be ruled out. Some
30 of the remaining aspects to consider are sensory-motor integration and the ability to
31 respond appropriately to the stimulus. Certain tasks, including the actual test
32 condition for NPC, require that the subject must exert maximal convergence effort to
33 maintain single vision of a very near target. This most likely involves voluntary effort.
34 A question for further discussion is how the constellation of somatic symptoms,
35 cognitive impairments and fatigue, known to be associated with mTBI, may affect the
36 capacity to perform this test optimally. Our clinical observations during this study,
37 along with previous research, suggest that these factors can have contributory effects.
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3 In accordance to previous studies(3), a significant difference in accommodation
4 between mTBI and each of the control groups at the baseline was found in our study.
5 The mTBI group had a significantly lower accommodative amplitude compared to
6 non-injured controls at the baseline. It then recovered to a certain degree at follow-up,
7 but six mTBI patients still presented with deviations meeting the diagnostic criteria
8 for AI. This corresponds to almost half of the mTBI patients (n=13) who were
9 examined at the follow-up around three months after the injury. To our knowledge
10 there is quite limited research available regarding the expected course of spontaneous
11 improvement. There are some indications that spontaneous recovery may occur up to
12 a year after the injury, but also that AI may be part of persisting issues even long time
13 after the injury.(22, 23) Mechanisms contributing to slow or incomplete spontaneous
14 recovery of accommodation are unclear. Our findings, along with previous
15 observations,(22) indicate the importance of being aware of possible accommodative
16 disorders and their effects on the patient's capacity to perform daily activities.

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19 One third of the mTBI patients showed a deficient level of stereo acuity at baseline
20 (120-240), whilst at follow-up all but one performed normally, i.e., 60 or better. These
21 findings may suggest that the visual processing of disparity was particularly affected
22 in the mTBI group. Based on the improvement in stereo acuity we may speculate that
23 underlying factors affecting the ability to resolve and detect stereo disparity, such as
24 inadequate or inefficient vergence and/or accommodative function, improved with
25 time.(37)

26
27 We found that mTBI patients had significantly more visual symptoms as measured by
28 CISS score than orthopaedic and non-injured controls. Our findings about reporting
29 visual disturbances at near work after mTBI are consistent with a previous study.(3)
30 We found a significant correlation between CISS score and PFV at near in the mTBI
31 group. This may appear somewhat unexpected since the PFV was normal at group
32 level. The symptom score (CISS) was significantly higher in mTBI than in the control
33 groups. This may be an indication that most mTBI patients were indeed able to
34 perform normally on the PFV, but at a greater effort (causing symptoms). Objective
35 recordings of vergence eye movement have indicated this.(17)

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38 We were not able to replicate the findings of previous studies that found differences
39 in several measures of saccadic eye movements between mTBI patients and controls.

(3, 7, 13, 25) An explanation could be that changes in saccadic reaction time/latency are subtle, transient, and possibly only to be demonstrated directly after a trauma to the head. In our study, baseline optometric examination took place a few days after mTBI. Our findings are in line with a study of amateur boxers in which saccadic latency was measured at four time points, with baseline before the boxing match (pre-fight), and at 3 days, 7 days and 12 days after-fight, that is after blows to the head (10). Results in this study showed increased saccadic latency directly after the fight; however 12 days later the latency had returned to baseline. The small number of participants and lack of the description of mTBI criteria limit interpretation of findings in that study.

The strength of our study is having two control groups. Traumatic injury can generally impact on reporting of various symptoms, related to acute posttraumatic stress and pain. Therefore, to avoid confounding factors, we included a group of patients with minor orthopaedic injuries without trauma to the head, presenting at the same emergency department.

Study limitations

When the study population is small, there is always a risk for type II error, that is the risk of not revealing a true difference in the studied population. The differences found between mTBI patients and controls regarding oculomotor measures were few and the within group variations were large. The degree of overlap between groups and incomplete correlation between visual symptoms and visual measurements, suggest that caution is appropriate when interpreting findings in an individual patient, based on the current state of knowledge. However, several aspects merit further investigation. The sample size in the present study was based on power calculations from reports on long lasting vision and oculomotor problems in patients after mTBI.(4, 7, 8) To our knowledge there are no another published reports of visual problems including oculomotor changes in the early subacute phases in peer-reviewed journals. Possible bias in these studies could have led to an overestimation of the frequency of oculomotor changes and thus an overestimation of expected effect size in our power calculation and a risk of type II error.

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3 Study participants were 18-40 years old making the mTBI patient group in this
4 explorative study highly selective. This age limitation was chosen to minimize the
5 effect of presbyopia on study results. Our findings will have relevance regarding the
6 large number of young adults suffering head trauma, but will not be directly
7 applicable to older patients, which limits the generalisability.
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11 **Future recommendations**

12 Larger confirmatory studies are needed to clarify the clinical role the transient visual
13 disturbances observed in this study. The role of vergence and accommodation as
14 potential biomarkers for mTBI and their interplay with persisting symptoms such as
15 fatigue also needs further elucidation.
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18 Furthermore, investigations of visual disturbances after mTBI should aim to
19 determine if visual testing in subacute stage after mTBI could help to predict long
20 lasting symptoms and be a target for intervention to promote recovery.
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23 **CONCLUSIONS**

24 Some transient measurable visual changes regarding convergence were noted in
25 mTBI patients during the subacute period after injury. The finding of persistent
26 accommodative insufficiency in a substantial proportion of mTBI patients requires
27 further evaluation; this could be either a biomarker for persistent functional
28 impairment in neural networks, or a target for intervention to promote recovery, or
29 possibly both.
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43
44

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47 contributed to the analysis of results and interpretation of findings. CND, TP, MM
48 were main contributors to study design, contributed to data collection, analysis of
49 results and interpretation of the findings. AKG contributed to discussions on study
50 design, critically revised manuscript, and contributed to data analysis and
51 interpretation. All authors read, commented and approved the final manuscript.
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16 17 18 19 **FIGURE LEGENDS**

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21 Figure 1 Near point of convergence in mTBI group at baseline and at follow up
22 measured in cm. The lower the value, the better convergence performance. The box
23 indicates median, upper and lower quartile. The whiskers indicate min and max. The
24 x's indicate outliers and miniature squares indicate mean values.

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28 Figure 2 Deviation from expected accommodative amplitude. The lower the negative
29 value, the greater the deviation (insufficiency). Closer to zero is better. The box
30 indicates median, upper and lower quartile. The whiskers indicate min and max. The
31 x's indicate outliers, and miniature squares indicate mean values.

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35 Figure 3 CISS score versus positive fusional vergence in mTBI patients. Higher
36 positive fusion value corresponds to better function.

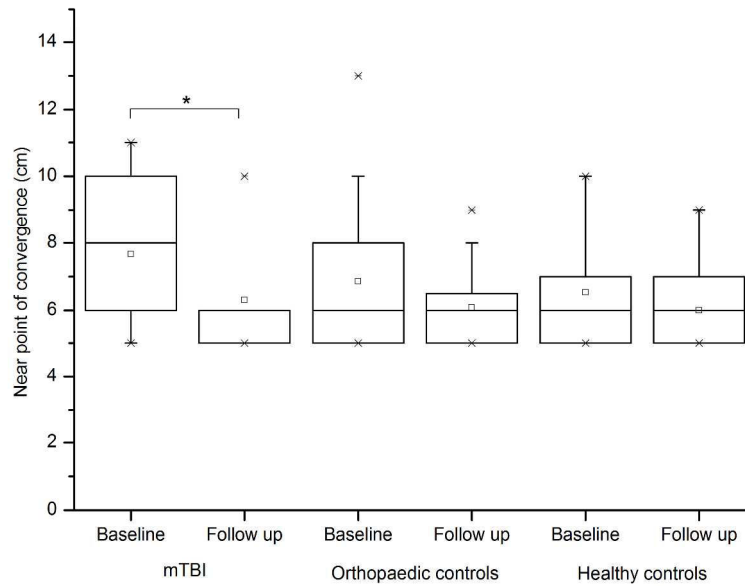


Figure 1 Near point of convergence in mTBI group at baseline and at follow up measured in cm. The lower the value, the better convergence performance. The box indicates median, upper and lower quartile. The whiskers indicate min and max. The x's indicate outliers and miniature squares indicate mean values.

288x201mm (300 x 300 DPI)

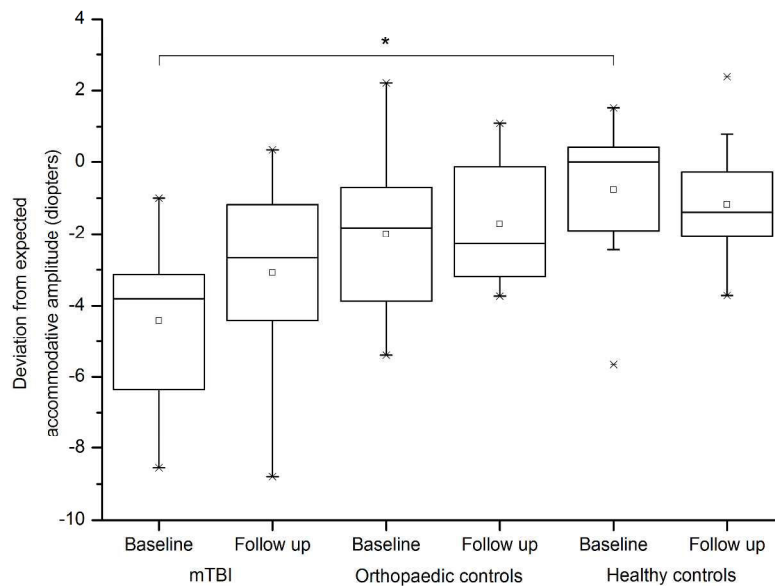


Figure 2 Deviation from expected accommodative amplitude. The lower the negative value, the greater the deviation (insufficiency). Closer to zero is better. The box indicates median, upper and lower quartile. The whiskers indicate min and max. The x's indicate outliers and miniature squares indicate mean values.

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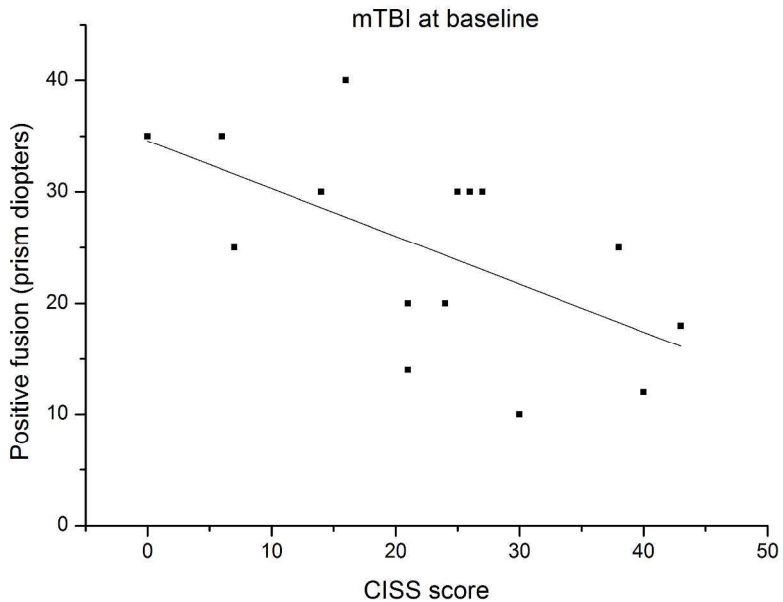


Figure 3 CISS score versus positive fusional vergence in mTBI patients. Higher positive fusion value corresponds to better function.

288x201mm (300 x 300 DPI)

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Research checklist

STROBE Statement - checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
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	8-9
Bias	9	Describe any efforts to address potential sources of bias	3
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	-
		(d) If applicable, explain how loss to follow-up was addressed	-
		(e) Describe any sensitivity analyses	-
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	10
		(b) Give reasons for non-participation at each stage	10
		(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	7
		(b) Indicate number of participants with missing data for each variable	11-13

		of interest	
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13
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	10-13
		(b) Report category boundaries when continuous variables were categorized	-
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
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	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
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	17

*Give information separately for exposed and unexposed groups.

NA – not applicable

BMJ Open

Longitudinal changes in oculomotor function in young adults with mild traumatic brain injury in Sweden– an exploratory prospective observational study

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Primary Subject Heading:	Rehabilitation medicine
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3 **Longitudinal changes in oculomotor function in young adults with**
4 **mild traumatic brain injury in Sweden– an exploratory prospective**
5 **observational study**
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39 statement)
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ABSTRACT

Objectives: To assess 1) whether visual disturbances can be demonstrated with objective measures more often in patients with mild traumatic brain injury (mTBI) than in orthopaedic controls and non-injured controls, 2) whether such objectively demonstrated disturbances change over time, and 3) whether self-reported visual symptoms after mTBI correlate with objectively measurable changes in visuomotor performance.

Design: A prospective, controlled, observational study, with assessments planned 7-10 and 75-100 days after injury.

Setting: Emergency department of a general hospital in Sweden.

Participants: Fifteen patients with mTBI, 15 patients with minor orthopaedic injury, 15 non-injured controls, aged 18-40 years.

Outcome measures: Visual examination including assessment of visual acuity, accommodation, eye alignment, saccades and stereo acuity. Symptom assessment using Convergence Insufficiency Symptoms Survey (CISS) and Rivermead Post-Concussion Symptoms Questionnaire.

Results: Assessments were performed 2-12 and 81-225 days after injury (extended time frames for logistical reasons). No significant difference was found between the mTBI and control groups regarding pro-saccades, anti-saccades and self-paced saccades at any time point. The accommodative amplitude was significantly lower in the mTBI group compare to non-injured controls at baseline. Six out of 13 patients with mTBI had accommodative insufficiency at follow-up. Near point of convergence in the mTBI group was receded at baseline and improved statistically significantly at follow-up. At baseline, patients with mTBI had significantly higher CISS score than orthopaedic and non-injured controls. For patients with mTBI the CISS score correlated with fusional vergence.

Conclusion: There were some transient measurable visual changes regarding convergence in patients with mTBI during the subacute period after the injury. Our findings of persistence of accommodative insufficiency in a considerable proportion

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3 of patients with mTBI suggest that this visual function should not be overlooked in
4 clinical assessment.
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7 **Key words:** neurology, mild traumatic brain injury, visual dysfunction, near point of
8 convergence, accommodation, posttraumatic symptoms.
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For peer review only

ARTICLE SUMMARY

Strengths and limitations of this study

- Prospective longitudinal design with measurement at two time points.
- Strict inclusion criteria for mTBI according to American Congress of Rehabilitation Medicine.
- Inclusion of both an uninjured control group and a group with minor orthopaedic injuries without trauma to the head, to control for non-specific effects of injury such as pain and distress.
- Study methods include several easily replicable optometric measurements.
- The generalisability of this study is limited because the sample of patients with mTBI was small in size and restricted in age range.

INTRODUCTION

There is a need for objective methods to assess and monitor recovery after mild traumatic brain injury (mTBI), as a base for developing evidence based clinical follow-up guidelines. Changes affecting accommodation and eye alignment have been highlighted recently as possible measurable correlates of symptoms related to mTBI.(1-4) A recent systematic review of oculomotor-based vision assessment to monitor changes after mTBI found preliminary but promising evidence.(5) It was concluded that measurement of oculomotor functions appeared useful in detecting changes after mTBI; however, the strength of evidence in currently available research is not yet sufficient enough to inform clinical guidelines.

Traumatic impact to the head, as in mTBI, may affect vision-related networks that are widely spread throughout the brain,(1, 6) and thus result in visual disturbances. Various visual impairments with a prevalence up to 70 percent have been found in patients with long lasting problems after mTBI.(4, 7, 8) However, these studies have several limitations such as retrospective design, selection bias, heterogeneity regarding severity of injury, and lack of appropriate control groups. Prospective studies with early assessment and follow-up of vision-related oculomotor changes after mTBI are scarce.(9, 10)

The ability to appropriately alter focus, align the eyes, and make gaze changes can be measured, and has been highlighted in several recent studies on mTBI.(11-14) Convergence is a nasalward eye movement for near vision.(15) Insufficient convergence is one of the most frequently described oculomotor changes after head injury.(16) Symptoms after mTBI, both direct visual symptoms (double vision, blurred vision) and indirect symptoms (increased effort at near work), might be attributed to impaired convergence. Convergence insufficiency (CI) was found in 42-48% of patients with mTBI in retrospective studies,(4, 7) and controlled studies of military personnel who have suffered blast-induced mTBI have shown a significant difference in near point of convergence (NPC).(3,7)

Fusional vergence aligns the two eyes and thereby provides for clear single vision. Impaired fusional vergence causes unstable binocular vision, which may present as losing one's place when reading, or blurred, or even double vision. Fusion vergence

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3 disorders may occur in about 3-6% of an otherwise healthy population with vision-
4 based symptoms,(17, 18) but may be significantly more frequent in traumatic brain
5 injury TBI patients.(19)
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8 Accommodation provides a clear optical image of an object at different distances
9 through the altering of refractive power in the crystalline lens. Symptoms of
10 accommodative disorders include blurred vision and impaired flexibility to alter focus
11 between near and far. A physiological deterioration of accommodative ability,
12 presbyopia, is expected with age. The current study therefore included pre-presbyopic
13 subjects of age 40 or younger. In an otherwise healthy pre-presbyopic population,
14 accommodative changes may be present in up to about 10 % of individuals with
15 vision complaints.(18, 20) Significantly more prevalent accommodative disorders
16 have been found in patients with mTBI in the sub-acute stage,(3) and also as part of
17 persisting issues.(21, 22)
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25 Saccades are rapid eye movements that shift the gaze to areas of interest in the visual
26 field. Through purposeful and accurate saccades executed in quick succession, the
27 environment can be scanned and functional visual field is increased. Thus, an efficient
28 saccadic performance is an important base for efficient and safe interaction with the
29 environment and for detailed work such as reading.(23) The initiation and
30 programming of saccades involves cognitive functions that are subserved by complex
31 neuronal networks involving different parts of the brain. Parameters of saccades, such
32 as latency and accuracy, have been shown to be affected after mTBI.(2, 9, 10, 24)
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39 In this study we aim to assess oculomotor and visual changes after mTBI
40 prospectively, and compare these to a control group unexposed to head injury but with
41 minor orthopaedic injury, and to a non-injured control group. The orthopaedic control
42 group is important for controlling for non-specific effects of pain and distress after
43 trauma to allow evaluation of brain injury specific effects.
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48 The study objectives are to assess: 1) whether visual disturbances can be
49 demonstrated with objective measures more often in patients with mTBI than in
50 orthopaedic controls and non-injured controls, 2) whether such objectively
51 demonstrated disturbances change over time, and 3) whether self-reported visual
52 symptoms after mTBI correlate with objectively measurable changes in visuomotor
53 performance.
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METHODS

This is a prospective controlled observational study on visual disturbances after mTBI, with two control groups, defined below. This article is the first report from this study. The setting was an emergency department (ED) of a large general hospital serving the north-east of Stockholm.

A power calculation was conducted: with an expected incidence of visual disturbances in 70 % in the mTBI group,(4, 7, 8) and 10 % in the control group(18, 20), 10 persons per group were needed to detect visual disturbances with 80 % power at alpha 0.05. With an expected drop out rate of 30 %, 15 persons were needed in each group.

Inclusion criteria

All study participants were 18-40 years of age. Other criteria for each of the three groups were as follows:

1. mTBI group:
 - a. Presented to the ED after acute blunt head trauma.
 - b. Met diagnostic criteria for mTBI according to American Congress of Rehabilitation Medicine (25): mTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (i) 1 or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale (GCS)(26) score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury.
 - c. Underwent CT-brain scan on clinical indication.

2. Orthopaedic control group:
 - a. Presented to the ED after minor trauma to the extremities without head trauma.
 - b. not requiring surgery.
3. Non-injured control group:
 - a. Individuals without traumatic injury, answering an advert recruiting to the study.

Exclusion criteria (any of the following):

- a. indication for neurosurgery
- b. previous moderate or severe traumatic brain injury
- c. any head injury in the previous year requiring medical attention
- d. presence of any contraindication for MRI (magnetic resonance imaging)
- e. progressive neurological disease or other medical conditions with expected short survival
- f. severe visual impairment or manifest strabismus
- g. need for help in activities of daily living before the current injury
- h. intoxication with alcohol at the time of the injury
- i. not fluent in Swedish

For demographic information, see Table 1.

Table 1 Demographic data

	mTBI patients	Orthopaedic controls	Non-injured controls
Age, median (range)	25.0 (18 – 39)	27.0 (18 – 40)	26.0 (19 – 36)
Men, n (%)	7 (47)	11(73)	9 (60)
Women, n (%)	8 (53)	4 (27)	6 (40)
GCS 15 (%)	14 (93)	N/A	N/A
GCS 14 (%)	1 (7)	N/A	N/A
Type of trauma: n (%)	Fall: 7 (47) Bicycle: 2 (13) Horse back riding: 2(13) Other: 4 (27)	Sports: 9 (60) Other: 6 (40)	

N/A – not applicable, GCS – Glasgow Coma Scale,

Data collection

Inclusion was conducted between January 2015 and January 2016, and was stopped when a total of 15 patients with mTBI, 15 orthopaedic controls and 15 non-injured controls were included, in accordance with the power calculation. Study patients were contacted by phone 1-3 days after injury. All study participants received written information about the study and gave informed consent.

All data related to the injury, GCS on arrival at the ED, and results of computerised tomography scan (CT-scan), were collected from the medical records. Demographic data were collected by interview at the baseline examination.

All study participants were scheduled to be assessed twice: at baseline, in the subacute phase, (for trauma patients, 7-10 days after the trauma), and at follow-up - 75-100 days after first assessment. Due to recruitment difficulties, and in order to minimize dropout, the time frame for the first and second assessment was extended. The median time between injury and baseline assessment was 6.0 days (range 4-12 days) for patients with mTBI, and 8.0 days, (range 2-9 days) for orthopaedic controls. The median time between baseline and follow-up was 95 days (range 81-225) for patients with mTBI, and 108 days (range 87-324) for orthopaedic controls. No significant difference was found between patients with mTBI and the orthopaedic control group regarding time between the injury and assessments (baseline and follow-up).

Neuropsychological testing and visual assessment were performed at different time points on the same day or on the day before or after.

Patients with mTBI and orthopaedic controls underwent examination with structural magnetic resonance imaging (MRI) and resting state functional MRI of the brain at baseline and at follow-up. All participants rated anxiety, depression and fatigue using Hospital Anxiety and Depression Scale (HADS)(27) and Fatigue Severity Scale (FSS),(28) and underwent neuropsychological testing. These data and imaging results will be reported separately.

Among the consecutive patients who were invited to participate in the study, a total of ninety-nine declined; 17 mTBI and 82 orthopaedic subjects. Of those who declined, 88 % of mTBI and 64 % of orthopaedic subjects were men, and there was no difference regarding age between participating and non-participating individuals. The reasons stated for not participating were lack of time and inconvenience.

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3 Two individuals in the mTBI group and two individuals in the orthopaedic control
4 group were lost to follow-up despite several follow-up phone calls and letters.
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7 **Assessments**

8 The visual examination was performed by licensed optometrists, using standard
9 optometric clinical methods. It included assessment of visual acuity at far and near,
10 refractive error, stereo acuity, near point of accommodation, facility (flexibility) of
11 accommodation, near point of convergence (NPC) with an accommodative target,
12 non-strabismic eye-turn (heterophoria), eye motility and fusional vergence. Diagnosis
13 of visual dysfunctions were based on established diagnostic criteria.(29) NPC was
14 measured using the push-up method (RAF-ruler). Positive fusional vergence (PFV)
15 was measured with a prism bar. In both cases the patient is instructed to try as hard as
16 possible to maintain single vision and to report when perceiving double vision.
17 Meanwhile, the examiner carefully observes eye alignment in order to verify the
18 patient's response. The expected accommodative amplitude was defined according to
19 the Hofstetter formula ($18.5 - 1/3 \text{ age}$). (29) Diagnosis of accommodative insufficiency
20 (AI) required amplitude less than minimum expected according to the Hofstetter
21 formula ($15 - 1/4 \text{ age}$). Diagnosis of convergence insufficiency (CI) required near point
22 of convergence ≥ 6 cm plus at least one of the following; reduced PFV at near (< 20
23 prism diopters) or divergent heterophoria at least four prism diopters greater at near
24 than at distance.(29) Saccadic eye movements were recorded (spatial res 0.15 degrees;
25 temporal res 300 Hz) using an eye tracker (Tobii TX300, Tobii Corp., Stockholm,
26 Sweden, www.tobii.com). The participant was positioned 60 cm directly in front of
27 the eye tracker display. Three test paradigms were applied to test (1) visually induced
28 pro-saccades; mean latency and gain, 2) anti-saccades; latency of correctly performed
29 saccades and proportion of erroneous saccades, (3) self-paced saccades; number of
30 saccades performed in 30 seconds and mean intersaccadic interval (ms). The stimuli
31 consisted of a dot with a diameter of 5 mm (0.5 degrees). In the pro-saccade paradigm
32 the participant fixated a centered cross and then re-fixated to a dot that appeared at 2,
33 4, 6, or 8 degrees to the left or right of the cross. In the anti-saccade paradigm the
34 participant viewed a centered cross and then rapidly looked in the opposite direction
35 to that of a dot presented 8 degrees to the left or right of the centre. In the self-paced
36 saccade paradigm two dots were simultaneously presented for 30 seconds at 8 degrees
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3 to the left and right of centre. The participant was instructed to move the gaze rapidly,
4 as many times as possible, between the dots.
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7 At baseline and follow-up, all study participants self-rated their symptoms using the
8 Rivermead Post-Concussion Symptoms Questionnaire (RPQ),(30) and the
9 Convergence Insufficiency Symptom Survey (CISS).(31, 32) The RPQ is based on a
10 Likert scale and includes 16 items with ratings: 0 "no symptoms", 1 "no more of a
11 problem or transient symptoms", 2-4 "mild to severe" symptoms. A total sum of all
12 symptom scores ("mild to severe", excluding ratings of 1) is calculated, with a
13 maximum score of 64. Three or more symptoms after mTBI describes
14 "postconcussional syndrome" in the International Classification of Diseases, 10th
15 revision.(33) The CISS is a validated and reliable instrument(31) that evaluates near
16 work-related visual symptoms. It includes assessment of direct symptoms, such as
17 blur and double vision, as well as indirect symptoms (e.g., difficulty maintaining
18 concentration, sleepiness while reading, headache and ocular discomfort). The survey
19 includes 15 questions with ratings from 0 "never" to 4 "always" for assessment of
20 visual symptoms. The total score is 60 and the cut-off score for abnormal levels of
21 symptoms is 21. This value gives good sensitivity (97.8 %) and specificity (87 %) in
22 otherwise healthy young adults who have presented to optometrists with visual
23 symptoms.(32)
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35 **Data analyses**

36 All data were analysed using SPSS 23. Parametric statistics was used for oculomotor
37 measures (accommodation, convergence, fusional vergens and saccades). A two-way
38 repeated measures ANOVA was used for analysing the within-subject factors
39 (baseline vs. follow-up) and the between subject factor (effect of group). Post-hoc
40 tests were performed using Holm-Bonferroni adjustment. Fischer's exact test was
41 applied for analysis of the categorical data.
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45 Nonparametric Kruskal-Wallis (three groups), Mann-Whitney U (two groups, post-
46 hoc analysis), Wilcoxon sign rank tests and Spearman's rank correlation were used
47 for comparison of ordinal data from questionnaires (CISS and RPQ). Two-tailed p-
48 values were used with a critical significance level of $p < 0.05$.
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RESULTS

Two of the 15 patients with mTBI had pathological findings on CT-scan of the brain: one had a small subdural haemorrhage and the other a small subarachnoid haemorrhage. Neither required surgery.

Visual examination

No cranial nerve palsies or direct trauma related eye pathology was found.

Accommodation

A significant interaction effect was found for the deviation from expected accommodative amplitude ($df=2$, $F=4.406$, $p=0.028$). The ensuing post-hoc analysis showed significantly reduced accommodative amplitude in the mTBI group compared to non-injured controls at baseline ($p=0.001$) (Figure 1) but no significant difference between patients with mTBI and orthopaedic controls. There were no significant differences between the mTBI group and either of the control groups at follow-up. Six out of 13 patients with mTBI still had reduced accommodative amplitude at follow-up, which met the diagnostic criteria for AI. No significant differences in accommodative facility were found within or between groups or test occasions.

(Insert Figure 1 here)

Convergence

There were no significant differences between the mTBI group and both control groups at either occasion. NPC improved in the mTBI group between baseline and follow-up. Statistical analysis showed a significant interaction effect ($df=2$, $F=3.793$, $p=0.042$) and the ensuing pairwise analysis showed a significant difference for the mTBI group ($p=0.015$) (Figure 2). There were no significant differences between or within the control groups.

(Insert Figure 2 here)

Fusional vergence

The analysis of fusional vergence did not show any significant differences at the group level at any time point.

Stereo acuity

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3 Five out of 15 of the patients with mTBI showed a reduced level of stereo acuity at
4 baseline (120-240 seconds of arc) whilst at follow-up, all but one performed normally
5 (60 seconds of arc or less). In the orthopaedic group three subjects performed at the
6 level of 120-240 seconds of arc at baseline, and two of these performed similarly at
7 follow-up. All non-injured controls performed normally at both test occasions.
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10 11 12 **Saccade performance**

13 In the pro-saccade task, no significant difference in latency or gain was found
14 between groups or test occasions. No significant differences within or between groups
15 were found in the self-paced saccade task. In the anti-saccade task all groups
16 performed well at both test occasions with no statistically significant differences in
17 latency or proportion of erroneous saccades (ANOVA).
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20 21 22 **Assessment of visual symptoms**

23 There was a significant difference between the three groups regarding CISS score at
24 the baseline (df=2, p=0.003) (Kruskal-Wallis test). Patients with mTBI had more
25 visual symptoms with near work, compared to the two control groups, as measured by
26 the CISS score at baseline: patients with mTBI vs. orthopaedic controls (U=47.5,
27 p=0.012) and patients with mTBI vs. non-injured controls (U=38.0, p=0.02) (Mann-
28 Whitney U test). The median value of the CISS score in the mTBI group at baseline
29 was 24. It then decreased to 19 at follow-up but the change did not reach statistical
30 significance (Wilcoxon Sign Ranks test). The CISS score was below cut-off level at
31 both time points in the control groups.
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34 At baseline nine out of 12 patients with mTBI were identified with CI/AI using the
35 CISS (Figure 3a). At follow-up, seven patients with mTBI still had CI/AI (Figure 3b);
36 one with CI and six with AI. Three of these patients scored as symptomatic on CISS.
37 However, no association between CISS and CI/AI was found (Fisher's exact test).
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42 (Insert Figure 3 here)

43 In the mTBI group, CISS scores at baseline correlated with reduced positive fusional
44 vergence measured at near, i.e. the capacity to maintain clear single vision while
45 performing near work ($r=-0.6$; $p=0.02$) (Figure 4).
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50 (Insert Figure 4 here)

Symptoms measured by the RPQ

There was a significant difference, regarding the sum of symptom scores on the RPQ, between the three groups at baseline ($df=2$, $p<0.001$) and at follow-up ($df=2$, $p=0.001$) (Kruskal-Wallis test). At baseline, the RPQ sum of symptom scores was significantly greater in the mTBI group compared to the orthopaedic control group ($U=40.0$, $p=0.002$) and to non-injured controls ($U=29.5$, $p<0.001$) (Mann-Whitney U test). A significant difference was found in the sum of symptom scores at follow-up, between the mTBI group and the orthopaedic control group ($U=27.0$, $p=0.003$), and between the mTBI group and non-injured controls ($U=24.0$, $p<0.001$) (Mann-Whitney U test). Sum of symptom scores decreased in the mTBI group over time but the difference did not reach statistical significance ($p=0.092$) (Wilcoxon signed rank test).

DISCUSSION

We have observed differences in visual measurements between a well-defined mTBI group and two control groups. We also objectively measured transient visual disturbances in the mTBI group.

In agreement with a previous study(3), a significant difference in accommodation between the mTBI group and each of the control groups at the baseline was found in our study. The mTBI group had a significantly lower accommodative amplitude compared to non-injured controls at baseline. This then recovered to a certain degree at follow-up, but six patients with mTBI still had deviations meeting the diagnostic criteria for AI. This corresponds to almost half of the patients with mTBI ($n=13$) who were examined at the follow-up around three months after the injury. We know little regarding the expected course of spontaneous improvement in accommodation. There are some indications that AI may be part of persisting issues even in the long term after injury.(21, 22) Therefore it may be necessary to consider therapeutic intervention when appropriate, e.g. spectacle lenses for near work and/or vision therapy.(34)

A somewhat unexpected result was the non-significant difference in NPC between the groups. This is in contrast to findings on NPC performance by Capo-Aponte and co-workers.(3) However, we found a significant change in NPC in the mTBI group between the baseline and follow-up. The mean NPC at baseline of these patients with mTBI was just within 10 cm, which may or may not be considered clinically

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3 meaningful,(15, 29) and therefore not pose a clinical sign for further examination of
4 CI. Receded NPC has previously been proposed as a potentially sensitive vision-based
5 biomarker after mTBI(14) and our findings tentatively support this.
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8 The mechanism behind the spontaneous recovery of NPC in the present patient
9 sample remains to be understood. The convergence responses are based on visual
10 processing of binocular disparity and correct ocular motor alignment through
11 vergence eye movements. Given the recovery of NPC, any manifest structural injury
12 affecting motor function (vergence eye movements) can probably be ruled out. Some
13 of the remaining aspects to consider are sensory-motor integration and the ability to
14 respond appropriately to the stimulus. Certain tasks, including the actual test
15 condition for NPC, require that the subject must exert maximal convergence effort to
16 maintain single vision of a very near target. This most likely involves voluntary effort.
17 A question for further discussion is how the constellation of somatic symptoms,
18 cognitive impairments and fatigue, known to be associated with mTBI, may affect the
19 capacity to perform this test optimally. Our clinical observations during this study,
20 along with previous research, suggest that these factors can have contributory effects.
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32 One third of the patients with mTBI showed a deficient level of stereo acuity at
33 baseline (120-240 seconds of arc), whilst at follow-up all but one performed normally.
34 These findings may suggest that the visual processing of disparity was particularly
35 affected in the mTBI group. Based on the improvement in stereo acuity we may
36 speculate that underlying factors affecting the ability to resolve and detect stereo
37 disparity, such as inadequate or inefficient vergence and/or accommodative function,
38 improved with time.(35)
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44 We were not able to replicate the findings of previous studies that found differences in
45 several measures of saccadic eye movements between patients with mTBI and
46 controls. (3, 7, 13, 24) An explanation could be that changes in saccadic reaction
47 time/latency are subtle, transient, and possibly only to be demonstrated directly after a
48 trauma to the head. In our study, baseline optometric examination took place a few
49 days after mTBI. Our findings are in line with a study of amateur boxers in which
50 saccadic latency was measured at four time points, with baseline before the boxing
51 match (pre-fight), and at 3 days, 7 days and 12 days after-fight, that is after blows to
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3 the head (10). Results in this study showed increased saccadic latency directly after
4 the fight; however 12 days later the latency had returned to baseline. The small
5 number of participants and lack of the description of mTBI criteria limit interpretation
6 of findings in that study.
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10 We found that patients with mTBI had significantly more visual symptoms as
11 measured by CISS score than orthopaedic and non-injured controls. Our findings on
12 reported visual disturbances at near work after mTBI are consistent with a previous
13 study.(3) We found a significant correlation between CISS score and PFV at near in
14 the mTBI group. This may appear somewhat unexpected since the PFV was normal at
15 the group level. The symptom score (CISS) was significantly higher in the mTBI
16 group than in the control groups. This may be an indication that most patients with
17 mTBI were indeed able to perform normally on the PFV, but at a greater effort
18 (causing symptoms). Objective recordings of vergence eye movement have indicated
19 this.(36)
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23 The patients sustaining a trauma to the head in this study reported significantly more
24 symptoms on the RPQ and CISS compared to both controls groups at baseline. The
25 symptoms decreased at follow-up, but the change was not statistically significant.
26 However, the role of brain injury for these symptoms, especially for patients with
27 long-term problems after mTBI, has been questioned.(37) Several factors have been
28 suggested to affect symptom reporting after mTBI, e.g., recall bias and
29 biopsychosocial factors. Furthermore, previous studies have demonstrated that similar
30 symptoms are also present after any trauma, presumably due to emotional distress and
31 pain related to the injury.(37, 38) The strength of our study is having two control
32 groups. Traumatic injury can generally impact on reporting of various symptoms,
33 related to acute posttraumatic stress and pain. Therefore, to avoid confounding
34 factors, we included a group of patients with minor orthopaedic injuries without
35 trauma to the head, presenting at the same emergency department.
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38 **Study limitations**

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40 When the study population is small, there is always a risk for type II error, that is the
41 risk of not revealing a true difference in the studied population. The differences found
42 between patients with mTBI and controls regarding oculomotor measures were few
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3 and the within group variations were large. The degree of overlap between groups and
4 incomplete correlation between visual symptoms and visual measurements, suggest
5 that caution is appropriate when interpreting findings in an individual patient, based
6 on the current state of knowledge. However, several aspects merit further
7 investigation. The sample size in the present study was based on power calculations
8 from reports on long lasting vision and oculomotor problems in patients after
9 mTBI.(4, 7, 8) Possible bias in these studies could have led to an overestimation of
10 the frequency of oculomotor changes and thus an overestimation of expected effect
11 size in our power calculation and a risk of type II error.
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18 Study participants were 18-40 years old making the mTBI patient group in this
19 explorative study highly selective. This age limitation was chosen to minimize the
20 effect of presbyopia on study results. Our findings will have relevance regarding the
21 large number of young adults suffering head trauma, but will not be directly
22 applicable to older patients, which limits the generalisability.
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28 **Future recommendations**

29 Larger confirmatory studies are needed to clarify the clinical relevance of the transient
30 visual disturbances observed in this study. The role of vergence and accommodation
31 as potential biomarkers for mTBI and their interplay with persisting symptoms such
32 as fatigue also needs further elucidation. Furthermore, investigations of visual
33 disturbances after mTBI should aim to determine if visual testing in the subacute
34 phase after mTBI could help to predict long lasting symptoms and be a target for
35 intervention to promote recovery. Our findings, along with previous observations,
36 (21) indicate the importance of not overlooking possible accommodative disorders in
37 the overall assessment of the patient's capacity to return to daily activities.
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45 **CONCLUSIONS**

46 Some transient measurable visual changes regarding convergence were noted in
47 patients with mTBI, during the subacute period after injury. The finding of persistent
48 accommodative insufficiency in a substantial proportion of patients with mTBI
49 requires further evaluation; this could be either a biomarker for persistent functional
50 impairment in neural networks, or a target for intervention to promote recovery, or
51 possibly both.
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Contributors: GM and JJ contributed to design of the study, were responsible for data collection, wrote initial draft of manuscript, performed statistical analysis, and contributed to the analysis of results and interpretation of findings. CND, TP, MM were main contributors to study design, contributed to data collection, analysis of results and interpretation of the findings. AKG contributed to discussions on study design, critically revised the manuscript, and contributed to data analysis and interpretation. All authors read, commented and approved the final manuscript.

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Competing interests: None declared.

Patient consent: All patients gave written informed consent.

Ethics approval: Ethics approval was obtained from the Regional ethical review board in Stockholm, diary number 2014/597-31/1. The study adhered to the tenets of the Helsinki Declaration.

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

Data sharing statement: Further data may be available from the authors. Please contact the corresponding author.

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FIGURE LEGENDS

Figure 1 Deviation from expected accommodative amplitude. The lower the negative value, the greater the deviation (insufficiency). Closer to zero is better. The miniature squares indicate mean values. The box indicates median, upper and lower quartile. The whiskers indicate min and max.

Figure 2 Near point of convergence in the mTBI group at baseline and at follow up measured in cm. The lower the value, the better convergence performance. The miniature squares indicate mean values. The box indicates median, upper and lower quartile. The whiskers indicate min and max.

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3 Figure 3 Two-by-two matrix of the association between CI/AI and CISS score at
4 baseline (a) and at follow-up (b).
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7 Figure 4 CISS score versus positive fusional vergence in patients with mTBI. Higher
8 positive fusion value corresponds to better function.
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10 11 12 13 **LIST OF ABBREVIATIONS**

14 AI - Accommodative Insufficiency

15 ANOVA – Analysis of Variance

16
17 CI – Convergence Insufficiency

18
19 CISS – Convergence Insufficiency Symptoms Survey

20
21 CT-scan – computerised tomography scan

22
23 ED – emergency department

24
25 FSS – Fatigue Severity Scale

26
27 GCS – Glasgow Coma Scale

28
29 HADS – Hospital Anxiety and Depression Scale

30
31 MRI - magnetic resonance imaging

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33 mTBI – mild traumatic brain injury

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35 N/A – not applicable

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37 NPC – Near Point of Convergence

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39 PFV – Positive Fusional Vergence

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41 RAF-ruler – Royal Air Force ruler

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43 RPQ – Rivermead Post-Concussion Symptoms Questionnaire

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45 TBI – traumatic brain injury

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47 TNO - test for stereoscopic vision (The Netherlands Organisation for Applied
48 Scientific Research)
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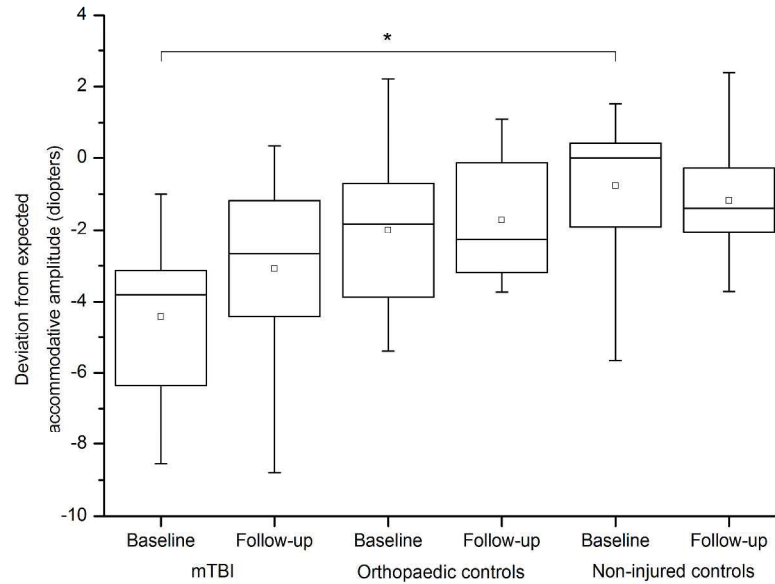


Figure 1 Deviation from expected accommodative amplitude. The lower the negative value, the greater the deviation (insufficiency). Closer to zero is better. The miniature squares indicate mean values. The box indicates median, upper and lower quartile. The whiskers indicate min and max.

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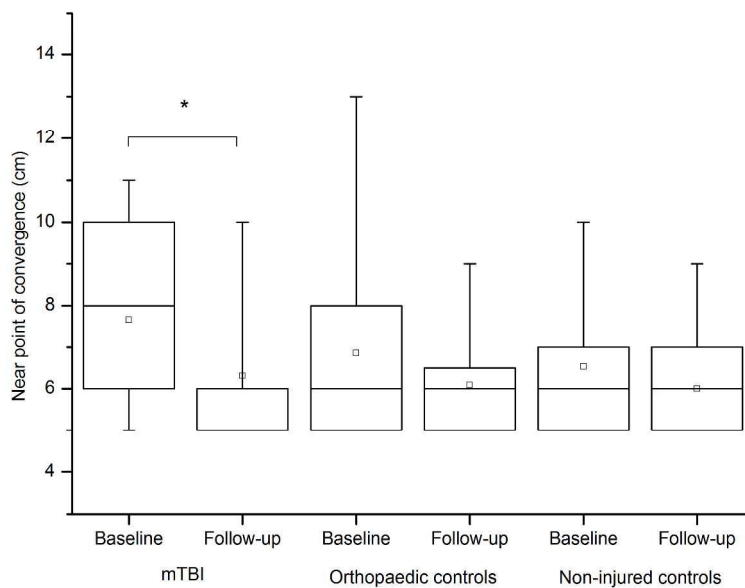


Figure 2 Near point of convergence in the mTBI group at baseline and at follow up measured in cm. The lower the value, the better convergence performance. The miniature squares indicate mean values. The box indicates median, upper and lower quartile. The whiskers indicate min and max.

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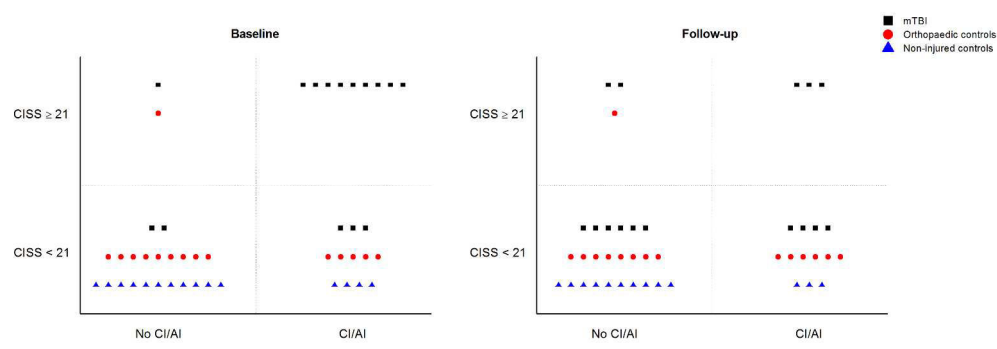


Figure 3 Two-by-two matrix of the association between CI/AI and CISS score at baseline (a) and at follow-up (b).

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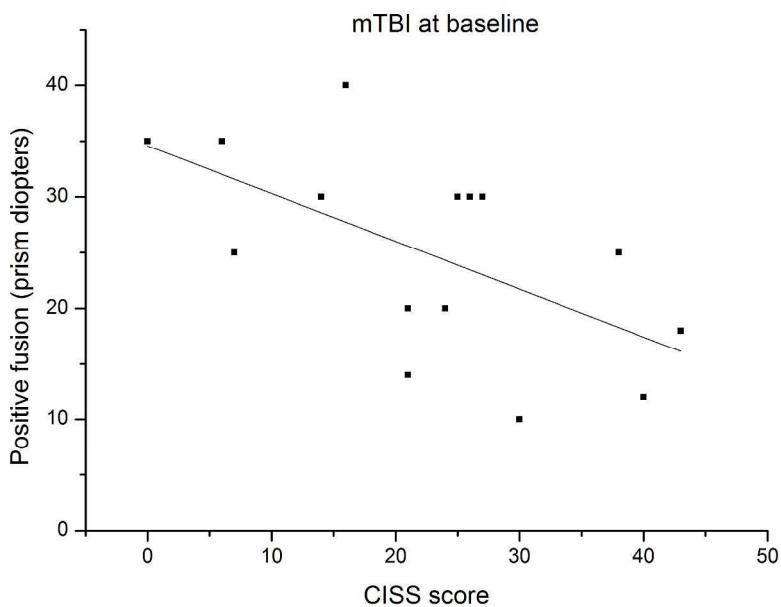


Figure 4 CISS score versus positive fusional vergence in patients with mTBI. Higher positive fusion value corresponds to better function.

288x201mm (300 x 300 DPI)

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Research checklist

STROBE Statement - checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
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	8-9
Bias	9	Describe any efforts to address potential sources of bias	3
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	-
		(d) If applicable, explain how loss to follow-up was addressed	-
		(e) Describe any sensitivity analyses	-
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	10
		(b) Give reasons for non-participation at each stage	10
		(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	7
		(b) Indicate number of participants with missing data for each variable	11-13

		of interest	
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13
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	10-13
		(b) Report category boundaries when continuous variables were categorized	-
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
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	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
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	17

*Give information separately for exposed and unexposed groups.

NA – not applicable

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Longitudinal changes in oculomotor function in young adults with mild traumatic brain injury in Sweden– an exploratory prospective observational study

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3 **Longitudinal changes in oculomotor function in young adults with**
4 **mild traumatic brain injury in Sweden– an exploratory prospective**
5 **observational study**
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ABSTRACT

Objectives: To assess 1) whether visual disturbances can be demonstrated with objective measures more often in patients with mild traumatic brain injury (mTBI) than in orthopaedic controls and non-injured controls, 2) whether such objectively demonstrated disturbances change over time, and 3) whether self-reported visual symptoms after mTBI correlate with objectively measurable changes in visuomotor performance.

Design: A prospective, controlled, observational study, with assessments planned 7-10 and 75-100 days after injury.

Setting: Emergency department of a general hospital in Sweden.

Participants: Fifteen patients with mTBI, 15 patients with minor orthopaedic injury, 15 non-injured controls, aged 18-40 years.

Outcome measures: Visual examination including assessment of visual acuity, accommodation, eye alignment, saccades and stereo acuity. Symptom assessment using Convergence Insufficiency Symptoms Survey (CISS) and Rivermead Post-Concussion Symptoms Questionnaire.

Results: Assessments were performed 4-13 and 81-322 days after injury (extended time frames for logistical reasons). No statistically significant difference was found between the mTBI and control groups regarding saccade performance and stereo acuity at any time point. The accommodative amplitude was significantly lower in the mTBI group compared to non-injured controls at baseline. Six out of 13 patients with mTBI had accommodative insufficiency at follow-up. Near point of convergence in the mTBI group was receded at baseline and improved statistically significantly at follow-up. At baseline, patients with mTBI had significantly higher CISS score than orthopaedic and non-injured controls. For patients with mTBI the CISS score correlated with fusional vergence.

Conclusion: There were some transient measurable visual changes regarding convergence in patients with mTBI during the subacute period after the injury. Our findings of persistence of accommodative insufficiency in a considerable proportion

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3 of patients with mTBI suggest that this visual function should not be overlooked in
4 clinical assessment.
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7 **Key words:** neurology, mild traumatic brain injury, visual dysfunction, near point of
8 convergence, accommodation, posttraumatic symptoms.
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ARTICLE SUMMARY

Strengths and limitations of this study

- Prospective longitudinal design with measurement at two time points.
- Strict inclusion criteria for mTBI according to American Congress of Rehabilitation Medicine.
- Inclusion of both an uninjured control group and a group with minor orthopaedic injuries without trauma to the head, to control for non-specific effects of injury such as pain and distress.
- Study methods include several easily replicable optometric measurements.
- The generalisability of this study is limited because the sample of patients with mTBI was small in size and restricted in age range.

INTRODUCTION

There is a need for objective methods to assess and monitor recovery after mild traumatic brain injury (mTBI) as a base for developing evidence based clinical follow-up guidelines. Changes affecting accommodation and eye alignment have been highlighted recently as possible measurable correlates of symptoms related to mTBI.(1-4) A recent systematic review of oculomotor-based vision assessment to monitor changes after mTBI found preliminary but promising evidence.(5) Although measurement of oculomotor functions appears useful in detecting changes after mTBI, the current evidence does not have sufficient strength to inform clinical guidelines.

Traumatic impact to the head, as in mTBI, may affect vision-related networks that are widely spread throughout the brain,(1, 6) and thus result in visual disturbances. Various visual impairments with a prevalence up to 70 percent have been found in patients with long lasting problems after mTBI.(4, 7, 8) However, these studies have limitations such as retrospective design, selection bias, heterogeneity regarding severity of injury, and lack of appropriate control groups. Prospective studies with early assessment and follow-up of vision-related oculomotor changes after mTBI are scarce.(9, 10)

The ability to appropriately alter focus, align the eyes, and make gaze changes can be measured, and has been highlighted in several recent studies on mTBI.(11-14) Convergence is a nasalward eye movement for near vision.(15) Insufficient convergence is one of the most frequently described oculomotor changes after head injury.(16) Symptoms after mTBI, both direct visual symptoms (double vision, blurred vision) and indirect symptoms (increased effort at near work), might be attributed to impaired convergence. Convergence insufficiency (CI) was found in 42-48% of patients with mTBI in retrospective studies,(4, 7) and controlled studies of military personnel who have suffered blast-induced mTBI have shown a significant difference in near point of convergence (NPC).(3,7)

Fusional vergence aligns the two eyes and thereby provides for clear single vision. Impaired fusional vergence causes unstable binocular vision, which may present as losing one's place when reading, or blurred, or even double vision. Fusional vergence

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3 disorders may occur in about 3-6% of a population with vision-based symptoms who
4 are otherwise healthy.(17, 18) but may be significantly more frequent in traumatic
5 brain injury TBI patients.(19)
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8 Accommodation provides a clear optical image of an object at different distances
9 through the altering of refractive power in the crystalline lens. Symptoms of
10 accommodative disorders include blurred vision and impaired flexibility to alter focus
11 between near and far. A physiological deterioration of accommodative ability,
12 presbyopia, is expected with age. The current study therefore included pre-presbyopic
13 subjects of age 40 or younger. In an otherwise healthy pre-presbyopic population,
14 accommodative changes may be present in up to about 10 % of individuals with
15 vision complaints.(18, 20) Significantly more prevalent accommodative disorders
16 have been found in patients with mTBI in the sub-acute stage(3) and at a later stage as
17 part of persisting issues.(21, 22)
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25 Saccades are rapid eye movements that can direct the gaze to areas of interest in the
26 visual field. Through purposeful and accurate saccades executed in quick succession,
27 the environment can be scanned and functional visual field is increased. Thus, an
28 efficient saccadic performance is an important base for efficient and safe interaction
29 with the environment and for detailed work such as reading.(23) The initiation and
30 programming of saccades involves cognitive functions that are subserved by complex
31 neuronal networks involving different parts of the brain. Parameters of saccades, such
32 as latency and accuracy, have been shown to be affected after mTBI.(2, 9, 10, 24)
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39 In this study we aim to assess oculomotor and visual changes after mTBI
40 prospectively, and compare these to a control group unexposed to head injury but with
41 minor orthopaedic injury and to a non-injured control group. The orthopaedic group
42 allows evaluation of brain injury-specific effects by controlling for non-specific
43 effects of pain and distress after trauma.
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48 The study objectives are to assess: 1) whether visual disturbances can be
49 demonstrated with objective measures more often in patients with mTBI than in
50 orthopaedic controls and non-injured controls, 2) whether such objectively
51 demonstrated disturbances change over time, and 3) whether self-reported visual
52 symptoms after mTBI correlate with objectively measurable changes in visuomotor
53 performance.
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METHODS

This is a prospective controlled observational study on visual disturbances after mTBI, with two control groups, defined below. This article is the first report from this study. The setting was an emergency department (ED) of a large general hospital serving the north-east of Stockholm.

A power calculation was conducted: with an expected incidence of visual disturbances in 70 % in the mTBI group,(4, 7, 8) and 10 % in the control group(18, 20), 10 persons per group were needed to detect visual disturbances with 80 % power at alpha 0.05. With an expected drop out rate of 30 %, 15 persons were judged necessary in each group.

Inclusion criteria

For all study participants, age between 18 and 40 years was a necessary criterion for inclusion. Other criteria for each of the three groups were as follows:

1. mTBI group:

- a. Presented to the ED after acute blunt head trauma.
- b. Met diagnostic criteria for mTBI according to American Congress of Rehabilitation Medicine(25): mTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification included: (i) 1 or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale (GCS)(26) score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury.

c. CT of the brain performed on the basis of clinical need, as assessed by the ED doctor.”

2. Orthopaedic control group:

- a. Presented to the ED after minor trauma to the extremities without head trauma.
- b. Did not require surgery.

3. Non-injured control group:

- a. Individuals who had not suffered traumatic injury and who answered an advert recruiting to the study.

Exclusion criteria (any of the following):

- a. indication for neurosurgery
- b. previous moderate or severe traumatic brain injury
- c. any head injury in the previous year requiring medical attention
- d. presence of any contraindication for MRI (magnetic resonance imaging)
- e. progressive neurological disease or other medical conditions with expected short survival
- f. severe visual impairment or manifest strabismus
- g. need for help in activities of daily living before the current injury
- h. intoxication with alcohol at the time of the injury
- i. not fluent in Swedish

For demographic information, see Table 1.

Table 1 Demographic data

	mTBI patients	Orthopaedic controls	Non-injured controls
Age, median (range)	25.0 (18 – 39)	27.0 (18 – 40)	26.0 (19 – 36)
Men, n (%)	7 (47)	11(73)	9 (60)
Women, n (%)	8 (53)	4 (27)	6 (40)
GCS 15 (%)	14 (93)	N/A	N/A
GCS 14 (%)	1 (7)	N/A	N/A

Type of trauma:	Fall: 7 (47)	Sports: 9 (60)
n (%)	Bicycle: 2 (13)	Other: 6 (40)
	Horse back riding: 2(13)	
	Other: 4 (27)	

N/A – not applicable, GCS – Glasgow Coma Scale,

Data collection

Subject recruitment was conducted between January 2015 and January 2016, and was stopped when a total of 15 patients with mTBI, 15 orthopaedic controls, and 15 non-injured controls were enrolled, in accordance with the power calculation. Study patients were contacted by phone 1-3 days after injury. All study participants received written information about the study and gave informed consent.

All data related to the injury, GCS on arrival at the ED, and results of computerised tomography (CT) of the brain, were collected from the medical records. Demographic data were collected by interview at the baseline examination.

All study participants were scheduled to be assessed twice: at baseline, in the subacute phase, (for trauma patients, 7-10 days after the trauma), and at follow-up - 75-100 days after the injury. Due to recruitment difficulties, and in order to minimize dropout, the time frame for the first and second assessment was extended.

Neuropsychological testing and visual assessment were performed at different time points on the same day or on the day before or after. The median time between injury and baseline visual assessment was 7 days (range 4-13 days) for patients with mTBI, and 8 days, (range 7-12 days) for orthopaedic controls. The median time between injury and follow-up visual assessment was 103 days (range 81-232) for patients with mTBI, and 108,5 days (range 87-322) for orthopaedic controls. No statistically significant difference was found between patients with mTBI and the orthopaedic control group regarding time between the injury and assessments (baseline and follow-up).

Patients with mTBI and orthopaedic controls underwent examination with structural magnetic resonance imaging (MRI) and resting state functional MRI of the brain at baseline and at follow-up. All participants rated anxiety and depression using Hospital Anxiety and Depression Scale (HADS)(27), and fatigue using Fatigue Severity Scale (FSS)(28), and underwent neuropsychological testing. These data and imaging results will be reported separately.

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3 Among the consecutive patients who were invited to participate in the study, a total of
4 ninety-nine declined; 17 mTBI and 82 orthopaedic subjects. Of those who declined,
5 88 % of mTBI and 64 % of orthopaedic subjects were men, and there was no
6 difference regarding age between participating and non-participating individuals. The
7 reasons stated for not participating were lack of time and inconvenience.
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9 Two individuals in the mTBI group and two individuals in the orthopaedic control
10 group were lost to follow-up despite several follow-up phone calls and letters.
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15 **Assessments**

16 The visual examination was performed by licensed optometrists, using standard
17 optometric clinical methods. It included assessment of visual acuity at far and near,
18 refractive error, stereo acuity, near point of accommodation, facility (flexibility) of
19 accommodation, near point of convergence (NPC) with an accommodative target,
20 non-strabismic eye-turn (heterophoria), eye motility and fusional vergence. Diagnosis
21 of visual dysfunctions were based on established diagnostic criteria.(29) NPC was
22 measured using the push-up method (RAF-ruler). Positive fusional vergence (PFV)
23 was measured with a prism bar. In both cases the patient is instructed to try as hard as
24 possible to maintain single vision and to report when perceiving double vision.
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26 Meanwhile, the examiner carefully observes eye alignment in order to verify the
27 patient's response. Expected accommodative amplitude was calculated according to
28 the Hofstetter formula ($18.5 - 1/3 \text{ age}$). (29) Diagnosis of accommodative insufficiency
29 (AI) required amplitude less than minimum expected according to the Hofstetter
30 formula ($15 - 1/4 \text{ age}$). Diagnosis of convergence insufficiency (CI) required near point
31 of convergence ≥ 6 cm plus at least one of the following; reduced PFV at near (< 20
32 prism diopters) or divergent heterophoria at least four prism diopters greater at near
33 than at distance.(29) Saccadic eye movements were recorded (spatial res 0.15 degrees;
34 temporal res 300 Hz) using an eye tracker (Tobii TX300, Tobii Corp., Stockholm,
35 Sweden, www.tobii.com). The participant was positioned 60 cm directly in front of
36 the eye tracker display. We used three test paradigms: (1) pro-saccades; 2) anti-
37 saccades; and (3) self-paced saccades. The stimuli consisted of a dot with a diameter
38 of 5 mm (0.5 degrees). In the pro-saccade paradigm the participant fixated a centered
39 cross and then re-fixated to a dot that appeared at 2, 4, 6, or 8 degrees to the left or
40 right of the cross. The performance was characterised with mean latency and
41 positional gain. In the anti-saccade paradigm the participant viewed a centered cross
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3 and then rapidly looked in the opposite direction to that of a dot presented 8 degrees
4 to the left or right of the centre. The performance was characterized with the latency
5 of correctly performed saccades and proportion of erroneous saccades. In the self-
6 paced saccade paradigm two dots were simultaneously presented for 30 seconds at 8
7 degrees to the left and right of centre. The participant was instructed to move the gaze
8 rapidly, as many times as possible, between the dots. The performance was
9 characterised with number of saccades performed in 30 seconds and mean
10 intersaccadic interval (ms).
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16 At baseline and follow-up, all study participants self-rated their symptoms using the
17 Rivermead Post-Concussion Symptoms Questionnaire (RPQ),(30) and the
18 Convergence Insufficiency Symptom Survey (CISS).(31, 32) The RPQ is based on a
19 Likert scale and includes 16 items with ratings: 0 "no symptoms", 1 "no more of a
20 problem or transient symptoms", 2-4 "mild to severe" symptoms. A total sum of all
21 symptom scores ("mild to severe", excluding ratings of 1) is calculated, with a
22 maximum score of 64. The CISS is a validated and reliable instrument(31) that
23 evaluates near work-related visual symptoms. It includes assessment of direct
24 symptoms, such as blur and double vision, as well as indirect symptoms (e.g.,
25 difficulty maintaining concentration, sleepiness while reading, headache and ocular
26 discomfort). The survey includes 15 questions with ratings from 0 "never" to 4
27 "always" for assessment of visual symptoms. The total score is 60 and the cut-off
28 score for abnormal levels of symptoms is 21. This value gives good sensitivity (97.8
29 %) and specificity (87 %) in otherwise healthy young adults who have presented to
30 optometrists with visual symptoms.(32)
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42 **Data analyses**

43 All data were analysed using SPSS 23. Parametric statistics was used for oculomotor
44 measures (accommodation, convergence, fusional vergence and saccades). A two-way
45 repeated measures ANOVA was used for analysing the within-subject factors
46 (baseline vs. follow-up) and the between subject factor (effect of group). Post-hoc
47 tests were performed using Holm-Bonferroni adjustment. Fischer's exact test was
48 applied for analysis of the categorical data.
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54 Nonparametric Kruskal-Wallis (three groups), Mann-Whitney U (two groups, post-
55 hoc analysis), Wilcoxon sign rank tests and Spearman's rank correlation were used
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3 for comparison of ordinal data from questionnaires (CISS and RPQ) and stereo acuity.
4 Two-tailed p-values were used with a critical significance level of $p < 0.05$.
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6 7 **RESULTS**

8 Two of the 15 patients with mTBI had pathological findings on CT of the brain: one
9 had a small subdural haemorrhage and the other a small subarachnoid haemorrhage.
10 Neither required surgery. No cranial nerve palsies or direct trauma related eye
11 pathology was found.
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14 15 16 Visual examination 17 Accommodation

18 A significant effect of interaction between group and test occasions was found in the
19 ANOVA for the deviation from expected accommodative amplitude ($df=2$, $F=4.406$,
20 $p=0.028$). The post-hoc analysis showed significantly reduced accommodative
21 amplitude in the mTBI group compared to non-injured controls at baseline ($p=0.001$)
22 (Figure 1) but no statistically significant difference between patients with mTBI and
23 orthopaedic controls. There were no statistically significant differences between the
24 mTBI group and either of the control groups at follow-up. Six out of 13 patients with
25 mTBI still had AI at follow-up (12 out of 15 patients at baseline) compared to 5 out of
26 12 orthopaedic controls (no change over time) and 2 out of 15 non-injured controls at
27 follow-up (no change over time). No statistically significant differences in
28 accommodative facility were found within or between groups or test occasions.
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37 (Insert Figure 1 here)
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39 40 Convergence

41 The ANOVA showed a significant interaction effect ($df=2$, $F=3.793$, $p=0.042$) and the
42 post-hoc analysis showed a significant difference (improvement) in the mTBI group
43 between baseline and follow-up ($p=0.015$) (Figure 2). There were no statistically
44 significant differences between or within the control groups.
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51 52 Fusional vergence

53 The ANOVA on fusional vergence did not show any significant differences at the
54 group level at any time point.
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Stereo acuity

No statistically significant difference was found between groups or test occasions regarding stereo acuity (Kruskal-Wallis). Five out of 15 of the patients with mTBI showed a reduced level of stereo acuity at baseline (120-240 seconds of arc) whilst one patient showed a reduced level at follow-up (60 seconds of arc or less). In the orthopaedic group three subjects performed at the level of 120-240 seconds of arc at baseline, and two of these performed similarly at follow-up. All non-injured controls performed normally at both test occasions.

Saccade performance

In the pro-saccade task, no statistically significant difference in latency or gain was found between groups or test occasions (ANOVA). No significant differences within or between groups were found in the self-paced saccade task. In the anti-saccade task all groups performed well at both test occasions with no statistically significant differences in latency or proportion of erroneous saccades.

Assessment of visual symptoms

There was a statistically significant difference between the three groups regarding CISS score at the baseline ($df=2$, $p=0.003$) (Kruskal-Wallis test). Patients with mTBI had more visual symptoms with near work, compared to the two control groups, as measured by the CISS score at baseline: patients with mTBI vs. orthopaedic controls ($U=47.5$, $p=0.012$) and patients with mTBI vs. non-injured controls ($U=38.0$, $p=0.02$) (Mann-Whitney U test). The median value of the CISS score in the mTBI group at baseline was 24. It then decreased to 19 at follow-up but the change did not reach statistical significance (Wilcoxon Sign Ranks test). The CISS score was below cut-off level at both time points in the control groups.

At baseline nine out of 12 patients with mTBI were identified with CI/AI using the CISS (Figure 3). At follow-up, seven patients with mTBI still had CI/AI (Figure 3); one with CI and six with AI. Three of these patients scored as symptomatic on CISS. However, no association between CISS and CI/AI was found (Fisher's exact test).

(Insert Figure 3 here)

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3 In the mTBI group, CISS scores at baseline correlated with reduced positive fusional
4 vergence measured at near, i.e. the capacity to maintain clear single vision while
5 performing near work ($r=-0.6$; $p=0.02$) (Figure 4).
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8 (Insert Figure 4 here)
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10 **Symptoms measured by the RPQ**

11 There was a significant difference, regarding the sum of symptom scores on the RPQ,
12 among the three groups at baseline ($df=2$, $p<0.001$) and at follow-up ($df=2$, $p=0.001$)
13 (Kruskal-Wallis test). At baseline, the RPQ sum of symptom scores was significantly
14 greater in the mTBI group compared to the orthopaedic control group ($U=40.0$,
15 $p=0.002$) and to non-injured controls ($U=29.5$, $p<0.001$) (Mann-Whitney U test). A
16 significant difference was found in the sum of symptom scores at follow-up, between
17 the mTBI group and the orthopaedic control group ($U=27.0$, $p=0.003$), and between
18 the mTBI group and non-injured controls ($U=24.0$, $p<0.001$) (Mann-Whitney U test).
19 Sum of symptom scores decreased in the mTBI group over time (median value of the
20 RPQ sum of symptom scores decreased from 22 at baseline to 6 at follow-up), but the
21 difference did not reach statistical significance ($p=0.092$) (Wilcoxon signed rank test).
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31 **DISCUSSION**

32 We have observed differences in visual measurements between a well-defined mTBI
33 group and two control groups. We also objectively measured transient visual
34 disturbances in the mTBI group.
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38 In agreement with a previous study(3), a significant difference in accommodation
39 between the mTBI group and each of the control groups at the baseline was found in
40 our study. The mTBI group had statistically significantly lower accommodative
41 amplitude compared to non-injured controls at baseline. Accommodative amplitude
42 then recovered to a certain degree at follow-up, but almost half of the patients with
43 mTBI still had deviations meeting the diagnostic criteria for AI. We know little
44 regarding the expected course of spontaneous improvement in accommodation. There
45 are some indications that AI may be part of issues even in the long term after
46 injury.(21, 22) Therefore it may be necessary to consider therapeutic intervention
47 when appropriate, e.g. spectacle lenses for near work and/or vision therapy.(33)
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3 A somewhat unexpected result was the non-significant difference in NPC between the
4 groups. The finding of non-significant differences in NPC among groups is in contrast
5 to that by Capo-Aponte and co-workers.(3) However, we found a significant change
6 in NPC in the mTBI group between the baseline and follow-up. The mean NPC at
7 baseline of these patients with mTBI was just within 10 cm, which may or may not be
8 considered clinically meaningful,(15, 29) and therefore not pose a clinical sign for
9 further examination of CI. Receded NPC has previously been proposed as a
10 potentially sensitive vision-based biomarker after mTBI(14) and our findings
11 tentatively support this.
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18 The mechanism behind the spontaneous recovery of NPC in the present patient
19 sample remains to be understood. The convergence responses are based on visual
20 processing of binocular disparity and correct ocular alignment through vergence eye
21 movements. Given the recovery of NPC, any manifest structural injury affecting
22 motor function (vergence eye movements) can probably be ruled out. Some of the
23 remaining aspects to consider are sensorimotor integration and the ability to respond
24 appropriately to the stimulus. Certain tasks, including the push-up method for
25 measuring NPC used in the current study, require that the subject exert maximal
26 convergence effort to maintain single vision of a very near target. This most likely
27 involves voluntary effort. A question for further discussion is how the constellation of
28 somatic symptoms, cognitive impairments and fatigue, known to be associated with
29 mTBI, may affect the capacity to perform this test optimally. Our clinical
30 observations during this study, along with previous research, suggest that these factors
31 can have contributory effects. (19)
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41 One third of the patients with mTBI showed a deficient level of stereo acuity at
42 baseline (120-240 seconds of arc), whilst at follow-up only one showed deficiency
43 (> 60 seconds of arc). These findings may suggest that the visual processing of
44 disparity was particularly affected in the mTBI group in the acute stage. Based on the
45 improvement in stereo acuity we may speculate that underlying factors affecting the
46 ability to resolve and detect stereo disparity, such as inadequate or inefficient
47 vergence and/or accommodative function, improved with time.(34)
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53 We were not able to replicate the findings of previous studies that found differences in
54 measures of saccadic eye movements between patients with mTBI and controls. (3, 7,
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3 13, 24) An explanation could be that changes in saccadic reaction time/latency are
4 subtle, transient, and possibly only to be demonstrated directly after a trauma to the
5 head. In our study, baseline optometric examination took place a few days after
6 mTBI. Our findings are in line with a study of amateur boxers in which saccadic
7 latency was measured at four time points, with baseline before the boxing match (pre-
8 fight), and at 3 days, 7 days and 12 days after-fight, that is after blows to the head
9 (10). Results in this study showed increased saccadic latency directly after the fight;
10 however 12 days later the latency had returned to baseline. The small number of
11 participants and lack of the description of mTBI criteria limit interpretation of
12 findings in that study.
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20 We found that patients with mTBI had significantly more visual symptoms as
21 measured by CISS score than orthopaedic and non-injured controls. Our findings on
22 reported visual disturbances at near work after mTBI are consistent with a previous
23 study.(3) We found a significant correlation between CISS score and PFV at near in
24 the mTBI group. This correlation may appear somewhat unexpected since the PFV
25 was normal at the group level. The symptom score (CISS) was significantly higher in
26 the mTBI group than in the control groups. The elevated symptom score may be an
27 indication that most patients with mTBI were indeed able to perform normally on the
28 PFV, but at a greater effort (causing symptoms). Objective recordings of vergence eye
29 movement have demonstrated an association between symptoms and inefficient
30 vergence performance.(35)
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39 The patients sustaining a trauma to the head in this study reported significantly more
40 symptoms on the RPQ and CISS compared to both controls groups at baseline. The
41 symptoms decreased at follow-up, but the change was not statistically significant.
42 However, the role of brain injury for these symptoms, especially for patients with
43 long-term problems after mTBI, has been questioned.(36) Several factors have been
44 suggested to affect symptom reporting after mTBI, e.g., recall bias and
45 biopsychosocial factors. Furthermore, previous studies have demonstrated that similar
46 symptoms are also present after any trauma, presumably due to emotional distress and
47 pain related to the injury.(36, 37) The strength of our study is having two control
48 groups. Traumatic injury can generally impact on reporting of various symptoms,
49 related to acute posttraumatic stress and pain. Therefore, to avoid confounding
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3 factors, we included a group of patients with minor orthopaedic injuries without
4 trauma to the head, presenting at the same emergency department.
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6 7 **Study limitations**

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10 When the study population is small, there is always a risk for type II error, that is the
11 risk of not revealing a true difference in the studied population. The differences found
12 between patients with mTBI and controls regarding oculomotor measures were few
13 and the within group variations were large. The degree of overlap between groups and
14 incomplete correlation between visual symptoms and visual measurements suggest
15 that caution is appropriate when interpreting findings in an individual patient based on
16 the current state of knowledge. However, several aspects merit further
17 investigation. The sample size in the present study was based on power calculations
18 from reports on long lasting vision and oculomotor problems in patients after
19 mTBI.(4, 7, 8) Possible bias in these studies could have led to an overestimation of
20 the frequency of oculomotor changes and thus an overestimation of expected effect
21 size in our power calculation and a risk of type II error.
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30 Study participants were 18-40 years old making the mTBI patient group in this
31 explorative study highly selective. This age limitation was chosen to minimize the
32 effect of presbyopia on study results. Our findings will have relevance regarding the
33 large number of young adults suffering head trauma, but will not be directly
34 applicable to older patients, which limits the generalisability.
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39 **Future recommendations**

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41 Larger confirmatory studies are needed to clarify the clinical relevance of the transient
42 visual disturbances observed in this study. The role of vergence and accommodation
43 as potential biomarkers for mTBI and their interplay with persisting symptoms such
44 as fatigue also need further elucidation. Furthermore, investigations of visual
45 disturbances after mTBI should aim to determine if visual testing in the subacute
46 phase after mTBI could help to predict long lasting symptoms and be a target for
47 intervention to promote recovery. Our findings, along with previous observations,(21)
48 indicate the importance of not overlooking possible accommodative disorders in the
49 overall assessment of the patient's capacity to return to daily activities.
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CONCLUSIONS

Some transient measurable visual changes regarding convergence were noted in patients with mTBI during the subacute period after injury. The finding of persistent accommodative insufficiency in a substantial proportion of patients with mTBI requires further evaluation. Accommodation insufficiency could be either a biomarker for persistent functional impairment in neural networks, or a target for intervention to promote recovery, or possibly both.

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Contributors: GM and JJ contributed to design of the study, were responsible for data collection, wrote initial draft of manuscript, performed statistical analysis, and contributed to the analysis of results and interpretation of findings. CND, TP, MM were main contributors to study design, contributed to data collection, analysis of results and interpretation of the findings. AKG contributed to discussions on study design, critically revised the manuscript, and contributed to data analysis and interpretation. All authors read, commented and approved the final manuscript.

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Competing interests: None declared.

Patient consent: All patients gave written informed consent.

Ethics approval: Ethics approval was obtained from the Regional ethical review board in Stockholm, diary number 2014/597-31/1. The study adhered to the tenets of the Helsinki Declaration.

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

Data sharing statement: Further data may be available from the authors. Please contact the corresponding author.

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55 **FIGURE LEGENDS**

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3 Figure 1 Deviation from expected accommodative amplitude. The lower the negative
4 value, the greater the deviation (insufficiency). Closer to zero is better. The miniature
5 squares indicate mean values. The box indicates median, upper and lower quartile.
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7 The whiskers indicate min and max.
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10 Figure 2 Near point of convergence in the mTBI group at baseline and at follow up
11 measured in cm. The lower the value, the better convergence performance. The
12 miniature squares indicate mean values. The box indicates median, upper and lower
13 quartile. The whiskers indicate min and max.
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17 Figure 3 The association between CISS score and the presence of accommodative or
18 convergence insufficiency in patients with mTBI, orthopaedic controls and non-
19 injured controls. The findings at baseline and at follow-up are presented in a two-by-
20 two matrix.
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24 Figure 4 CISS score versus positive fusional vergence in patients with mTBI. Higher
25 positive fusion value corresponds to better function.
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30 LIST OF ABBREVIATIONS

31 AI - Accommodative Insufficiency

32 ANOVA – Analysis of Variance

33 CI – Convergence Insufficiency

34 CISS – Convergence Insufficiency Symptoms Survey

35 CT – computerised tomography

36 ED – emergency department

37 GCS – Glasgow Coma Scale

38 MRI - magnetic resonance imaging

39 mTBI – mild traumatic brain injury

40 NPC – Near Point of Convergence

41 PFV – Positive Fusional Vergence

42 RAF-ruler – Royal Air Force ruler

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RPQ – Rivermead Post-Concussion Symptoms Questionnaire

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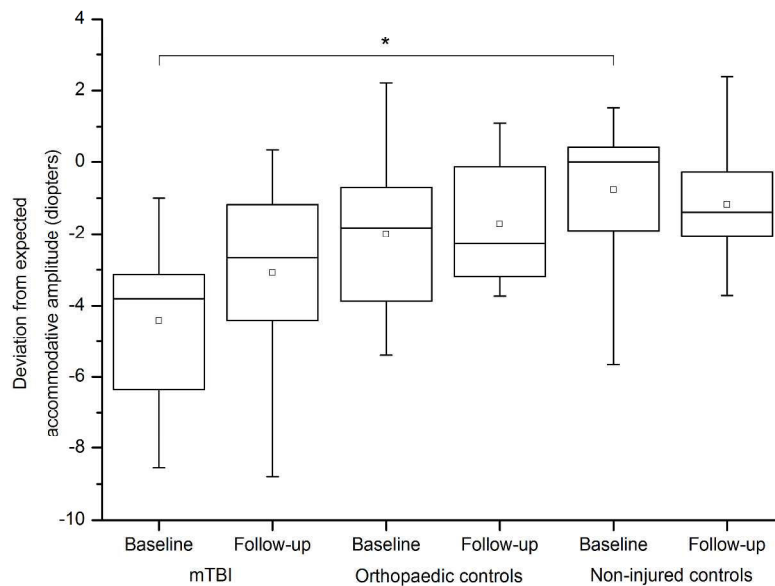


Figure 1 Deviation from expected accommodative amplitude. The lower the negative value, the greater the deviation (insufficiency). Closer to zero is better. The miniature squares indicate mean values. The box indicates median, upper and lower quartile. The whiskers indicate min and max.

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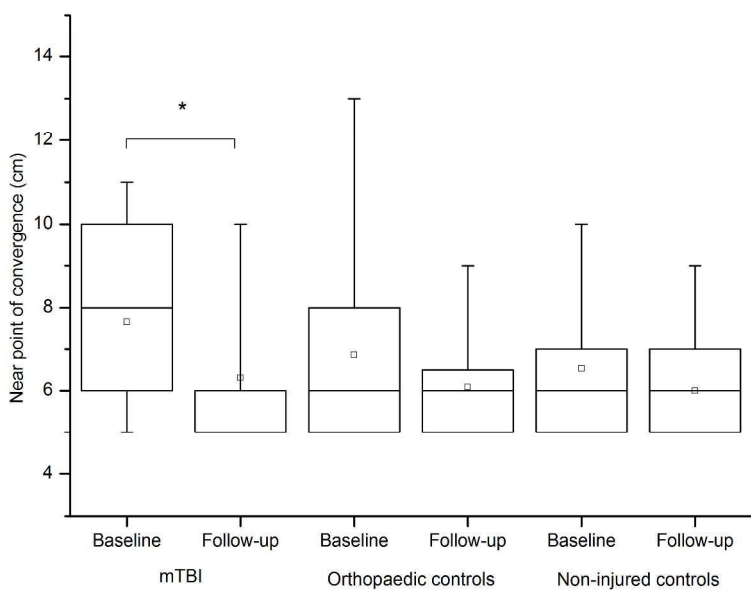


Figure 2 Near point of convergence in the mTBI group at baseline and at follow up measured in cm. The lower the value, the better convergence performance. The miniature squares indicate mean values. The box indicates median, upper and lower quartile. The whiskers indicate min and max.

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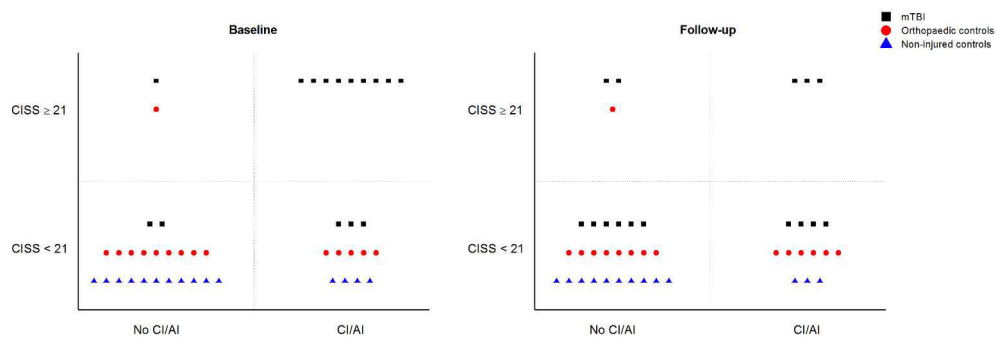


Figure 3 The association between CISS score and the presence of accommodative or convergence insufficiency in patients with mTBI, orthopaedic controls and non-injured controls. The findings at baseline and at follow-up are presented in a two-by-two matrix.

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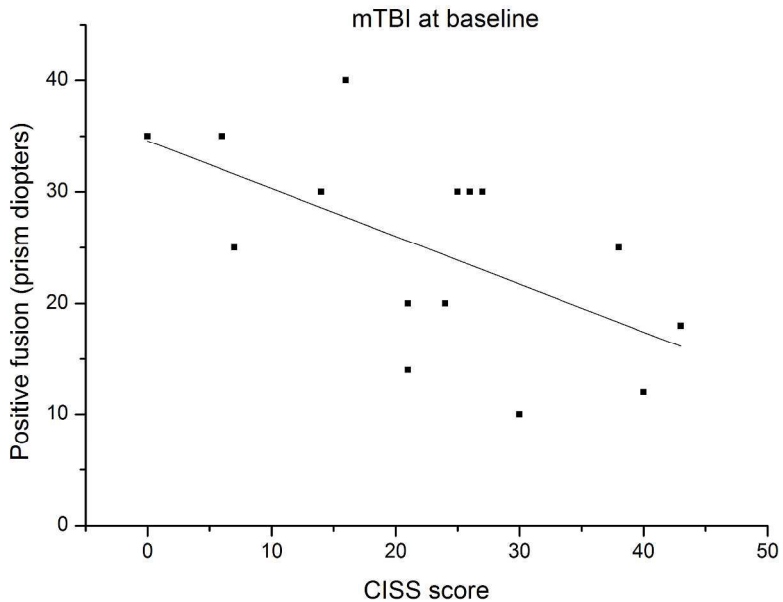


Figure 4 CISS score versus positive fusional vergence in patients with mTBI. Higher positive fusion value corresponds to better function.

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Research checklist

STROBE Statement - checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
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	8-9
Bias	9	Describe any efforts to address potential sources of bias	3
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	-
		(d) If applicable, explain how loss to follow-up was addressed	-
		(e) Describe any sensitivity analyses	-
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	10
		(b) Give reasons for non-participation at each stage	10
		(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	7
		(b) Indicate number of participants with missing data for each variable	11-13

		of interest	
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13
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	10-13
		(b) Report category boundaries when continuous variables were categorized	-
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
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	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
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	17

*Give information separately for exposed and unexposed groups.

NA – not applicable