BMJ Open Sport & Exercise Medicine

Use of physical exertion to enhance objective testing following mild traumatic brain injury: a systematic review

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To cite: Forch K, Pedersen M, Reid D, *et al*. Use of physical exertion to enhance objective testing following mild traumatic brain injury: a systematic review. *BMJ Open Sport & Exercise Medicine* 2025;**11**:e002385. doi:10.1136/bmjsem-2024-002385

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjsem-2024-002385).

Accepted 29 March 2025

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ABSTRACT

Background Assessment of recovery from mild traumatic brain injury (mTBI) is complex and challenging. Post-exertion testing, where individuals undergo objective testing following physical exercise, has shown promise in identifying mTBI-related impairments that may not be evident at rest, but could hinder a safe return to sport.

Objectives To conduct a systematic review to determine if physical exertion affects objective physiological or sensorimotor tests differently in individuals with mTBI compared with healthy controls.

Methods A systematic search of 11 databases and five trial registries on 30 May 2024 identified reports that: (i) compared individuals aged 12–65 years within 12 months of mTBI against healthy control participants, (ii) investigated the effects of a single session of physical exertion and (iii) collected before, during or after exertion, objective measures of physiological or sensorimotor function. Risk of bias was assessed with the Risk Of Bias In Non-randomized Studies of Interventions tool. Results were analysed descriptively.

Results The review included 22 studies with 536 participants wih mTBI. Risk of bias was deemed high. At rest, 8/22 (36%) studies detected differences in physiological responses between participants wih mTBI and healthy control participants. During or after exertion, 21/22 (96%) studies detected differences in physiological responses, including cardiovascular, respiratory and cerebral autoregulation.

Conclusion The findings indicate that objective testing during or after physical exertion can enhance the ability to detect mTBI-related impairments in various physiological parameters, and this concept could be considered when monitoring recovery and return to sport. Further studies are needed.

PROSPERO registration number CRD42023411681.

WHAT IS ALREADY KNOWN

⇒ Athletes returning to sports after mild traumatic brain injury (mTBI) have twice the risk of a subsequent injury.
⇒ Symptom reporting is not a sensitive marker of recovery.
⇒ mTBI commonly impacts the autonomic and sensorimotor systems.

WHAT ARE THE NEW FINDINGS

⇒ Objective measures such as heart rate variability pre-exertion and post-exertion can highlight mTBI impairments not detectable at rest, and should be considered when assessing readiness for return to play.
⇒ Further work exploring the effect of physical exertion on sensorimotor measures is required.

INTRODUCTION

Mild traumatic brain injury (mTBI), also known as concussion, is induced by biomechanical forces, such as acceleration, deceleration or rotation, transmitted to the brain following a blow to the body or head.[1] The pathophysiology of mTBI can involve microstructural axonal damage caused by the warping of the neural tissue during the injury event,[2] and a neurometabolic cascade and consequent energy crisis.[3] To be considered mild, the TBI will be characterised by a loss of consciousness <30 min, post-traumatic amnesia <24 hours and a Glasgow Coma Scale score of 13–15.[4]

Athletes returning to play (RTP) after mTBI have approximately double the risk of subsequent injury, either musculoskeletal or another mTBI.[5 6] One hypothesis for this risk is lingering dysfunction and incomplete recovery.[7 8] Symptom reporting is used clinically as one of the main indicators of mTBI recovery; however, symptoms are non-specific markers of underlying physiological recovery.[9 10] There is a growing body of evidence that subjective symptom recovery can occur before brain metabolism,[11] connectivity[12 13] and blood flow[14] have normalised. This gap between symptom resolution and full recovery is supported by reports of athletes with sports-related mTBI (SR-mTBI) who no longer have symptoms and have returned to

play, yet still have a range of measurable impairments including diminished sensorimotor and neuromuscular control,[15] altered cardiac autonomic modulation,[16] impaired cerebral autoregulation,[17] visuomotor deficits,[18] locomotor navigation issues, reduced dual-task gait speed, and altered gait and landing kinematics.[19] This suggests that these asymptomatic individuals have not yet recovered, and that relying on symptom resolution alone may leave them vulnerable to further injury. The reliance on subjective symptoms for clinical decisions is further complicated by the under-reporting of symptoms, which is common in amateur[20] and professional[21] sports.

To reduce reliance on symptom reporting as the primary indicator of mTBI recovery, experts have highlighted the importance of including objective measurements in RTP testing.[22 23] In current practice, any objective measures, such as balance testing and oculomotor examination, are completed in a resting state.[1] However, in a sporting context, the demands on the physical systems are much higher and assessment at rest has a potential ceiling effect.

A range of mTBI reports have demonstrated that physical exertion can highlight impairments in various objective measurements that are not detectable at rest.[24–28] This suggests that RTP assessment could incorporate post-exertion testing, where a selection of physical measurements (eg, visual tracking, balance, gait) are undertaken following physical exertion to 'objectively' determine if an individual is ready to RTP or whether they are likely to experience a decline in performance when they begin to train or compete.

In current clinical practice, exertional tolerance testing (ETT) is recommended in mTBI management to assess an athlete's tolerance to aerobic exercise and to determine if, and at what intensity, symptoms are produced.[1] However, ETT relies on the reporting of symptoms to identify exercise intolerance,[29 30] and is not currently widely used to detect objective impairments that could indicate incomplete physiological recovery in asymptomatic individuals.

Replicating sport-specific demands through exertional testing has proven valuable in the domain of cognitive assessment. Several studies agree that post exertion, many concussed participants show a decline in cognitive performance that was not detected at rest.[31–33] Cognition represents one domain where lingering impairments would contribute to an increase in injury risk.[34] Impairments of the visual and balance systems, or dysfunction in the autonomic systems resulting in decreased oxygen delivery or abnormal fatigue, could also represent an injury risk.[35]

Previous reviews have been limited to the use of exertion testing within ETT paradigms only[36] or were limited to objective autonomic measures[37 38] excluding other physical measures such as sensorimotor function. Thus, a systematic review is warranted to explore the use of various types of physical exertion testing to detect a range of objective physical mTBI impairments. The aim of this systematic review was to determine if physical exertion affects objective measures of physiological and sensorimotor function differently in individuals with mTBI compared with healthy control participants. The findings may provide further guidance about which measures could be considered for inclusion in RTP post-exertion testing protocols following mTBI.

METHOD

Protocol and registration

The systematic review was prospectively registered in the PROSPERO database (CRD42023411681, registration ID 20230803; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=411681) and was conducted per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[39]

Information sources

The final literature search was conducted on 30 May 2024 in the following databases and registers: Scopus, Web of Science, EBSCO (MEDLINE, CINAHL, SPORTDiscus), Ovid (PsycINFO; AMED; Emcare; Cochrane Methodology Register; Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Cochrane Clinical Answers; Health Technology Assessment; MEDLINE and EPub Ahead of Print, In-Process, In-Data Review & Other Non-Indexed Citations), ANZ Clinical Trials Registry, International Standard Randomised Controlled Trial Number Register, WHO International Trials Registry Platform and PEDro.

Search strategy

The search terms included synonyms related to three combined concepts (mTBI; objective assessment; and exertion) (see online supplemental file 1:A for full search details).

Selection process

Two authors (KF, NT) completed independent screening of title and abstract, and full text as necessary, against the eligibility criteria provided in table 1. A third author (SO) was consulted in the case of disagreement. Records were imported into an Endnote X9 library and duplicates were removed. Records were then exported to Rayyan systematic review software[40] for screening. In addition to database searching, manual searching of relevant literature identified in the database search was conducted. No automated or semi-automated screening methods were used. Authors of primary studies were contacted to determine eligibility if this was not possible from the published report.

Data collection process and data items

Data extraction was completed by the primary author, a sample was cross-checked by a second author (SO), and conflicts were discussed if required. The following data were extracted: study objective, design, sample demographics (age, sex), sport-related or non-sport-related

Table 1 Eligibility criteria

	Inclusion criteria	Exclusion criteria
Target population (P)	Participants aged 12–65 years of age with mTBI within 12 months of injury.	Moderate and/or severe mTBI, animal studies.
Intervention (I)	A single session of physical exertion, defined as any repeated bodily movement produced by skeletal muscles that results in energy expenditure.[86]	Physical exertion that was comparable to postural change, for example, a single sit-to-stand movement or transitioning from lying to sitting.
Comparison population (C)	A control group of non-injured healthy participants, OR pre-injury data for the population with mTBI (ie, a baseline measure).	
Outcomes (O)	Reporting of outcomes of objective measurements of physiological and/or sensorimotor function assessed before physical exertion (pre), AND during and/or immediately post-physical exertion. These measures could include cardiovascular (eg, heart rate variability), cerebral autoregulation (eg, cerebral blood flow velocity), respiratory (eg, $FETCO_2$), sensorimotor (eg, King-Devick, balance) or other (eg, cortisol) parameters.	Subjective, patient-reported measures. Objective measures not taken within the same session.
Analysis	Statistical analysis enabling comparison of the effect of exertion on objective measures in mTBI and healthy participants.	
Study design	Experimental study design. This could include studies with a physical exertion intervention only (single intervention, repeated-measures study, pre-intervention and post-intervention only), or comparison of physical exertion versus rest condition (two interventions, repeated-measures, crossover study), at one or multiple timepoints.	Studies exploring the effect of the intervention outside of a single session.
Publication type	English language, peer-reviewed journal articles.	Case studies, reviews, expert opinions, conference abstracts.

$FETCO_2$, fraction of end-tidal carbon dioxide; mTBI, mild traumatic brain injury.

injury, type of sport, any matching of playing position with control participants, time since injury, symptom status (symptomatic vs asymptomatic), symptom severity, assessment timepoints, intervention type and dosage, objective measures and the physical system being assessed, measurement technique, subgroups, statistical analyses, power calculation, dropouts and deviations and summarised results. In the case of missing quantitative results data, study authors were contacted, and for one paper,[41] the means were extracted from figures within the text.

Study risk of bias assessment

Included studies were assessed by two authors (KF, NT), independently, for risk of bias using the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool,[42] for non-randomised intervention studies, and the Risk of Bias 2 (ROB-2) tool[43] for randomised controlled trials (RCTs). Seven domains were considered that can be a source of bias, and each domain was scored as 'no information', 'low', 'moderate', 'serious' or 'critical' risk of bias. Each study was also given an overall risk of bias score. The studies were discussed, and if consensus could not be reached, a third author (SO) was consulted. Prior to consensus, a linear weighted Cohen's kappa coefficient for level of agreement for each domain and overall score was calculated for studies assessed with the ROBINS-I and is provided in online supplemental file 1:D.

Synthesis methods

A descriptive analysis was undertaken. Findings were grouped according to the physical system being assessed (ie, cardiovascular (CV), respiratory, visual). Study characteristics were summarised in tables, and findings were synthesised according to the mean between-group differences in each outcome measure category. Meta-analysis was precluded due to the heterogeneity of study designs.

RESULTS

Study selection

Figure 1 provides the PRISMA flow chart showing study selection. After screening by title and abstract, 132 records were retrieved for full-text review. Of these, 110 were excluded, with the most common reasons for exclusion being ineligible study design (absence of a control group or measures not taken in

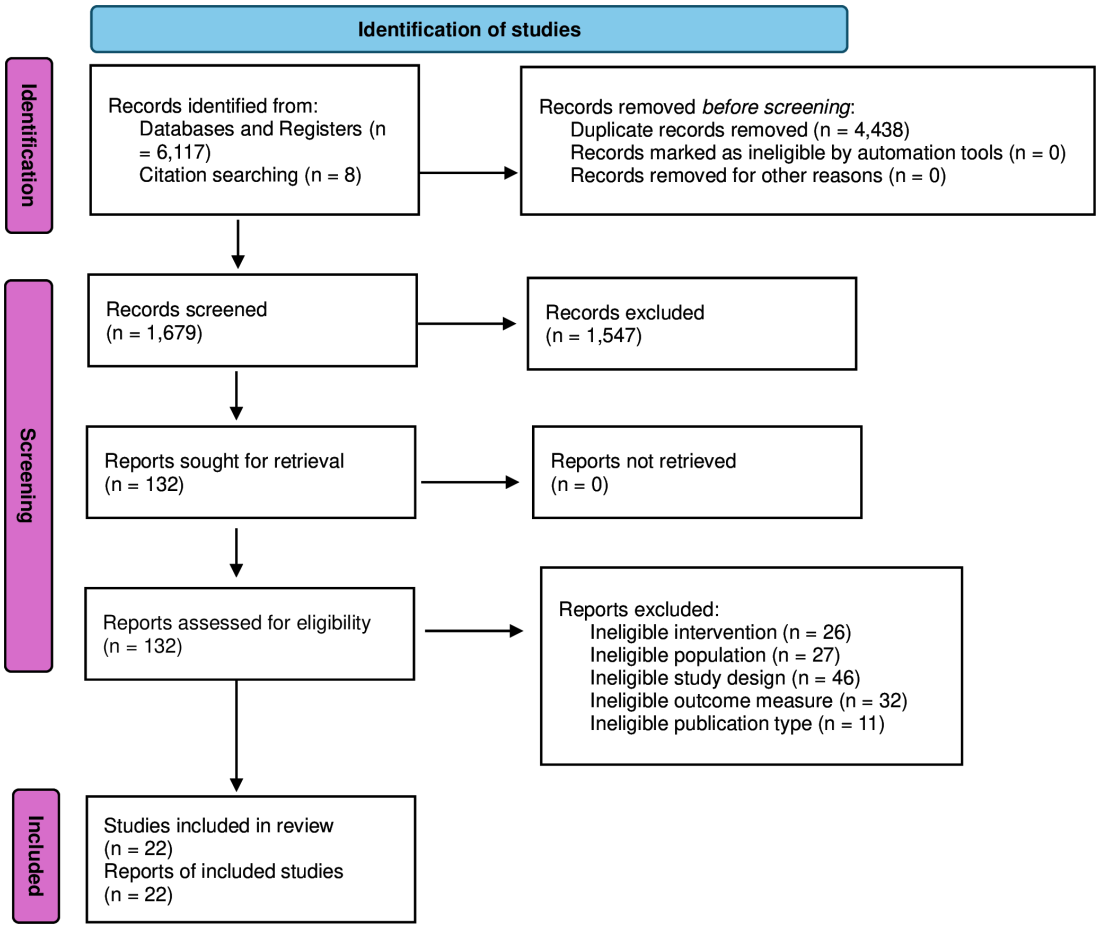

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

a single session) or ineligible population (>12 months since injury, healthy participants only or inclusion of participants with moderate and/or severe mTBI). Full detail of reports excluded at the full-text stage is provided in online supplemental file 1:E. Thus, 22 studies were ultimately included in the review. None of the included studies had multiple reports. No amendments were made to the registered protocol.

Study characteristics

Study design, participant demographics, outcome measures, timepoints and summarised results are presented in table 2. Detailed results of significance for individual studies are presented in online supplemental file 1:F.

Population characteristics

A total of 536 participants with mTBI and 601 control participants were included across the 22 studies, with a mean age for participants with mTBI of 19 years (range 12–43 years). Three studies[44–46] used pre-injury (ie, baseline) data as a control group, while the remaining 19 studies made comparisons with a healthy control group. Musacchio *et al*[47] investigated non-sport-related mTBI (primarily motor vehicle accidents). Four studies enrolled participants with a combination of SR and non-SR-mTBI.[28 48–50] One study did not report the injury mechanism.[51] The remaining 16 studies included only participants with sport-related injuries in their mTBI group. The mTBI populations included individuals with varying times since injury, ranging from within 72 hours to up to 12 months. Six studies[16 25 44–46 52] assessed males only and one study assessed females only.[24] The remaining studies had a combination of males and females, or did not report gender.[12 48]

Symptom status

Symptom status varied between studies. In five studies,[28 41 44 51 53] all participants with mTBI were symptomatic during testing, while in six studies,[12 16 25 52 54 55] all participants with mTBI were asymptomatic.

In four studies,[24 45 46 50] the participants with mTBI were symptomatic at the first timepoint and asymptomatic at the second timepoint. Four studies[27 47 49 56] included both symptomatic and asymptomatic participants, and two of these studies analysed subgroups based on symptoms.[27 49] Two studies[26 48] did not specify symptom status, and another study[57] only reported symptom status for the first of two out of three timepoints.

Table 2 Characteristics and results of individual studies

Study and study design	Population and comparator: mTBI Age in years±SD (% female) Time since injury *categorised* ψ, mean±SD Symptom status	Population and comparator: Healthy Age in years±SD (% female)	Intervention(s)	Outcome(s)	Between-group differences in objective measures: Pre-exertion (rest)	Between-group differences in objective measures: During/Post-exertion
Abaji et al.[16] Cross-sectional (C-S), two-group, single-intervention, one timepoint	N=12 SRC 21±1 y, 0%♀ *Subacute to chronic* 95±63 d Asympt.	N=12 healthy 22±2 y, 0%♀	*Mode*: isometric hand grip *Intensity:* 30% MVC *Duration*: 3 min	*Cardiovascular* LF power, HF power, LF:HF ratio, RMSSD, ApEN	Nil between-group differences in outcomes at rest	↓ HF power and ↑ LF:HF ratio in mTBI during exertion
Bishop et al.[44] C-S, two-group, single intervention, one timepoint	N=12 SRC 19±3 y, 0%♀ *Acute* 2.2±0.7 d, sympt., PCSS 24.25±14.26	N=89 healthy 17±2 y, 0%♀	*Mode*: cyclical 10 s squat hold, 10 s rest in standing for 5 min *Intensity:* body weight *Duration:* ×14 (mean)	*Cardiovascular* LF, HF power, LF:HF ratio, RMSSD, ApEn, HR, SDHR, MAP, DBP, SBP	Nil between-group differences in outcomes at rest	↓ NN50 and pNN50 and ↓ peak SDHR during squat, ↓ SDHR during stand phase in mTBI, ↓ change in MAP, SBP, DBP and SDHR in late phase of squat in mTBI
Clark et al.[48] C-S, two-group, single intervention, one timepoint	N=8 SRC and non-SRC age: 18–26 y, sex NR Time NR, symptoms NR	N=9 healthy, age and sex NR	*Mode:* exercycle *Intensity:* ↑ every 2 min *Duration:* ≅8 min	*Cerebral autoregulation* TERC murmur via auscultation	Nil between-group differences in outcomes at rest	↓ in HR (≈30 bpm) at which TERC murmur was heard in mTBI
Clausen et al.[24] C-S, two-group, single intervention, two timepoints	N=9 SRC 23±6 y, 100%♀ *Subacute to chronic* T1: 63±21 d, sympt., PCSS severity 19 T2: T1+6 weeks, asympt.	N=13 healthy 21±3 y, 100%♀	*Mode*: treadmill *Intensity:* 3 min (4.8 km/hour and 0% incline), incline ↑ 2% every 2 min until test terminated *Duration:* NR	*Cardiovascular/ Cerebral autoregulation/ Respiratory* SBP, DBP, V_E, VO_2, $PETCO_2$, MCAv	T1: ↑ in HR at baseline in mTBI group. mTBI group had ↓ V_E T2: nil between-group differences	T1: mTBI group ↓ V_E. ↑ in PETCO2 and MCAv at all workloads. T2: nil between group differences
Galea et al.[49] C-S, two-group, single intervention, one timepoint	N=73 with SRC (n=38) and non-SRC (n=35) 26±16 y, 41%♀ *Subacute to chronic* 72 d (range 28–182) Subgrouped: sympt. (n=36), asympt. (n=35), severity NR	N=39 healthy 27±13 y, 56%♀	*Mode:* treadmill - BCTT *Intensity:* 1 min at 5.3 km/hour and 0% incline, then incline ↑ 1% every min until reached 15%, speed ↑ 0.2 km/hour every min until termination/21 min. *Duration:* 3–21 min	*Cardiovascular* HR as a %MHR, HR rest, HR max	Nil between-group differences in outcomes at rest	↑ HR during first 4 min, ↓ final HR in mTBI. BCTT test duration is less in sympt. TBI subgroup, with ↓ overall HR change
Gall et al.[25] C-S, two-group, single intervention, two timepoints	N=14 with SRC 18±0 y, 0%♀ *Acute* T1: 5±1 d, T2: T1+5 d Asympt.	N=14 healthy 18±0 y, 0%♀	*Mode*: exercycle, *Intensity*: 2 min warm up, 10 min steady state at low/ moderate intensity *Duration:* ≅12 min	*Cardiovascular* RR interval, SDRR, LF power, HF power, LF:HF ratio, total power	Nil between-group differences in outcomes at rest	↓ mean RR interval, ↓ LF and HF power during exertion at both timepoints

Continued

Table 2 Continued

Study and study design	Population and comparator: mTBI Age in years±SD (% female) Time since injury *categorised* ψ, mean±SD Symptom status	Population and comparator: Healthy Age in years±SD (% female)	Intervention(s)	Outcome(s)	Between-group differences in objective measures: Pre-exertion (rest)	Between-group differences in objective measures: During/Post-exertion
Gall et al.[52] C-S, two-group, single intervention, two timepoints	N=14 with SRC, subgrouped: MT, n=9; and NMT, n=5 18±1 y, 0%♀ *Acute* T1: MT group, 6.7±1.8 d; NMT group, 2.0±0.5 d T 2: T1. + 5 d Asympt.	N=14 healthy 19±0 y, 0%♀	*Mode*: exercycle *Intensity:* 2 min warm up, 10 min steady state followed by 40 s high-intensity bouts to failure *Duration:* 15.7–19 min	*Cardiovascular* HR rest, HR max, HR recovery	Nil between-group differences in outcomes at rest	MT group had a ↑ HR during steady state and ↑ rise in HR over time and completed ↓ high-intensity bouts at both timepoints. NMT group had no differences from healthy
Haider et al.[41] C-S, two-group, two interventions, two timepoints	N=20 with SRC 16±1 y, 40%♀ *Acute* T1: 5.6±2.8 d T2: within 3 d of T1 Sympt., severity NR	N=20 healthy 16±1 y, 40%♀	T1: *mode:* treadmill—BCTT *Intensity:* 1 min at 5.2 km/hour (or 5.8 if height >178 cm) 0% incline, incline ↑ 1% every 1 min until 15%, then ↑ 0.6 km/hour every min until test termination / 21 min, cool down 2 min at 3.2 km/hour, 0% *Duration:* 7.5–18 min T2: *mode:* exercycle *Intensity:* ↑ every 2 min as per BCBT *Duration:* 8.5–32.2 min	*Cardiovascular* HR	Nil between-group differences in outcomes at rest	Significance tests not conducted. Figures showed trend towards ↓ HR through first five stages in mTBI and greater change in HR over time≈
Hinds et al.[50] C-S, two-group, single intervention, two timepoints	N=40 with SRC and non 15 y (range 12–18y) (42.5%♀) *Acute, subacute* T1: 5±1 d, Sympt., severity NR T2: 'at recovery', days NR, Asympt.	N=30 healthy 16 y (range 13–18y) (40%♀)	*Mode:* treadmill—BCTT *Intensity:* ↑ every 1 min as per BCTT, details NR *Duration:* NR	*Cardiovascular* HR	Symptomatic mTBI at T1 had a ↓ HR at the start of the test than healthy	Nil between-group differences in outcomes after exertion
Howell et al.[57] C-S, two-group, single intervention, two timepoints	N=40 with SRC 18±2 y, 55%♀ *Acute, subacute* T1: 12.5±4.7 d Sympt., severity NR T2: 73.3±9.5 d Symptom status NR	N=37 healthy 18±2 y, 62%♀	*Mode:* exercycle *Intensity:* ↑ every 2 min as per YMCA ramped protocol *Duration:* ≅15 min	*Cardiovascular/ cerebral autoregulation/ respiratory* HR, BP, $FETCO_2$, MCAv	Nil between-group differences in outcomes at rest	Moderate relationship between cerebrovascular responses to CO_2 at rest and cerebrovascular responses to exertion-induced changes in $FETCO_2$ in mTBI group, but weak and non-significant in controls

Continued

Table 2 Continued

Study and study design	Population and comparator: mTBI Age in years±SD (% female) Time since injury *categorised* ψ, mean±SD Symptom status	Population and comparator: Healthy Age in years±SD (% female)	Intervention(s)	Outcome(s)	Between-group differences in objective measures: Pre-exertion (rest)	Between-group differences in objective measures: During/Post-exertion
Kochick et al.[54] C-S, twogroup, single intervention, one timepoint	N=52 with SRC 16±2 y, 32.7%♀ *Subacute* 21±15 d Asympt.	N=52 healthy 17±2 y, 46%♀	*Mode:* EXiT Test *Aerobic component:* treadmill *Intensity:* 2 min warm up, then 10 min of a 30 s interval protocol alternating between fast (13.7 ♂, 11.3 ♀ km/hour) and slow (8.8 ♂, 7.2 ♀ km/hour) running *Duration:* ≅12 min *Dynamic component:* dynamic exercises and 5 COD tasks *Intensity:* paced at 25 bpm for circuit, other tasks maximum speed, 30 s rest in between. *Duration:* ≅18 min	*Cardiovascular* HR, BP	Nil between-group differences in outcomes at rest	mTBI group had ↓ postexertion DBP
La Fountaine et al.[26] C-S, two-group, single intervention, two timepoints	N=10 with SRC 19±1 y, 20%♀ Subgrouped: RTP <1/52 (n=6) and RTP >1/52 (n=4) *Acute* T1: 48 hours Symptom status NR T2: T1+1 week Symptom status NR	N=7 healthy 20±1 y, 14%♀	*Mode*: isometric hand grip *Intensity:* 30% MVC *Duration*: 3 min	*Cardiovascular* Finger arterial pulse wave morphology	↓ SysSlope in mTBI versus controls at rest at T1 and T2	↓ SysSlope (an indicator of stroke volume) in mTBI versus controls with exertion at both timepoints
Lawrence et al.[27] C-S, two-group, single intervention, two timepoints	N=46 with SRC 15±2 y, 43.5%♀ Subgrouped: fast recovery (FRG) and slow recovery (SRG) *Acute* T1: 5.0±2.4 d Sympt., PCSS 30.8±18.1 T2: 12 d FRG: asympt., SRG: sympt., severity NR	N=30 healthy 16±1 y, 27%♀	*Mode:* treadmill—BCTT *Intensity:* 1 min at 5.2 km/hour (or 5.8 if height >178 cm) and 0% incline, incline ↑ 1% every 1 min until maximum incline reached or patient cannot continue *Duration:* NR	*Visual* King-Devick (K-D) time[87] Abnormal saccades and smooth pursuit	Slower K-D completion in SRG at both timepoints	SRG did not improve K-D test time postexertion at both timepoints. Both healthy and FRG improved K-D time postexertion at both timepoints

Continued

Table 2 Continued

Study and study design	Population and comparator: mTBI Age in years±SD (% female) Time since injury *categorised* ψ, mean±SD Symptom status	Population and comparator: Healthy Age in years±SD (% female)	Intervention(s)	Outcome(s)	Between-group differences in objective measures: Pre-exertion (rest)	Between-group differences in objective measures: During/Post-exertion
Morissette et al.[28] C-S, twogroup, single intervention, one timepoint	N=34 with SRC and non-SRC 16±1 y, 44%♀ *Subacute* 44.8±26.8 d Sympt., PCSS 27.9±19.8	N=40 healthy 16±1 y, 67.5%♀	*Mode:* treadmill—BCTT *Intensity:* 1 min at 5.2 km/hour (or 5.8 if height >178 cm) and 0% incline, incline ↑ 1% every 1 min until reached 15%, then speed ↑ 0.6 km/hour every min until test termination / protocol completed (21 min) *Duration:* mean duration 8–24 min	*Cardiovascular/ Respiratory* HR, BP VO_2, VCO_2, V_E	Nil between-group differences in outcomes at rest	mTBI group had ↑ peak DBP, ↓ peak SBP, ↓ peak VO_2, VCO_2 and V_E
Musacchio et al.[47] C-S, two-group, single intervention, two timepoints	N=37 at T1, n=26 at T2, all non-SRC (78.4% MVA) 32±11 y, 45.9%♀ *Acute, subacute* T1: 7±3 d, n=25/37 Sympt., RPQ 20.0±15.5 T2: 30 d, n=13/26 Sympt., RPQ 17.0±15.2	N=24 healthy 39±11 y, 41.7%♀ *Acute, aubacute*	T1 & T2: *mode:* treadmill—modified BCTT *Intensity:* 1 min at 5.2 km/hour and 0% incline, incline ↑ every 1 min until 15 min, pause after 5 min for 2 min to collect saliva *Duration:* NR	*Saliva* Cortisol	↑ cortisol in mTBI group	Cortisol more reactive to exertion in individuals 1 week post-mTBI. ↓ total BCTT duration in mTBI group at T1, but not 2
Siedlecki et al.[51] C-S, twogroup, single intervention, one timepoint	N=5, mechanism NR 22±5 y, 20%♀ *Subacute—chronic* > 8 weeks but <12 months Sympt., PCSS 19.8±8.6	N=17 healthy 22.5±2 y, 63%♀	*Mode:* treadmill *Intensity:* 3 min at 'self-selected walking pace', then rest 2 min, then 3 min at an intensity 25% ↑ than previous 3 min. *Duration:* ≅6 min	*Respiratory* $FETCO_2$, RR	mTBI group had ↑ $FETCO_2$	mTBI group had ↑ $FETCO_2$ during exertion

Continued

Table 2 Continued

Study and study design	Population and comparator: mTBI Age in years±SD (% female) Time since injury *categorised* ψ, mean±SD Symptom status	Population and comparator: Healthy Age in years±SD (% female)	Intervention(s)	Outcome(s)	Between-group differences in objective measures: Pre-exertion (rest)	Between-group differences in objective measures: During/Post-exertion
Sinnott et al.[55] C-S, twogroup, single intervention, one timepoint	N=23 with SRC 16±2 y, 56.5%♀; n=13 age NR, 30.8%♀ for HRV outcomes *Subacute* 18.5±12.3 d Asympt.	N=23 healthy 16±2 y, 56.5%♀; n=13 age NR, 30.8%♀ for HRV outcomes	*Mode:* EXiT test *Aerobic component:* treadmill *Intensity:* 2 min warm up, then 10 min of a 30 s interval protocol alternating between fast (13.7 ♂, 11.3 ♀ km/hour) and slow (8.8 ♂, 7.2 ♀ km/hour) running. *Duration:* ≅12 min *Dynamic component:* dynamic circuit, ball toss jump and turn, and 5 COD tasks *Intensity:* paced at 25 beat/min for circuit, other tasks maximum speed, 30 s rest in between *Duration:* ≅18 min	*Cardiovascular* Full group: HR, BP, HRV subgroup: RR interval, SDNN, RMSSD, pRR50, total power, VLF, LF, HF, LFnu, HFnu, LF:HF ratio	Nil between-group differences in outcomes at rest	post-EXiT RMSSD and SDNN ↓ in mTBI group
Slobounov et al.[12] C-S, two-group, single intervention, one timepoint	N=17 with SRC 21±2 y, sex NR *Acute* 10±2 d Asympt.	N=17 healthy 21±2 y, sex NR	*Mode:* exercycle YMCA Stress Test *Intensity:* ×4 3 min stages at increasing resistance *Duration:* ≅15 min	*Imaging* fMRI	Functional interhemispheric connectivity ↓ in mTBI group	Functional interhemispheric connectivity ↓ in mTBI group after exertion, and during recovery
Woerhle et al.[56] C-S, two-group, single intervention, two timepoints	N=19 with SRC 15±2 y, 42%♀ *Acute, subacute* T1: 12±10 d, all sympt., PCSS 16±12 T2: days NR, n=7/19 sympt., PCSS 17.0±15.2	N=16 healthy 15±2 y, 37.5%♀	*Mode*: isometric hand grip *Intensity:* 30% MVC *Duration*: 30 s contraction, unclear if more than one trial	*Cardiovascular* HR, BP, RMSSD	Nil between-group differences in outcomes at rest at both timepoints	Change in HR ↓ in mTBI during IHGC at T1 only
Worts et al.[53] Randomised, twogroup, three-interventions, one timepoint	N=19 with SRC 16±1 y, 32%♀ *Acute* 4.5±1.3 d Sympt., PCSS 31.4±21.3	N=11 healthy 16±1 y, 36%♀	*Mode:* treadmill *Intensity:* 5 min warm up, then treadmill adjusted to achieve target HR (40% or 60% MHR) and maintain it for 20 min *Duration:* approximately 25 min No exercise group: seated rest 20 min	*Cardiovascular/Visual* BP, HR, RMSSD, LF%, HF%, LF:HF ratio, NPC, K-D time	MAP ↑ in 40 hours group at rest	MAP ↑ in mTBI 40 hours group during exertion RMSSD was ↓ in mTBI 60 hours group during exertion

Continued

Table 2 Continued

Study and study design	Population and comparator: mTBI Age in years±SD (% female) Time since injury *categorised* ψ, mean±SD Symptom status	Population and comparator: Healthy Age in years±SD (% female)	Intervention(s)	Outcome(s)	Between-group differences in objective measures Pre-exertion (rest)	Between-group differences in objective measures During/Post-exertion
Wright et al.[45] C-S, two-group, single intervention, one (healthy) or four (mTBI) timepoints	N=14 with SRC 19±1 y, 0%♀ *Acute, subacute* T1: ≤72 hours, Sympt., PCSS 24.8±20.3 T2: 14 d, Asympt. T3: 30 d, Asympt.	N=14 at pre-injury (baseline) 19±1 y, 0%♀	*Mode*: set 1: cyclical 5 s squat hold, 5 s rest in standing, repeat. Set 2: cyclical 10 s squat hold, 10 s rest in standing, repeat. *Intensity:* body weight *Duration:* ≅10 min (5 min per set)	*Cardiovascular/Cerebral autoregulation* HR, MAP, MCAv $PETCO_2$	Nil between-group differences in outcomes at rest	↑ diastolic gain and ↓ phase (response speed) in mTBI group at 0.10 Hz, at T1 and T2, but not different to controls at T3
Wright et al.[46] C-S, two-group, single intervention, one (healthy) or four (mTBI) timepoints	N=18 with SRC 19±2 y, 0%♀ *Acute, subacute* T1: ≤72 hours, Sympt., PCSS 25.1±19.0 T2: 14 d, Asympt. T3: 30 d, Asympt.	N=73 healthy pre-injury (baseline) 19±1 y, 0%♀	*Mode*: set 1: cyclical 5 s squat hold, 5 s rest in standing, repeat. Set 2: cyclical 10 s squat hold, 10 s rest in standing, repeat. *Intensity:* body weight, 90° knee angle *Duration:* ≅10 min (5 min per set)	*Cardiovascular/Cerebral autoregulation* HR, MAP, MCAv $PETCO_2$	Nil between-group differences in outcomes at rest	↓ phase (response speed) in mTBI group at 0.10 Hz, at T1 and T2, but not different to controls at T3

Age in years rounded to 0 dp; other results rounded to 1 dp when available; between-group differences are presented when statistically significant ($p<0.05$) with ↑ (significantly higher value in mTBI vs controls) and ↓ (significantly lower value in mTBI vs controls); ψ postinjury timepoints are defined as acute (≤14 days), subacute (15 days–3 months) and chronic (>3 months).[88]
♀, females; ♂, males; ≈, approximated from graphs presented in article (significance not reported); ≅, approximately equal to; ApEn, approximate entropy; Asympt., asymptomatic; BCBT, Buffalo Concussion Bike Test; BCTT, Buffalo Concussion Treadmill Test; BP, blood pressure; COD, change of direction; d, days; DBP, diastolic blood pressure; $FETCO_2$, fraction of end-tidal carbon dioxide; $FETO_2$, fraction of end-tidal oxygen; fMRI, functional MRI; HF, high frequency in ms^2; HR, heart rate; IHGC, isometric hand grip contraction; LF, low frequency in ms^2; MAP, mean arterial pressure; MCAv, middle cerebral artery blood flow velocity; MHR, maximum heart rate; MT, missed time; mTBI, mild traumatic brain injury; MVA, motor vehicle accident; MVC, maximum voluntary contraction; n, number; NMT, no missed time; NPC, near point convergence; NR, not reported; nu, normalised units; PCSS, Post-Concussion Symptom Scale Severity score; $PETCO_2$, partial pressure of end-tidal carbon dioxide; pRR50, % of RR intervals >50 ms; RMSSD, root mean square of the successive differences between normal heartbeats; RPQ, Rivermead Post-Concussion Questionnaire; RR, respiratory rate; RR interval, the period between two consecutive electrocardiographic R waves; RTP, return to play; SDNN, SD of normal to normal intervals; sec, second; SRC, sports-related concussion; Sympt, symptomatic; SysSlope, systolic slope of the arterial pressure wave, calculated from the rate of rise (change in pressure divided by change in time) of the systolic upstroke; TERC, transient exertion-related carotid; V_E, minute ventilation; VLF, very low frequency in ms^2; y, years.

Interventions

Interventions varied from traditional aerobic testing methods, for example, exercycle[12 25 48 52 57] and treadmill[24 27 28 41 47 49–51 53] protocols, to multidirectional exercises,[54 55] to repeated squat-stands,[44–46] to isolated hand-grip contractions.[16 26 56] Details of interventions are provided for the reader's reference in table 2.

Outcomes and testing timepoints

Of the 22 included studies, 10 studies measured the impact of exertion on outcome measures at a single testing session, 10 studies at two testing sessions (after injury, and then after recovery; between 5 days and 6 weeks apart), and two studies had participants return for three testing sessions (72 hours, 2 weeks and 1 month after injury). The outcome measures were categorised as CV such as heart rate (HR), blood pressure (BP) or heart rate variability (HRV, 17 studies); cerebral autoregulation such as cerebral blood flow velocity (CBFV, five studies); respiratory (four studies); visual (two studies); imaging (one study using functional MRI (fMRI)) and hormonal (one study of cortisol levels). For less well-known outcome measurements, definitions and their interpretation are provided in table 3 for the reader's reference.

Risk of bias in studies

Risk of bias scoring for the non-RCTs is presented in figure 2.[58] All papers except one[28] had an overall score of 'serious' or 'critical' risk of bias. The level of agreement between multiple risk of bias domains was moderate (kappa 0.59) for the two independent assessors before any consensus discussion. Domain-specific agreement and justification of assessment is provided in the online supplemental materials. Common areas of concern for bias included uncontrolled confounders, lack of detail around recruitment and how many participants were approached versus enrolled in the study, lack of blinding of outcome assessors, unreliable outcome measurement and a lack of prospective trial registration with preplanned analyses and a sample size calculation. Only one RCT was included in the review[53]; it was assessed using the ROB-2 tool[43] and was deemed to have 'some concerns' regarding the overall risk of bias. Additionally, only one trial registration was identified without a corresponding publication, so the risk of reporting bias was considered low.

Results of syntheses of individual studies

Cardiovascular

Seventeen papers explored CV outcomes across various postinjury timepoints. Before exertion, only four of 17 studies showed differences in CV outcomes between mTBI and healthy control participants, whereas during or after exertion, 16 of 17 papers reported significant between-group differences.

Six studies measured HRV. None of the papers found differences between healthy controls and participants with mTBI before exertion. However, with exertion, all six studies showed between-group differences, with decreased HRV in the mTBI groups. Specifically, the participants with mTBI demonstrated decreased SD of HR,[44 55 56] low frequency (LF) power,[25] high frequency (HF) power,[16] root mean square of consecutive RR interval differences (RMSSD)[53 55] and percentage of consecutive RR intervals that differ by >50 ms during recovery periods,[44] when compared with the healthy groups.

For measures of resting HR, 12 of 13 studies found no significant differences between mTBI and healthy before exertion,[12 16 26 28 45 46 49 50 52–56] while one small study (n=9) of females with subacute to chronic mTBI found higher resting HRs.[24] A comparison of changes in HR across studies requires a matched exertion stimulus. Five studies evaluated changes in HR in response to the Buffalo Concussion Treadmill Test (BCTT), but findings were conflicting. Hinds *et al*[50] found adolescents with symptomatic acute mTBI (n=40) had a significantly lower HR at the start of the BCTT, but no difference from controls in the rate HR increased with each minute of increasing exercise intensity. They noted no differences at a second testing timepoint when the mTBI group was asymptomatic. Haider *et al*[41] also studied adolescents with acute mTBI (n=20) and observed a trend towards decreased HR in participants with mTBI during the early stages of a BCTT. For less acute populations, Galea *et al*[49] studied individuals with subacute to chronic mTBI (n=73) and observed higher HRs during the first four stages of a BCTT, whereas Howell *et al*[57] (n=40 young adults with acute mTBI) and Morissette *et al*[28] (n=34 adolescents with subacute mTBI) found no between-group difference in the early stages of the BCTT. Likewise, there were inconsistent outcomes regarding overall HR changes in studies that used the BCTT—some reported no difference,[28 50 57] others observed smaller overall HR changes,[49] while one study reported larger HR changes[27] in the mTBI groups.

Eight studies explored BP changes, yielding mixed results. Four of the eight studies suggested no difference in BP between mTBI and healthy participants during lower limb cycling (n=40),[57] 30% maximum voluntary contraction (MVC) handgrip (n=19),[56] treadmill and dynamic circuit training (n=23)[55] and treadmill walking at 60% max HR (n=6).[53] Three studies found differences in systolic BP (SBP) and diastolic BP (DBP) between mTBI and healthy groups. Two of these studies[24 28] found that participants with mTBI had lower peak SBP and higher peak DBP than healthy participants during a progressive treadmill test; however, the exertion was not dose-matched between groups as the participants with mTBI stopped exercising earlier. A single study had a different result, showing lower DBP in mTBI (n=52), although their groups were not matched for age or activity level.[55] Two studies showed contrasting differences in measures of mean arterial pressure (MAP) during exertion; one study found small but statistically significant increases in MAP in a mTBI subgroup (n=9) during treadmill walking at 40% max HR,[53] while the other study

Table 3 Outcome measurement definitions and interpretation

Measure	Unit	Description	Interpretation
Time-domain HRV measures[67 89]			
RR interval	ms	Time interval between two consecutive RR waves on an ECG waveform	Shorter interval indicates higher heart rate
NN interval	ms	The interval between successive normal heartbeats	Shorter interval indicates higher heart rate
SDNN	ms	SD of NN intervals	Higher value indicates greater variability in heart rate
SDRR	ms	SD of RR intervals	Higher value indicates greater variability in heart rate
pNN50	%	Percentage of consecutive RR intervals that differ by >50 ms	Higher value can indicate greater sympathetic activity
RMSSD	ms	Root mean square of consecutive RR interval differences	Higher value can indicate greater parasympathetic activity
Frequency-domain HRV measures[67 89]			
LF peak	Hz	Peak frequency of the low-frequency band	Higher value can indicate greater sympathetic activity
LF power	ms^2	Absolute power of the low-frequency band	
LFnu	nu	Relative power of the low-frequency bands in normal units	
LF power	%	Relative power of the low-frequency band	
HF peak	Hz	Peak frequency of the high-frequency band	Higher value can indicate greater parasympathetic activity
HF power	ms^2	Absolute power of the high-frequency band	
HFnu	nu	Relative power of the high-frequency bands in normal units	
HF power	%	Relative power of the high-frequency band	
LF:HF	%	Ratio of LF-to-HF power	Higher value can indicate sympathetic dominance
Non-linear HRV measures[67 89]			
ApEn		Approximate entropy, a statistical measure of the regularity and unpredictability of a time series	Higher value can indicate a more complex and less predictable system, suggestive of greater variability and adaptability
Respiratory measures[90]			
$PETCO_2$	mm Hg	Partial pressure of CO_2 in the exhaled breath at the end of expiration, provides an indirect indicator of arterial CO_2 levels	Higher value can indicate inadequate removal of CO_2 through hypoventilation, or reduced cardiac output
$FETCO_2$	mm Hg	The concentration of CO_2 in the exhaled breath during normal tidal breathing, provides insight into overall CO_2 elimination	Higher value can indicate inadequate removal of CO_2 through hypoventilation, or reduced cardiac output
VO_2	mL/min	The rate at which oxygen is consumed for energy production	Higher value can indicate the body is able to absorb and use oxygen efficiently during exertion
VCO_2	mL/min	The rate at which CO_2 is produced as a by-product of aerobic metabolism	Higher value relative to VO_2 can suggest decreased exercise efficiency or cardiopulmonary limitations
VE	mL/min	Minute ventilation, total volume of air exhaled from the lungs per minute	Lower VE can indicate hypoventilation

Continued

Table 3 Continued

Measure	Unit	Description	Interpretation
RR		Respiratory rate	Normal is 12–20 breaths per minute at rest. Higher value can indicate hyperventilation, lower value can indicate hypoventilation
Cerebral autoregulation measures[60]			
MCAv	cm/s	Velocity of blood flow through middle cerebral artery	Higher value may indicate increased cerebral blood flow, that is, hyperperfusion
Oculomotor measures			
NPC	cm	Near point convergence refers to the closest point at which one can maintain single binocular vision while focussing on a target	Higher NPC (>8 cm) can indicate abnormalities in the ability to maintain convergence[71]
King-Devick	s	Rapid number naming test, requiring saccadic function and visual tracking	Longer time to complete can indicate oculomotor impairment[70]

HRV, heart rate variability.

(n=12) found smaller changes in MAP during the later phase of repeated 10 s squat holds.[44] Thus, overall, BP findings were mixed.

Cerebral autoregulation

Five papers examined cerebral autoregulation measures. None of these papers found significant differences between mTBI and healthy controls prior to exertion, but four of the five reported differences during exertion. Two studies examined how quickly the cerebrovascular system responded to changes in BP, by looking at the timing offset (latency) and gain (response magnitude) between BP oscillations and middle cerebral artery velocity oscillations during repeated squat-stands.[45 46] Compared with healthy participants, mTBI groups had more delayed cerebral autoregulation responses that were of increased magnitude, particularly during diastole, the heart's relaxation phase; these changes were observed in the first 14 days after injury but had normalised by 30 days.[45 46] One study found females (n=6) with subacute to chronic mTBI had higher CBFV than healthy participants at all workloads during a progressive treadmill test.[24] In contrast, another study found no differences in mean CBFV in participants (n=40) with acute to subacute mTBI.[57] The latter study observed a stronger relationship between $FETCO_2$ and CBFV during exertion in the mTBI group compared with controls.[57] Clark *et al*[48] (n=8) reported on the presence of a carotid bruit heard through auscultation during stationary cycling; the bruit occurred at a lower HR in mTBI than in healthy participants.

Respiratory

Four studies reported on the effect of exertion on respiratory measures. Three found significant differences between healthy and mTBI groups suggestive of hypoventilation,[24 28 51] while Howell *et al*[57] found no differences.

Visual

Two studies[27 53] investigated visual measures before and after exertion. Lawrence *et al*[27] reported differences between mTBI (n=46) and healthy (n=30) groups, where healthy participants improved their King-Devick (K-D) completion time after exertion and mTBI did not. Subgroup analysis indicated that this difference was restricted to the 'Slow Recovery Group' participants who were still symptomatic at the second testing timepoint a week later. The 'Fast Recovery Group' had no differences from healthy control participants. Worts *et al*[53] observed no significant difference between adolescents with acute mTBI (n=19) and those who were healthy (n=11) in their near point convergence (NPC) distance and K-D test times after exertion.

Imaging

Slobounov *et al*[12] used fMRI imaging and reported decreased functional interhemispheric connectivity in acute, asymptomatic young adults with SR-mTBI compared with healthy control participants before and after exertion.

Cortisol

One study examined salivary cortisol. Musacchio *et al*[47] showed increased cortisol levels before exertion, and increased cortisol reactivity to exertion in adults with non-sport-related mTBI compared with healthy participants. This reactivity to exertion was noted 1-week postinjury but had improved by 30 days.

DISCUSSION

This is the first systematic review to synthesise studies that have used physical exertion to highlight differences in objective physical tests between individuals with and without mTBI, with the intention of informing the development of objective post-exertion testing following

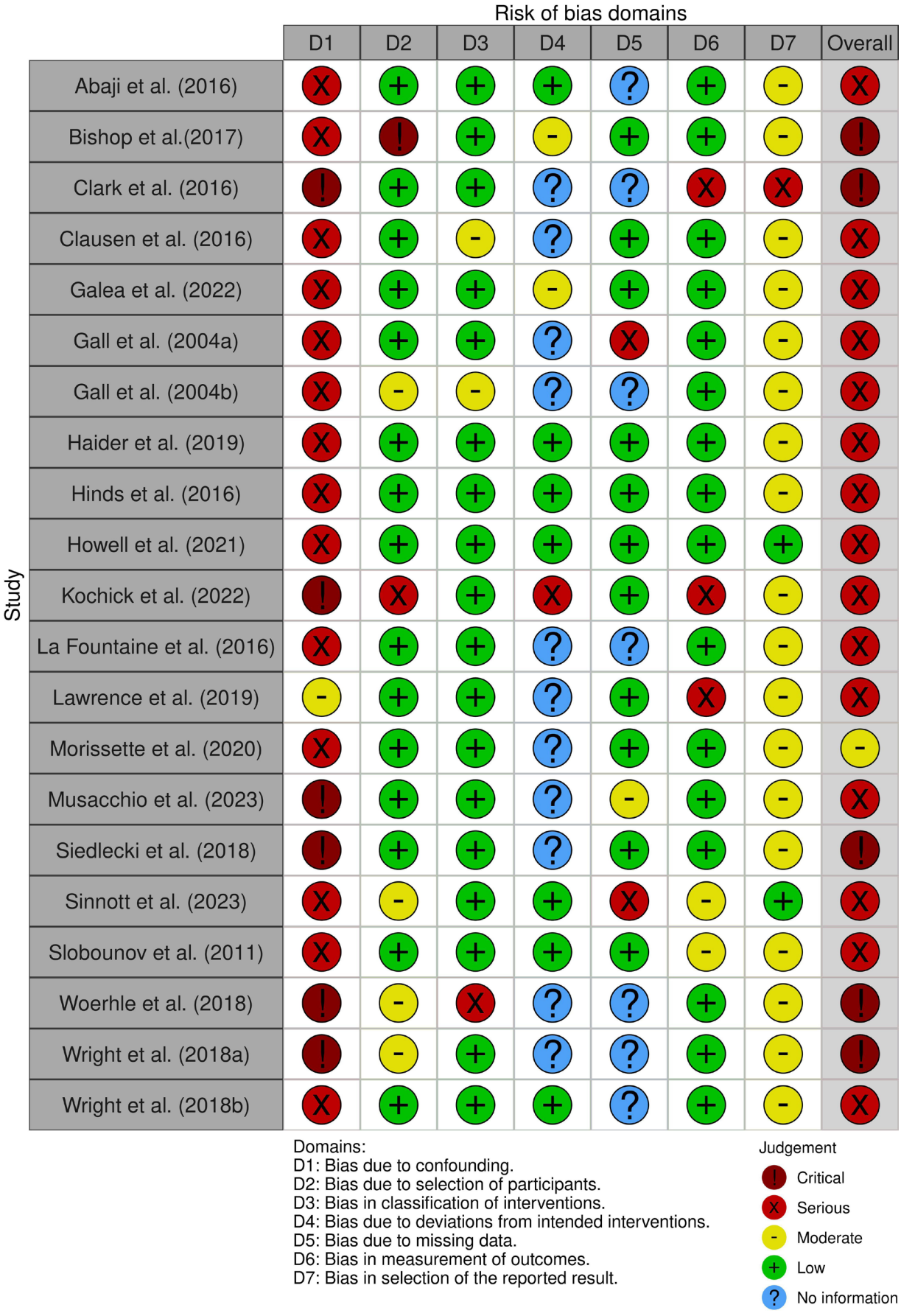

Figure 2 Risk of bias assessment results of non-randomised studies using the Risk Of Bias In Non-randomized Studies of Interventions tool.

mTBI. This field is receiving growing recognition due to the limitations of relying solely on symptom reporting.[20] The review findings affirm the potential for using objective exertion-based testing to enhance the detection of mTBI impairments. The findings hold significance for sporting populations, as six studies tested asymptomatic individuals with mTBI who were at the point of, or had already returned to play, yet found significant impairments during or after physical exertion.[12 16 25 45 46 55] The included studies were deemed to have a high risk of bias due to methodological flaws. While this limits the certainty of the findings, they still offer guidance for developing clinical testing protocols.

Effects of physical exertion on objective measurements

The review findings demonstrated that at rest, 8/22 (36%) studies detected impairments or differences in physiological responses between individuals with mTBI and healthy controls. In contrast, during or after exertion, 21/22 (96%) studies reported such differences. This suggests that physical exertion can 'sharpen' mTBI assessment tools, particularly outcomes associated with autonomic dysfunction.

Autonomic dysfunction or dysautonomia, where there is an imbalance of the sympathetic and parasympathetic nervous systems, is common following mTBI,[38] suggesting involvement of the central autonomic networks.[59] The healthy groups in this review showed dynamic autonomic responsiveness during exertion, with higher HRV,[16] BP change[46] and haemodynamic responses[26] relative to the task, and increased parasympathetic activity during recovery periods.[50] In contrast, in the mTBI groups, physical exertion induced either heightened or blunted sympathetic activity, suggesting dysautonomia following mTBI is more complex than the scales tipped in one direction. For example, many findings indicated sympathetic dominance, such as reduced RMSSD and RR intervals.[53 55] However, other findings indicated blunted sympathetic drive and/or reduced parasympathetic withdrawal. For example, Hinds *et al*[50] reported that participants with symptomatic mTBI had a decreased HR at the onset of exertion, which normalised following symptom resolution.

The impact of mTBI on cerebral autoregulation appears complex. Optimal cerebral blood flow (CBF) is achieved through the interplay of several mechanisms that prevent hypoperfusion or hyperperfusion.[60 61] The brain requires a steady level of O_2 to maintain optimal function and support the continuous energy demands of neural activity.[62] Areas of the brain with higher metabolic demands (indicated by increased CO_2 or decreased O_2 levels) receive increased blood flow through cerebral vasodilation.[63] Furthermore, cerebral blood vessels respond to increases in systemic pressure by vasoconstricting to prevent excessive blood flow to the brain.[60] These autoregulatory mechanisms are known to be impaired following severe TBI[64]; however, findings in this review of altered CBF during physical exertion[45 46] suggest they are also impacted following mTBI. Some studies in this review showed evidence of greater dysfunction in participants with delayed recovery or higher symptom burden.[26 27 49 52] This aligns with literature in more severe TBI, where the degree of autonomic-CV uncoupling correlates with the severity of neurological injury.[64]

mTBI also impacts on mechanisms that usually remove excessive circulating CO_2.[37] In healthy individuals, the expected response to physical exertion is an increase in ventilation to expire excess CO_2.[62] However, the mTBI groups of two studies[24 51] had higher end-tidal CO_2 than the healthy groups during walking tasks, with either no difference in respiratory rate[51] or hypoventilation.[24] Clausen *et al*[24] explored the link between this excessive CO_2 and CBF, given changes in CO_2 are a powerful mediator of CBF.[65] They found the increased CO_2 levels in participants with mTBI led to increased MCA blood flow velocity during exertion, which likely explained the participants' decreased exercise tolerance due to headache and dizziness.[24] This suggests that following mTBI, individuals may not respond adequately to rising CO_2 produced during exertion, leading to increased CBF and symptoms. This reinforces the need to test for this dysfunction prior to return to sport.

Only two studies[27 53] explored sensorimotor measures, both oculomotor tests and presented contrasting findings. Therefore, the effects of exertion on measures of sensorimotor performance require further exploration. This is particularly relevant in the context of sport, where any exertion-based deterioration in sensorimotor function could increase the risk of further injury.

Potential measurements for inclusion in post-exertion testing

The review findings have highlighted a range of objective measurements that appear to be sensitive to the effects of mTBI, particularly following physical exertion. While further research is needed, some of these measures could be considered for inclusion in post-exertion testing protocols in addition to cognitive testing.[31]

HR, whether at rest or measured as a change over time, does not consistently reflect autonomic impairments. In contrast, HRV appears to be a more useful measure in the assessment of mTBI.[66] All six of the included HRV studies reported decreased HRV in participants with mTBI, indicating some impairment in the normal dynamic responsiveness of HR to physical exertion.[67] Time-domain measures such as RMSSD are more robust to confounders than frequency domain, and tend to provide more stable and reliable assessments of HRV in short measurement periods (<5 min).[67] Of the six studies that used time-domain measures, five found decreased HRV during or after exertion in participants with mTBI,[25 44 53 55 56] and one (with a mean of 95 days post-injury) found no change.[16] Regarding the five studies that reported frequency-domain HRV parameters,[16 25 44 53 55] only two of the five studies found significant differences between mTBI and healthy participants; these were small, male-only, samples and found decreased HF power,[16 25]

decreased LF power[25] and increased LF:HF ratio during exertion.[16] This suggests that for short measurement periods, time-domain measures may be more useful, and relatively simple to collect with a chest strap HR monitor.

Respiration measurements showed increased $FETCO_2$,[51] and decreased minute ventilation,[24 28] indicating a trend towards reduced CO_2 sensitivity and hypoventilation with an impact on CBF.[24] Measures of gas exchange and cerebral autoregulation may be challenging to implement in clinical settings. However, these findings can enhance understanding of the mechanisms underlying exertion-induced exacerbation of mTBI impairments, and may also help identify specific exercises—such as those involving repeated postural change—that effectively challenge autonomic function and cerebral autoregulation responses.

Despite this review's focus on objective outcomes, it was noted that several studies found that self-reported perceived exertion during equivalent physical exertion was significantly higher in their mTBI groups.[28 50 54] Thus, clinicians should be aware that self-reporting of increased effort relative to the exertional demands could indicate mTBI impairment.

Autonomic parameters, such as the CV outcomes described in this review, have been the focus of much of the research to date.[37] However, research measuring self-reported symptoms has shown that physical exertion can exacerbate symptoms associated with sensorimotor dysfunction in athletes with mTBI who are asymptomatic prior to exertion.[68 69] While the only two studies that included sensorimotor measures provided contrasting results, the larger of these studies by Lawrence *et al*[27] (n=46) demonstrated that individuals who do not have improved K-D performance following exertion are at risk of prolonged mTBI recovery. The smaller study by Worts *et al*[53] (n=15) found no difference in K-D performance or NPC pre-exertion or post-exertion in participants with mTBI; however, results were limited by large interindividual variability in K-D test times. Therefore, pre-exertion or post-exertion K-D testing is encouraged, particularly given this visual tool[70] is simple and accessible in a clinical setting. NPC is commonly impacted by mTBI,[71] not affected by exertion in healthy athletes,[72 73] and also easily incorporated into testing and should therefore be considered.

Strengths and limitations: review process

This review was prospectively registered and involved a systematic search strategy. Two reviewers completed an independent screening process to identify the included studies and independent risk of bias assessment.

Subtle deficits in motor control are hypothesised to increase injury risk on return to sport.[74] However, no studies that directly assessed motor control performance were eligible for inclusion in the review, representing a limitation in addressing the study aim and in informing practice recommendations. The eligibility criterion excluding participants >12 months post-mTBI was intended to minimise confounding effects associated with extended time since injury, during which lifestyle changes and activity modifications may influence outcome measures in the presence of persisting symptoms.[4] This criterion unfortunately excluded several potentially relevant studies that included motor control measures[75–77] (see online supplemental file 1:E for excluded studies).

To be eligible for inclusion, studies were also required to measure outcomes at pre-exertion and post-exertion timepoints. Pretesting and post-testing enables within-subject comparisons, which can control for some of the individual variability in outcomes.[78] Multimodal exertional tests, where performance on the test itself is the outcome, such as the EXiT test[54 55] or POWAR-TOTAL,[79] were excluded due to a lack of pre-exertion, or baseline, comparison.

The age range for eligible studies was broad to capture the breadth of the research in this emerging field. However, this represents a confounding factor when interpreting the findings, due to the potential variability in physical and neural systems across the various cohorts.[80 81]

Strengths and limitations: included studies

The included studies had some limitations that impacted the certainty of the findings. Sample size is critical considering the large between-subject variability for many of the included variables, and only two studies discussed sample size calculation. The heterogeneity of methods, including variations in participant selection criteria, and outcome measures, reduced the ability to compare findings and draw definitive conclusions directly. As seen in table 2, there were differences in time since injury and symptom burden.

The wide range of exertion modes and intensities created challenges for comparison of physiological measures. However, in practice, clinicians are likely to vary the exertion exposure to align with the athlete's sport, such as using a sports-specific training session, or ensuring the athlete reaches a target HR intensity.[31] This review sought to understand the effects of physical exertion generally. As the body of evidence grows, it may be possible to explore whether specific types of exertion offer more value than others in various populations. In addition, in most cases, the exertion stimulus did not reflect the multidirectional, maximal effort demands of many sports, which limits its ecological validity in the context of RTP testing. Of the papers that did use a maximal effort[52] and/or multidirectional, dynamic component,[54 55] risk of bias was 'high'.

Most papers, except for Galea *et al*[49] and Sinnott *et al*,[55] did not account for participant exercise participation in the period postinjury for the mTBI groups. This makes it difficult to distinguish between deconditioning postinjury and pathophysiological exertion intolerance.[30] Future studies should collect acute and chronic workload data[82] and/or an index of cardiorespiratory fitness[83] to control for this confounder.

Future directions

More research is needed to explore clinical measures sensitive to differences in the effects of exertion in mTBI, and those associated with an increase in injury risk. Many of the included studies showed no differences beyond the subacute phase, or beyond clinical recovery. Future studies should focus on ensuring that these measures are sensitive enough to identify impairments that may contribute to the increased risk of subsequent injury. For example, balance impairments have been documented up to 2 years post-SR-mTBI,[15] and reduced dynamic balance has been linked with a higher risk of mTBI.[84] Physical exertion negatively impacts balance for up to 20 min in healthy athletes,[85] but its effect on athletes after mTBI remains to be seen, and future work in this area is encouraged. In the meantime, clinicians should consider incorporating physical objective measures both before and after exertion to help inform return-to-play decision-making.

CONCLUSION

Physical exertion appears to 'sharpen' objective assessment after mTBI and aid in highlighting impairments that are not detectable at rest. Synthesis of the reviewed papers indicated a blunting of the dynamic responsiveness of systems that maintain homeostasis under exertional challenge, and dysregulation of the autonomic nervous system appears to be a contributing factor. Preliminary evidence indicates that exertion may highlight dysfunction within the sensorimotor systems, as indicated by symptom provocation. Exertion-based changes in objective sensorimotor measures such as visual tracking, vestibular function or balance and gait are relatively unexplored in mTBI, yet impairment of these systems is likely associated with increased risk of injury. Thus, further investigation into the impact of physical exertion on visual, vestibular and motor performance tests is encouraged to better inform return-to-play expectations.

Contributors All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by KF, NT and SO. The first draft was written by KF, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. KF is the guarantor.

Funding This research is funded through a Health Research Council of New Zealand Fellowship awarded to KF.

Disclaimer The funding body has no input into the design of the research.

Competing interests KF receives a stipend from the Health Research Council of New Zealand. She also receives speaking and teaching fees associated with the topic of concussion. Further details are provided in the ICMJE Conflict of Interest form.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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