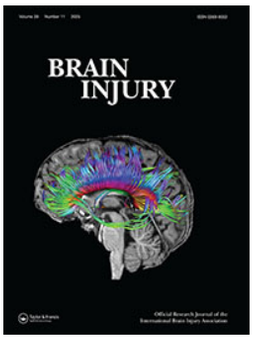

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The impact of concussion on the cardiac autonomic nervous system of adolescents: a systematic review

Keshen Pathmanathan[a], Ewan Maidment[b], and Simon M Walker[a]

[a]School of Biomedical Sciences, Faculty of Biological Sciences, University of Leeds, Leeds, UK; [b]Leeds Teaching Hospitals NHS Trust, Leeds, UK

ABSTRACT

Introduction: Concussions pose a serious threat to adolescents, with potential long-term effects. This systematic review considers whether cardiac autonomic nervous system dysfunction occurs post-concussion in adolescents.

Methods: Eight databases were searched on 30/5/24 using terms related to adolescents, concussion, and the cardiac autonomic nervous system. Included were full-text English articles comparing heart rate, blood pressure, or heart rate variability among adolescents with concussion history and controls. JBI critical appraisal tools assessed methodological quality. Meta-analysis was not performed due to inter-study methodological variations.

Results: Ten studies met the inclusion criteria. Two studies included participants with longer-term concussion histories. Eight studies involved exertion. Mixed results were found for all metrics. A greater percentage of results was significant during exertion; the lowest percentage was for resting heart rate variability (15%), whilst the highest was for heart rate under exertion (46.15%). Critical appraisal highlights methodological flaws. Studies often inappropriately manage confounding factors, and some selected controls inappropriately, such as using individuals with a history of concussion as controls.

Discussion: Evidence suggests possible cardiac autonomic dysfunction post-concussion, more apparent under exertion. Methodological limitations prevent definitive conclusions. Future research should better manage confounding factors to determine whether cardiac autonomic assessment can assist concussion diagnosis and management.

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Concussion; adolescents; cardiac autonomic nervous system; heart rate variability; blood pressure; mild traumatic brain injury; heart rate

Introduction

Concussion is a transient change in brain function, caused by biomechanical forces to the brain, which can lead to brief or prolonged symptoms (1). A study of adolescents in the United States found 24.6% self-reported individuals having been diagnosed with at least one concussion (2). Each concussion presents uniquely, often with a combination of physical, emotional, and cognitive symptoms. Physical symptoms can include headaches, dizziness, photophobia, phonophobia, nausea, and vomiting, whilst emotional symptoms can manifest as irritability, anxiety or depression. Cognitively, concussed individuals can feel confused and struggle with their concentration and memory, with sleep disturbances being another common feature (3). A link has been noted among retirees from contact, collision, and combat sports between experiencing multiple concussions and suffering from depression and cognitive impairment later in life (4), and repeated concussions may lead to neurodegenerative diseases, such as chronic traumatic encephalopathy (5). The growing evidence regarding the serious long-term consequences of repeated traumatic brain injuries highlights their profound and enduring impacts on mental and neurological health.

Several pathophysiological processes contribute toward an individual experiencing a concussion. The force to the brain leads to ionic fluctuations and the release of glutamate (6); this results in an energy crisis, which, alongside intracellular calcium influx, means the brain is susceptible to additional injuries (7). Inflammation, once thought to only be involved in more severe traumatic brain injuries, is also considered to play a key role (8). Concussions also lead to axonal damage, particularly in unmyelinated axons (9), and the impairment of neurotransmission (10).

A consequence of concussions may be autonomic nervous system (ANS) dysfunction. Part of the peripheral nervous system, the ANS is responsible for involuntary control of key physiological functions. These functions include cardiac parameters, such as heart rate (HR), heart rate variability (HRV), and blood pressure (BP), which are the metrics that are the focus of this review. The ANS also regulates a range of other bodily processes, including sweating, body temperature, and digestion (11). Consisting of sympathetic, parasympathetic, and enteric branches, the ANS is key for homeostasis. Whilst the sympathetic nervous system (SNS), commonly referred to as the 'fight or flight' system, readies the body to react to stress, the parasympathetic nervous system (PNS), often associated

CONTACT Simon M Walker s.m.walker@leeds.ac.uk School of Biomedical Sciences, Faculty of Biological Sciences, University of Leeds, Woodhouse Lane, Leeds LS2 9JT, UK

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with 'rest and digest,' is involved with relaxation and recovery. The enteric nervous system is primarily involved in gastrointestinal activities, and so it is the SNS and PNS that are fundamental to the cardiac ANS (12). The balance between these systems ensures cardiovascular stability, and disruption of this balance could have serious implications on cardiac parameters. Whilst the exact pathophysiology through which concussions can cause ANS dysfunction remains unknown, diffusion tensor imaging has found that the brainstem, which is the primary location for ANS control, was damaged post-concussion (13). Taking this into account, regaining ANS function has been suggested as an important component of recovering from a concussion (14). Cardiac parameters, such as HR, HRV, and BP, can be tested non-invasively, and relatively easily, and give an insight into autonomic function. All these parameters give an insight into the balance between the SNS and PNS, with HRV considered a particularly sensitive measure of autonomic balance (15). Thus, these parameters provide an invaluable insight into the impact of concussion on the ANS that can be easily used in clinical practice.

The current theories for how concussions lead to ANS dysfunction are split into direct and indirect mechanisms. Direct mechanisms may arise due to white matter disruption caused by axonal shearing and subsequent inflammation (16,17). Furthermore, damage to the central autonomic network, particularly the brainstem, thalamus, and basal ganglia, may predispose individuals to cardiac ANS dysfunction (18,19). Concussion induced altered cerebral blood flow to the insula, also part of the central autonomic network, may also play a role (20). Indirect mechanisms include concussions increasing the risk of other conditions, such as neurodegenerative disease, which can lead to ANS dysfunction (21). Additionally, post-concussion symptoms can lead to reduced physical activity. This can result in exercise intolerance, which is associated with ANS dysfunction (22). It is believed that these pathological changes could disrupt the balance between the PNS and SNS, resulting in ANS dysfunction.

Adolescence is a vital period for neurological development, and since adolescents' nervous systems differ from adults, they cannot be expected to be impacted identically by concussions (23). The hypothalamus, a key region in ANS regulation, primarily develops in early life, but it continues maturing into early adulthood. Key functions, including stress response and homeostasis, undergo significant refinement during puberty, driven by hormonal and neural changes (24). This period of plasticity may leave adolescents particularly vulnerable to concussions, but it could also mean they are able to recover ANS function more quickly. During this period of development, there are measurable changes in cardiac ANS function. HRV typically increases during adolescence, suggesting an increased parasympathetic tone. Both pubertal and post-pubertal HRV tend to be higher in males than females, potentially because of the impact of estrogen and progesterone on the ANS (25–27). Interestingly, a study on rats showed that younger rats recovered faster than adult rats from the post-concussion energy crisis (28); however, shorter recovery time does not necessarily mean less susceptibility to injury. Williams et al. (29) found that younger athletes are more likely to suffer prolonged symptoms following a concussion, which could impact their health and academic achievement (30). Furthermore, since adolescence is such a vital time for development, concussions during adolescence have the potential to seriously impact on individuals both psychosocially and academically (31,32). This risk highlights the importance of understanding the impact of concussions on adolescents specifically.

This is the first systematic review to investigate how concussion affects the cardiac ANS of adolescents. Previously, systematic reviews have looked at how concussion affects the cardiac ANS of adults (14,33), and individuals of a range of ages (34–36). The first of these systematic reviews was conducted by Blake et al. (34) in 2016, including both animal and human studies; they found limited evidence suggesting HR and HRV are affected post-concussion, both at rest and under exertion. However, they were unable to draw definitive conclusions due to poor study designs, inadequate sample sizes, inappropriate research settings, and differing outcome measures and analytical approaches. Charron et al. (33) focused on HRV and found that around half of the results were significantly different between concussed individuals and controls; like Blake et al. (34), they found limited evidence to suggest post-concussion autonomic dysfunction, with the studies' failure to control confounding factors having a major impact on the conclusions they could draw. Mercier et al. (14) similarly found that confounding factors were not adequately controlled and limited their conclusions. They did, however, find that whilst most studies did not find a difference between the HR, HRV, and BP of concussed individuals and controls at rest, under exertion differences in ANS function were noted across a wide variety of conditions, and timepoints. Pertab et al. (35) found that 33 of the 36 studies they included found some anomalies in the autonomic nervous system of concussed individuals; based on American Academy of Neurology criteria, they concluded that it is likely that concussion causes autonomic nervous system anomalies. The only meta-analysis was conducted by Wesolowski et al. (36); this meta-analysis of six studies, which included participants with an average age between 13 and 40, found that at rest the average time between consecutive normal heartbeats (MeanNN) and the standard deviation of the difference between successive heartbeats (SDNN) were significantly different between individuals with a history of concussion and controls. However, they did not find a significant difference between the resting root mean squared of successive intervals (RMSSD) of individuals with a history of concussion and controls. This meta-analysis is limited by the heterogeneity of the different studies, regarding age, gender, and time since concussion, which limits the strength of its findings.

In response to limitations identified in previous reviews, this systematic review has utilized a focused population of adolescent humans, limiting the impact of developmental heterogeneity as a confounding factor, and allowing for a more targeted exploration of this important group. To increase the reliability of the included evidence, only full-length articles published in peer-reviewed journals were considered.

Additionally, to allow for meaningful evaluation of concussion effects, this review only included studies that allowed for direct comparisons between concussed individuals and controls.

The primary aim of this review is to explore the literature on the impact of concussion on the cardiac ANS of adolescents. It seeks to identify patterns, inconsistencies, and limitations within the current literature, to help guide future research. The current gold-standard for diagnosing concussion is a structured history and examination (37); it is hoped that improved understanding of cardiac ANS changes could assist in the development of objective biomarkers, which may eventually be used to evaluate concussed adolescents both in the acute and recovery phases. This could not only assist in diagnosing concussions, but also alter how concussions are managed. Although the literature may not yet be sufficiently mature to support clinical use of such biomarkers, this review aims to highlight gaps in areas, such as study design, outcome measurement, and population definition. The fact that adolescents have not been specifically explored, and the failure of previous systematic reviews to reach a consensus, underscores the rationale behind conducting this systematic review.

Methods

This systematic review assesses the impact of concussion on the cardiac autonomic nervous system of adolescents. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were adhered to (38) and the review was registered with PROSPERO (registration number: CRD42024531447).

Ethical considerations

Ethics approval was not necessary as there was no primary data collection.

Information sources

The databases searched were CINAHL, Cochrane Central Register of Controlled Trials, Embase, PsycInfo, PubMed, Scopus, SportDiscus and Web of Science Core Collections.

Search strategy

As shown in Table 1, search terms were organized into three categories: adolescents, concussion, and cardiac ANS. Within each category, the Boolean operator OR joined search terms, and then the sets of words from each category are combined using AND. On 30/5/24, the terms were searched for within the title or abstract. The records that met the search criteria were exported into Endnote Online.

Eligibility criteria

Only full-text articles involving human participants published in English in peer-reviewed journals were considered for inclusion. Studies published over any time period were considered.

Table 1. Search terms separated by category.

Adolescent	Concussion	Cardiac ANS
Adolescen*	Concuss*	Autonomic nervous system
Youth	Brain injur*	ANS
Teen*	mTBI	Parasympathetic nervous system
Student	Head injur*	PNS
Pupil	Craniocerebral trauma	Sympathetic nervous system
Young	TBI	SNS
Juvenile		Heart rate
		HR
		HRV
		Pulse rate
		Blood pressure
		BP
		Syncope
		Vasovagal
		Tilt-table test
		Postural orthostatic tachycardia syndrome
		POTS
		Valsalva manoeuvre
		Valsalva maneuver
		Homeostasis
		Cerebral autoregulation
		Baroreflex
		Baroreceptor sensitivity
		BRS

Due to the limited volume of adolescent focused literature, a broad inclusion strategy was adopted. This involved including a range of physiological metrics. HRV was included since it is considered a highly sensitive measure of ANS function. HR and BP, whilst less sensitive markers of ANS function, are commonly measured in both research and clinical practice, and were therefore included to maximize the comprehensiveness, and clinical relevance of this review, whilst keeping it focused (39,40). In line with the broad eligibility criteria, the studies included assessed these metrics under diverse

Table 2. Inclusion criteria.

Population	Adolescents (aged between 10 and 19; if no age range is stated, the mean age ±2 standard deviations must fall between 10 and 19)
Exposure	Having had a concussion
Comparator	Adolescents (aged between 10 and 19; if no age range is stated, the mean age ±2 standard deviations must fall between 10 and 19) who are not acutely concussed
Outcomes	Measures of the cardiac ANS: HR, HRV, systolic blood pressure and diastolic blood pressure. Only one outcome measure is required to be in the article. Only statistical tests comparing concussed groups with controls were included; outcome numbers did not need to be explicitly stated, but the results of a statistical test in which the outcome is compared between control and concussion groups must be included, or the statistical test must be able to be conducted. If interaction analyses were conducted, only those analyses which incorporated 'group' as a factor were included
Study designs	Randomized controlled trials, cohort studies, cross-sectional studies, case-control studies, quasi-experimental studies

* is a truncation symbol used to capture word variants. For example, adolescen* retrieves results including adolescent, adolescents, and adolescence.

conditions and at different time points post-injury. Various study designs, including cross-sectional studies, were included. Further details of the inclusion criteria are shown in Table 2.

Study selection

Study selection began with the removal of duplicates. Following this, the titles and abstracts were screened to identify relevant articles. Finally, full-text articles were assessed for eligibility based on the stated inclusion criteria. The reference lists of all articles deemed eligible for the systematic review were searched to identify additional relevant articles. Two reviewers independently conducted this process. Any discrepancies were resolved through discussion between the two reviewers, and if this did not solve the dispute a third reviewer was consulted.

Contacting authors

For clarifications or additional information that would be useful for this systematic review, study authors were emailed up to two times.

Data extraction

Information regarding study design, participants' characteristics, concussion diagnosis, and timing, relevant cardiac ANS findings, and the test conditions were extracted from Excel. For data only available in graphs, authors were contacted to request the numerical data. If the numerical data were not provided, ImageJ was used to extract the data; similar tools to extract data from graphs have been found to be valid and reliable (41).

Quality assessment

JBI critical appraisal tools were used to assess the quality of each study, with specific checklists tailored to each study design. Although the type and number of questions varied between study designs, all the checklists assessed key aspects of study quality. This included assessing whether the study effectively managed confounding factors, reliably measured outcomes, and appropriately used statistical testing (54,55). For each of the questions, the possible answers were 'Yes,' 'Unknown' or 'No'; in all cases, the answer 'Yes' indicated good study quality. The answer 'Yes' was therefore considered a positive answer. Two reviewers independently reviewed the quality assessments. Any discrepancies were resolved through discussion between the two reviewers, and if this did not solve the dispute a third reviewer was consulted.

Data synthesis

Inconsistencies in study methodology, demographics, and post-concussion timing meant meta-analysis was not considered suitable. When possible, the percentage of male participants and the number of previous concussions in each study were calculated to aid comparisons. Some studies lacked statistical comparisons between concussion and control groups for certain metrics. In these cases, when the raw data were made available by the authors, normality testing was conducted using the Shapiro–Wilk test. If the raw data were not made available, normality was assessed by reading through the article. When data were presented as integer numbers in tables, ImageJ was used to extract data with greater precision prior to statistical testing. If the controls were assessed only once, each visit of the concussion group was compared to the one visit of controls. For normally distributed data, unpaired t-tests were conducted using the mean, standard deviation and sample size. For non-normally distributed data, statistical tests could only take place when the raw data were available; in this case, the Kruskal–Wallis test was used to compare the concussed individuals with controls. The Kruskal–Wallis test was conducted on data from Haider et al. (2019), whilst all other statistical tests conducted were unpaired t-tests. Statistical significance was set at $p \leq 0.05$. The percentage of significant results for each metric under exertion and at rest was calculated.

Results

Search results

The database search yielded 2521 results. Duplicate removal excluded 1097 records. Following the title and abstract screening, 66 records remained for full-text evaluation. Of the remaining records, 56 were excluded. The most common reason for exclusion was because the record was of the wrong type, with many being conference abstracts. There were 10 records that matched the inclusion criteria and searches through their references yielded no additional studies (Figure 1).

Study characteristics

Further details of the study characteristics and findings are displayed in Table 3. The included studies were three prospective cohort studies (43–45), five case–control studies (46–50), one quasi-experimental study (51) and one randomized controlled trial (RCT) (52). In eight of the studies, the participants were a mixture of males and females, whilst Harrison et al. (47) and Memmini et al. (48) utilized an entirely male sample. The participants tended to be physically active, but no studies gave a quantitative measure of activity level. The most common method to allocate individuals to the concussion group was diagnosis by a physician, although Harrison et al. (47) and Memmini et al. (48) allocated individuals to the concussion group by checking their medical records and a neuropsychologist's assessment. Relevant exclusion criteria should include medication and comorbidities affecting the ANS, and previously undiagnosed concussions. Only Memmini et al. (48) clearly excluded participants on all three criteria. Harrison et al. (47) excluded for comorbidities and undiagnosed concussions; while medication use was not a clearly specified exclusion criterion, no participants took medications, so the study effectively controlled for all three factors. Contrastingly, Balestrini et al. (43), Moir et al. (45),

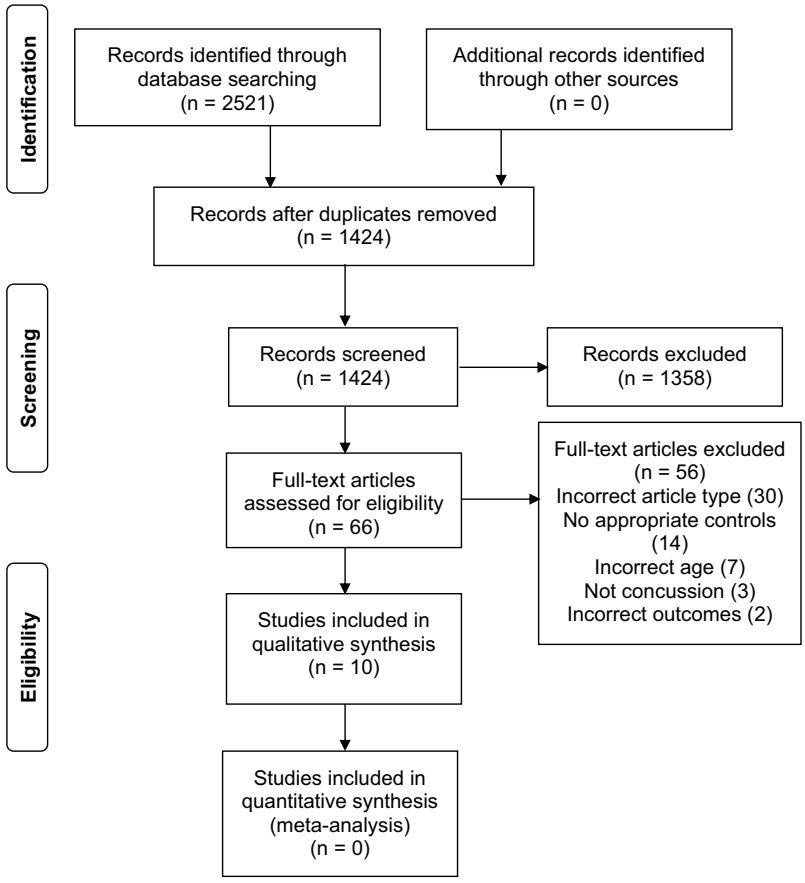

Figure 1. PRISMA flow diagram showing the study selection process (42).

Woehrle et al. (50) and Worts et al. (52) did not control for any of these factors in their study design. Harrison et al. (47), Memmini et al. (48) and Worts et al. (52) used controls without a concussion history; most of the other studies excluded controls whose concussion had been recent (the definition of recent varied from the previous 6 months to the previous year), but Pannicia et al. (49) and Woehrle et al. (50) did not specify their criteria for excluding controls with a previous concussion. Most of the studies focused on individuals who had been concussed recently, but Harrison et al. (47) and Memmini et al. (48) included those with a longer-term history of concussion, with Memmini et al. (48) excluding those whose concussion had occurred in the last 6 months. Eight studies assessed the ANS under exertion (44–48,50–52); details of the different stressors used are in Table 4. The different metrics assessed are detailed in Table 5.

Percentage of significant results

For this overview, HRV metrics were pooled together because there were a limited number of results for each individual metric. For every metric group, a higher proportion of results were significant under exertion than at rest. Across all studies, HRV at rest had the smallest percentage of significant results (15%), whilst exertion HR had the highest percentage of significant results (46.15%) (Figure 2).

Resting blood pressure

Full details are available in Supplementary Table S1. Both Balestrini et al. (43) and Haider et al. (44) found a decrease in the diastolic blood pressure (DBP) of concussed individuals over time, but the direction of this difference relative to controls varied between the studies. Balestrini et al. (43) found concussed individuals had significantly higher DBP at their first visit (15 ± 2 days post-concussion), but that this difference was no longer present at the final visit (5 weeks later or following medical clearance). Haider et al. (44) found no difference whilst the concussed individuals were symptomatic (5.98 ± 3.0 days post-concussion), but found that at the concussed group's final visit, after clinical recovery (46.27 ± 41.9 days post-concussion), DBP was significantly lower than controls in both the supine and standing positions.

Haider et al. (44) also found the same pattern with standing systolic blood pressure (SBP), which was significantly lower than controls after clinical recovery but was not significantly different whilst symptomatic; supine SBP, however, was not significantly different at either visit. Balestrini et al. (43) only

Table 3. Study characteristics and findings.

Author (year)	Sample description, age ± SD, (% male)	*Concussion diagnosis*, relevant exclusion criteria	Concussion group time since concussion	Conditions	Significant findings	Non-significant findings
Balestrini (2021)	n = 65 recently concussed recreational and competitive athletes, 15 ± 1 years (40.00%*); n = 54 age/activity matched controls from local sporting organizations with either no concussion Hx or concussion Hx but no concussion symptoms in previous six months, 14 ± 1 years, (53.70%*)	*Physician diagnosis*, no additional exclusion criteria	15 ± 2 days	Rest	1) DBP (concussed higher) 2) Supine, standing and seated HR (concussed higher) 3) RMSSD (group ×sex ×posture), seated female RMSSD (concussed lower)	1) SBP 2) Supine, standing and seated HR (group × sex and group × posture × sex) 3) RMSSD (group)
			5 weeks after first test, or after medical clearance	Rest	Seated HR (concussed higher)^	DBP^
Haider (2019)	n = 20 sport related concussion, 15.9 ± 1.1 years, (60.00%*); n = 20 age/sex matched athletic controls who participated in at least 1 organized sport with no concussion Hx in the past year, 15.9 ± 1.1 years, (60.00%)*	*Physician diagnosis*, excluded for focal neurological deficit, HR affecting meds, significant orthopedic injury and being unwilling to exercise	5.60 ± 2.84 days	Rest	HR (concussed lower)	
			5.60 ± 2.84 days	BCTT	HR after 2 minutes^, maximum HR^, difference between resting and maximum HR^ (concussed lower)	
			Within 3 days of first visit	Rest		HR
			Within 3 days of first visit	BCBT	HR after 2 minutes^, maximum HR^, difference between resting and maximum HR^ (concussed lower)	
Haider (2021)	n = 297 recently concussed mostly athletes without prolonged recovery, 15.04 ± 1.7 years, (58.6%); n = 214 height/weight matched and athletic controls with no concussion Hx in the past year, 14.96 ± 1.5 years, (58.4%)	*Physician diagnosis*, excluded for focal neurological deficit, HR affecting meds, Hx of moderate/severe TBI, cervical spine/ autoimmune/cardiac Hx	While symptomatic, 5.98 ± 3 days	Rest	Supine and standing HR (concussed lower)	Supine and standing SBP and DBP
			While symptomatic, 5.98 ± 3 days	1-minute supine-to-standing Orthostatic Hypotension Test	1) Mean change HR (concussed lower)	Mean change SBP and DBP
			After clinical recovery, 46.27 ± 41.9 days	Rest	1) Standing SBP, standing and supine DBP (concussed lower) 2) Standing HR (concussed lower)	1) Supine SBP 2) Supine HR
			After clinical recovery, 46.27 ± 41.9 days	1-minute supine-to-standing Orthostatic Hypotension Test	1) Mean change SBP (SBP of concussed increased after standing, controls decreased), mean change DBP (less decrease after standing in concussed) 2) Mean change HR (concussed lower)	

(*Continued*)

Table 3. (Continued).

Author (year)	Sample description, age ± SD, (% male)	*Concussion diagnosis*, relevant exclusion criteria	Concussion group time since concussion	Conditions	Significant findings	Non-significant findings
Harrison (2022)	n = 16 Midget-AAA ice hockey players with Hx of concussion, 16.06 ± 0.73 years, (100%); n = 18 age/BMI/sport/sex matched Midget-AAA ice hockey player controls with no concussion Hx, 15.98 ± 0.62 years, (100%)	*Medical record review and neuropsychologist assessment*, excluded for undiagnosed concussion and neurological/psychiatric/learning/cardiac ANS affecting conditions	While asymptomatic, 24.13 ± 17.7 months	Rest		1) HR (group and group × time) 2) RMSSD, SDNN, mean NN interval
			While asymptomatic, 24.13 ± 17.7 months	Cognitive task at rest	RMSSD, SDNN (concussed higher)	1) Mean HR 2) RMSSD (group × time), SDNN (group × time), Mean NN interval (group and group × time)
			While asymptomatic, 24.13 ± 17.7 months	Cognitive task after submaximal aerobic exercise	RMSSD, SDNN (concussed higher)	1) Mean HR 2) RMSSD (group × time), SDNN (group × time), Mean NN interval (group and group × time)
Memmini (2021)	n = 15 Midget-AAA ice hockey players with Hx of concussion more than 6 months ago, 16 ± 1 years, (100%); n = 18 age/height/mass/BMI matched Midget-AAA ice hockey player controls with no concussion Hx, 16 ± 1 years, (100%)	*Medical record review and neuropsychologist assessment*, excluded for undiagnosed concussion, medications and neurological/psychiatric/learning/cardiac ANS affecting conditions	While asymptomatic, 25.1 ± 17.6 months	Rest		1) Seated HR [controls vs Hx concussion and controls vs Hx one concussion vs Hx two plus concussions] 2) Seated RMSSD, seated SDNN
			While asymptomatic, 25.1 ± 17.6 months	Submaximal aerobic exercise	1) HR during recovery [controls vs Hx concussion] (Hx concussion higher), HR during recovery [controls vs Hx one concussion] (Hx one concussion higher), HR during recovery [controls vs Hx two plus concussions] (Hx two plus concussions higher) 2) SDNN recovery (group × time) [controls vs Hx concussion and controls vs Hx one concussion vs Hx two plus concussions]	1) HR recovery (group ×time) 2) RMSSD recovery (group and group × time), SDNN recovery (group)
Moir (2018)	n = 19 recently concussed, 15 ± 2 years, (31.58%*); n = 18 controls from athletic organizations with no concussion Hx in the past year, 15 ± 2 years, (50.00%*)	*Physician diagnosis*, no additional exclusion criteria	38 ± 61 days	At rest		1) Supine SBP and DBP 2) Supine HR
			38 ± 61 days	Sit-to-stand protocol		Mean change HR
Morissette (2020)	n = 34 sport-related concussion, 16.4 ± 1.2 years, (55.88%*); n = 40 physically active controls, 15.9 ± 0.8 years, (32.50%*)	*Physician diagnosis*, excluded for moderate/severe TBI Hx, abnormal neuroimaging, pregnancy, contraindications to exercise	While symptomatic, 44.8 ± 26.8 days	At rest		1) Male, female and total seated SBP and DBP 2) Male, female and total seated HR
			While symptomatic, 44.8 ± 26.8 days	Buffalo Concussion Treadmill Test	1) Total peak SBP (concussed lower) and total peak DBP (concussed higher) 2) Male peak HR (concussed lower)	1) Male and female peak SBP and DBP 2) Change in HR, female peak HR

(*Continued*)

Table 3. (Continued).

Author (year)	Sample description, age ± SD, (% male)	*Concussion diagnosis*, relevant exclusion criteria	Concussion group time since concussion	Conditions	Significant findings	Non-significant findings
Paniccia (2018)	n = 29 recently concussed athletes from local sport community organizations, 15 ± 1.48 years, 28% male n = 15 age/sex matched healthy controls from local sport community organizations, 15 ± 1.66 years, 27% male	*Physician diagnosis*, excluded for neurological/developmental/cardiac conditions or if symptomatic from previous concussion	1) While symptomatic, weekly assessment 2) Assessment 1,3 and 6 months after symptom resolution		HF (concussed higher)	RMSSD, SDNN, pNN50, HFnu
Woehrle (2020)	n = 19 recent sport-related concussion, 15 ± 2 years, (57.89%*); n = 16 healthy controls from community sports teams, 15 ± 2 years, (62.50%*)	*Clinical diagnosis*, no additional exclusion criteria	12 ± 10 days	At rest		1) Resting SBP and DBP 2) HR 3) RMSSD^
			12 ± 10 days	Isometric handgrip contraction	Change in HR (concussed lower)	1) SBP and DBP (group and group × time) 2) RMSSD (group and group ×time)
			At clinical discharge	Isometric handgrip contraction		Change in HR
Worts (2022)	n = 19 student athletes with recent sport-related concussion, 15.8 ± 1.4 years, (68%) n = 11 age/sex matched student-athlete controls from local high school sports teams with no concussion Hx, 16.3 ± 0.9 years, (64%)	*Sports medicine clinic diagnosis*, excluded for contraindications to exercise including severe symptoms	4.5 ± 1.3 days	Treadmill at 40% age-predicted maximum heart rate		RMSSD (group and group × time), LF:HF (group and group × time), LFnu (group and group × time)
			4.5 ± 1.3 days	Treadmill at 60% age-predicted maximum heart rate	RMSSD	RMSSD (group × time), LF:HF (group and group × time), LFnu (group and group × time)
			4.5 ± 1.3 days	Supine-to-seated transition		RMSSD (group and group × position), LF:HF (group and group × position), LFnu (group and group × position)

Data is presented as mean ± standard deviation.
Significance level set at $p \leq 0.05$.
*Calculated using information from study.
^This statistical test was conducted as part of this systematic review.
Abbreviations: BCTT = Buffalo Concussion Treadmill Test, BCBT = Buffalo Concussion Bike Test, DBP = diastolic blood pressure, Hx = history, HF = high frequency power, HFnu = high frequency normalized units, HR = heart rate, meds = medications, pNN50 = percentage of successive NNs that differ by more than 50 ms, RMSSD = root mean square of successive RR interval differences, SBP = systolic blood pressure, SD = standard deviation, SDNN = standard deviation of NN intervals, TBI = traumatic brain injury.

Table 4. Stressors used in each study.

First author (year)	Stressor	Stressor description
Haider (2019)	Buffalo Concussion Treadmill Test	Incremental exertion
	Buffalo Concussion Bike Test	Incremental exertion
Haider (2021)	1-minute supine-to-standing Orthostatic Hypotension Test	Moving from supine to standing
Harrison (2022)	Cognitive task at rest	Abstract cognitive challenge
	Cognitive task after submaximal aerobic exercise	Steady-state exertion followed by an abstract cognitive challenge
Memmini (2021)	Submaximal aerobic exercise	Steady state-exertion
Moir (2018)	Sit-to-stand protocol	Moving from sitting to standing
Morissette (2020)	Buffalo Concussion Treadmill Test	Incremental exertion
Woehrle (2020)	Isometric handgrip contraction	For 30 seconds, participants held an isometric handgrip contraction at 30% of their peak voluntary contraction strength.
Worts (2022)	Treadmill at 40% age-predicted maximum heart rate	Steady-state exertion
	Treadmill at 60% age-predicted maximum heart rate	Steady-state exertion
	Supine-to-seated transition	Participants were supine for 15-minutes, before moving to being seated.

Table 5. Metrics assessed in the studies.

Metric	Unit	Description (53)
Diastolic blood pressure	Millimeters of mercury (mm Hg)	The pressure in arteries during diastole
Systolic blood pressure	Millimeters of mercury (mm Hg)	The pressure in arteries during systole
Heart rate	Beats per minute (bpm)	Number of heartbeats per minute
Mean NN intervals	Milliseconds (ms)	Average time between adjacent QRS complexes caused by sinus node depolarization
HF	Milliseconds squared (ms^2)	Power in the high frequency range (0.15–0.4 Hz)
HFnu	Normalized units (nu)	Power in the high frequency range divided by the difference between total power and very low frequency (≤0.04 Hz), multiplied by 100
LF:HF	Not applicable	Ratio of low frequency power to high frequency power
LFnu	Normalized units (nu)	Power in the low frequency range divided by the difference between total power and very low frequency (≤0.04 Hz), multiplied by 100
pNN50	Percentage (%)	Percentage of consecutive RR intervals that differ by over 50 ms
SDNN	Milliseconds (ms)	Standard deviation of NN intervals
RMSSD	Milliseconds (ms)	Root mean square of successive differences between adjacent RR intervals

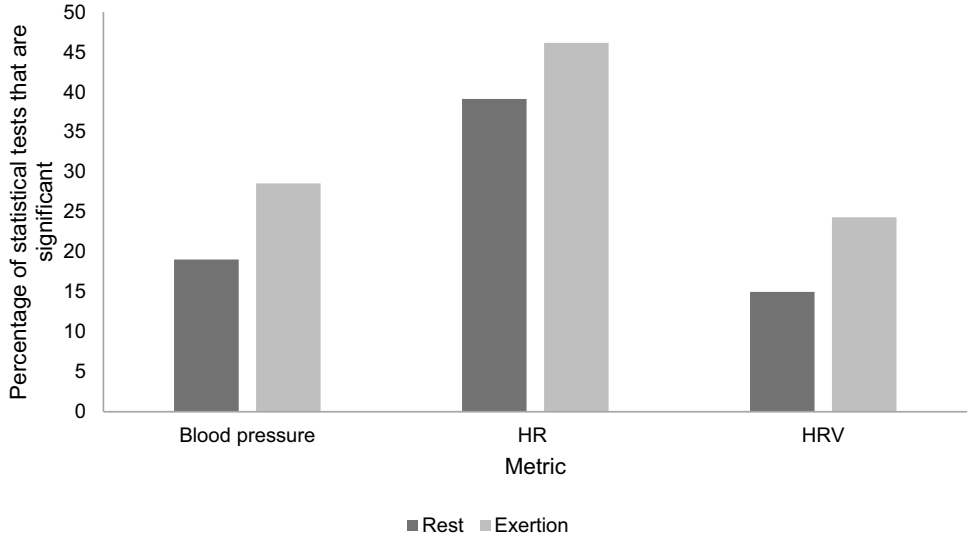

Figure 2. Percentage of results that are significant for each metric at rest and under exertion.

assessed SBP at the first visit, but found no difference between concussed individuals and controls. The remaining studies found no significant differences in resting blood pressure between concussed individuals and controls (45,50,51).

Exertional blood pressure

Full details are available in Supplementary Table S2. Haider et al. (44) and Morissette et al. (51) both found significant differences between the blood pressure of the concussion group and controls. Haider et al. (44) found at the final visit, after standing DBP decreased significantly less in concussed individuals than controls, and that SBP was significantly different from controls. However, like for resting BP, they found no significant differences at the first visit. Morrissette et al. (51) found that during the Buffalo Concussion Treadmill Test (BCTT) the peak SBP was significantly lower in concussed individuals than controls, whilst peak DBP was significantly higher in concussed individuals than controls. When participants were separated into their respective sexes, there were no significant differences in peak DBP or SBP between the concussion group and controls for either males or females. Woehrle et al. (50) used a different stressor to Haider et al. (44) and Morissette et al. (51), specifically, a 30-s isometric handgrip contraction at 30% maximum voluntary contraction. They found no significant difference in either SBP or DBP between concussed individuals and controls, in terms of both group and group × time.

Resting HR

Full details are available in Supplementary Tables S3 and S4. Three studies found significant differences in resting HR early post-concussion. Balestrini et al. (43) found that at the first visit of concussed individuals, HR was significantly higher in the concussion group than controls in all postures. Seated HR was compared at the final visit, and this significant difference remained. No significant interactions were found for group × sex or group × posture × sex. Contrastingly, both Haider et al. (44) and Haider et al. (46) found the HR of concussed individuals was significantly lower than controls at the first visit (5.98 ± 3.0 days post-concussion and 5.60 ± 2.84 days post-concussion respectively). Haider et al. (46) found this difference was no longer present at the final visit (in the 3 days after the initial visit), whilst Haider et al. (44) found that the difference remained in the standing position but had resolved when supine. The remaining studies found no significant difference in HR between the control and concussion groups (45,47,48,50,51).

Exertional HR

Full details are available in Supplementary Tables S5 and S6. Two studies found significant differences in the HR of the concussion group and controls when the BCTT and Buffalo Concussion Bike Test (BCBT) were used as stressors (46,51). During both the BCTT and BCBT, Haider et al. (46) found the concussion group had significantly lower HR than controls after 2 min, reached a significantly lower peak HR and had a significantly smaller difference between resting and maximum HR. Morissette et al. (51), who also used the BCTT, found the peak HR of concussed males was significantly lower than controls, but they did not find any significant difference between the control and concussion groups in the change in HR after 1, 2, 3, 4, or 5 min, or in the peak HR achieved of the female group or the combined sex group. Memmini et al. (48) similarly used an aerobic stressor, and they found a group main effect for post-aerobic exercise HR, but no significant group × time interaction; this was the case when comparing controls with the concussed group as a whole and when controls, individuals with a history of one concussion and individuals with a history of two or more concussions were compared. Exertion protocols that challenged participants with standing found varied results; whilst Haider et al. (44) observed that the concussion group had a significantly lower change in HR than controls following a supine-to-standing test at both their first visit and last visit, Moir et al. (45) found no significant difference in the change in HR following a sit-to-stand protocol. During a 30-s isometric handgrip contraction at 30% maximum voluntary contraction, there was a significantly lower change in HR in concussed adolescents than controls at the concussion group's first visit (12 ± 10 days post-concussion), but this was no longer the case at the second session, which took place a week later (50). No significant difference in the mean HR of concussed individuals and controls was observed during a cognitive task, whether this task was completed at rest or following submaximal aerobic exercise (47).

Rest HRV

Full details are available in Supplementary Tables S7 and S8. Balestrini et al. (43) did not find a main effect of group on root mean square of successive RR interval differences (RMSSD), but they did find a significant group × sex × posture interaction. Specifically, they found that RMSSD of seated females was significantly lower in concussed individuals than controls. Furthermore, Paniccia et al. (49) found that concussed individuals had significantly higher high-frequency power (HF) than controls but did not find any significant differences between concussed individuals and controls for percentage of successive NNs that differ by more than 50 ms (pNN50) or high frequency normalized units. The other studies that looked at RMSSD at rest found no significant difference between concussed individuals and controls (47–50), whilst no studies found significant differences when comparing concussed individuals and controls regarding resting standard deviation of NN intervals (SDNN) (47–49). Only Harrison et al. looked at mean NN intervals, and they found no significant difference between the concussion group and controls (47).

Exertional HRV

Full details are available in Supplementary Table S9 and S10. Harrison et al. (47) and Worts et al. (52) both had significant findings regarding RMSSD. Harrison et al. (47) found that RMSSD was significantly higher in the concussion group than controls during a cognitive task completed both at rest

Table 6. Critical appraisal of prospective cohort studies using the JBI critical appraisal tool (55).

Author (year)	1. Were the two groups similar and recruited from the same population?	2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	3. Was the exposure measured in a valid and reliable way?	4. Were confounding factors identified?	5. Were strategies to deal with confounding factors stated?	6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	7. Were the outcomes measured in a valid and reliable way?	8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	10. Were strategies to address incomplete follow up utilized?	11. Was appropriate statistical analysis used?	Percentage of questions answered yes
Balestrini (2021)	Y	Y	Y	N	N	U	Y	Y	U	U	Y	55
Haider (2021)	Y	Y	Y	N	N	U	Y	Y	N	N	Y	55
Moir (2018)	N	Y	Y	N	N	U	Y	Y	N	N	Y	45

Y Yes U Unknown N No

Y - Yes; U - Unknown; N - No.

Table 7. Critical appraisal of case–control studies using the JBI critical appraisal tool (55).

Author (year)	1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	2. Were cases and controls matched appropriately?	3. Were the same criteria used for identification of cases and controls?	4. Was exposure measured in a standard, valid and reliable way?	5. Was exposure measured in the same way for cases and controls?	6. Were confounding factors identified?	7. Were strategies to deal with confounding factors stated?	8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?	9. Was the exposure period of interest long enough to be meaningful?	10. Was appropriate statistical analysis used?	Percentage of questions answered yes
Haider (2019)	Y	Y	Y	Y	N	N	N	Y	Y	Y	70
Harrison (2022)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
Memmini (2021)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
Paniccia (2018)	Y	Y	Y	Y	N	N	N	Y	Y	Y	70
Woehrle (2020)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	90

Y Yes U Unknown N No

Y - Yes; U - Unknown; N - No.

and following submaximal aerobic exercise, but there was no group × time interaction. Similarly, Worts et al. (52) observed a main effect of group for RMSSD in individuals who exercised at 60% of their age-predicted maximum HR. This main effect for RMSSD was not seen in those exercising at 40% of their age-predicted maximum HR, and no group × time interactions were observed in RMSSD.

Contrastingly, other studies did not find significant effects. During aerobic exercise, Memmini et al. (48) did not find significant group or group × time interactions for RMSSD when comparing concussion groups with controls. Woehrle et al. (50) looked at RMSSD during isometric handgrip contraction, and found that neither the main effect of group nor the group × time interaction was statistically significant.

Table 8. Critical appraisal of a quasi-experimental study using the JBI critical appraisal tool (54).

Author (year)	1. Is it clear in the study what is the cause and what is the effect, (i.e. there is no confusion about which variable comes first)?	2. Was there a control group?	3. Were participants in any comparisons similar?	4. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	6. Were the outcomes of participants included in any comparisons measured in the same way?	7. Were outcomes measured in a reliable way?	8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	9. Was appropriate statistical analysis used?	Percentage of questions answered yes
Morissette (2020)	Y	Y	U	Y	N	Y	Y	Y	Y	89

Y Yes U Unknown N No

Y - Yes; U - Unknown; N - No.

Table 9. Critical appraisal of a randomized controlled trial using the JBI critical appraisal tool (56).

Author (year)	1. Was true randomization used for assignment of participants to treatment groups?	2. Was allocation to treatment groups concealed?	3. Were treatment groups similar at the baseline?	4. Were participants blind to treatment assignment?	5. Were those delivering the treatment blind to treatment assignment?	6. Were treatment groups treated identically other than the intervention of interest?	7. Were outcome assessors blind to treatment assignment?	8. Were outcomes measured in the same way for treatment groups?	9. Were outcomes measured in a reliable way?	10. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	11. Were participants analyzed in the groups to which they were randomized?	12. Was appropriate statistical analysis used?	13. Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Percentage of questions answered yes
Worts (2022)	Y	U	Y	U	U	Y	U	Y	Y	Y	N	Y	Y	62

Y Yes U Unknown N No

Y - Yes; U - Unknown; N - No.

Furthermore, Worts et al. (52) found no main effect of group, group × time or group × position interactions during transition from supine-to-seated for RMSSD, and also for LF:HF and LFnu. For LF:HF and Lfnu, there was no main effect of group or group × time for those exercising at either 40% or 60% of their age-predicted maximum HR.

Harrison et al. (47) also found a significantly higher SDNN in the concussion group than controls during the same

cognitive tasks. Memmini et al. (48) observed SDNN during exercise, and they found a significant group × time interaction, but no main effect of group. This was the case when comparing controls with the concussion group as a whole, and when the concussion group was subdivided into those with a history of exactly one concussion and those with a history of two or more concussion.

Critical appraisal

For four of the studies, more than 75% of the questions received a positive answer (47,48,50,51). For five of the studies, between 50% and 75% of the questions were answered positively (43,44,46,49,52). Moir et al. (45) had the lowest percentage of questions answered positively, with 45%. The prospective cohort studies all failed to deal adequately with confounding factors and there were issues regarding how incomplete follow-up was dealt with. Additionally, it was not made clear whether participants had any ANS dysfunction prior to their concussion (Table 6). For the case–control studies, the most common issues were regarding how controls were assessed for previous concussions and the management of confounding factors (Table 7). Morissette et al. (51) was the only quasi-experimental study, and its biggest issue was the lack of multiple assessments of the ANS (Table 8). In Worts et al. (52), the only RCT, it was unclear what blinding was used, and the analysis of participants who did not complete the trial (Table 9).

Discussion

This review examined the differences in cardiac ANS between adolescents who had suffered a concussion and controls, aiming to identify patterns and limitations in the existing literature, to help guide future research into the development of biomarkers. The reviewed literature provides a complicated picture without an obvious consensus. No metrics, whether measured at rest or during exertion, were found to be significant more than half the time. Under exertion and at rest, HR had the highest percentage of significant results (39.13% at rest; 46.15% under exertion), whilst HRV had the lowest (15% at rest; 24.32% under exertion). Whilst some studies show a clear picture of cardiac ANS dysfunction, others point toward a different conclusion, highlighting the inconsistency of the evidence.

Cardiac ANS dysfunction seems more pronounced under exertion than at rest, as demonstrated by a higher percentage of significant results under exertion for blood pressure (19.05% at rest; 28.57% under exertion), HR, and HRV. Significant differences in the cardiac ANS between the concussion group and controls were observed under a range of exertional conditions, including during aerobic exercise, after standing, during a cognitive task and during an isometric handgrip contraction test. There is limited evidence that higher intensity exercise is more likely to provoke cardiac ANS dysfunction; Worts et al. (52) found a main effect of group for RMSSD when exercise was conducted at 60% of the participants' age-predicted maximum HR, but not when they exercised at 40% of their age-predicted maximum HR. However, this result was not replicated for LF:HF or Lfnu. Interestingly, during cognitive tasks, there did not appear to be a difference in the results whether the cognitive task was conducted at rest or after submaximal aerobic exercise (47).

Research on how concussion affects resting HR reveals contrasting findings. Whilst several studies found no significant differences, the studies that found significant differences between concussion and control groups reported conflicting outcomes regarding the direction of the difference. Haider et al. (46) and Haider et al. (44) found the resting HR of the concussion group to be significantly lower than controls, whereas Balestrini et al. (43) found the concussion group to have a significantly elevated HR. This may reflect the fact that Haider et al. (46) recorded this HR before the participants exercised, which may have affected the HR of both groups. With regard to Haider et al. (44), this difference could be attributed to variability caused by using different measurement devices across sites. Whilst these variable results may demonstrate a highly variable impact of concussions on the cardiac ANS of adolescents, these inconsistencies more likely reflect the heterogeneity in study protocols and poor control of confounding variables, which limits the reliability of comparisons.

The results of Haider et al. (46) and Morissette et al. (51), who both evaluated HR during the BCTT but at different times post-concussion, provide an interesting insight into how the cardiac ANS changes over the post-concussion period. Whilst in Haider et al. (46) concussed individuals had significantly lower HR after 2 min, peak HR, and difference between resting and peak HR than controls, in Morissette et al. (51) the change in HR at minutes one through to five and peak HR were not significantly different between the concussion group and controls, although the peak HR of concussed males was significantly lower than controls. Haider et al. (46) assessed concussed individuals 5.6 ± 2.84 days post-concussion, whilst Morissette et al. (51) conducted the BCTT 44.8 ± 26.8 days post-concussion, so this points toward cardiac ANS dysfunction being present soon after concussion and then resolving. These differences could also be caused by the increased intensity of exercise used by Haider et al. (46), since they increased the treadmill speed by a greater amount each minute.

Memmini et al. (48) conducted a study that did not include individuals whose concussion had occurred in the last 6 months, assessing asymptomatic individuals 25.1 ± 17.6 months post-concussion. They found the main effect of grouping for HR post-aerobic exercise and a significant group × time interaction for SDNN post-aerobic exercise. Unlike Morissette et al. (51), this suggests that concussions may lead to long-term ANS dysfunction. This may suggest that ANS dysfunction is present acutely, then recovers before eventually returning as individuals return to more intense activity once asymptomatic. This is supported by Haider et al. (44), who found no significant differences between the concussion group and controls whilst symptomatic, but there were significant differences at a subsequent visit once clinically recovered. However, the difference in results may also be a reflection of methodological differences; whilst

Memmini et al. (48) went to great lengths to exclude controls with previous concussions, including screening controls for undiagnosed concussions, Morissette et al. (51) used 'healthy' controls, but did not mention their concussion history. Additionally, a number of confounders that Memmini et al. (48) controlled for, including caffeine intake and time of assessment, were not managed by Morissette et al. (51).

Sex differences should also be considered; Balestrini et al. (43) found a significant group × posture × sex interaction for RMSSD at rest, which suggests that how concussion affects resting RMSSD may vary between males and females. However, they did not find significant interactions for resting HR for either group × sex or group × posture × sex. Likewise, Morissette et al. (51) found that for blood pressure and resting HR the same relationships between concussed individuals and controls were seen for males and females. However, the peak HR of concussed males during the BCTT was significantly lower than controls, whilst for females there was no significant difference between the two groups. The fact that neither study controlled for confounding factors such as medication use, caffeine intake, time of assessment, recent exercise and concussion history of controls is likely to have contributed to the inconsistent results.

There are serious limitations within the literature, as evidenced by six of the 10 studies having less than 75% positive responses during critical appraisal. The foremost problem is the failure to report confounding factors and control them when possible. The list of confounding factors is extensive, as the ANS is extremely sensitive to both the internal and external environments, but should include medication use, cardiorespiratory fitness, stage of menstrual cycle, and past medical history, particularly concussion history of controls (14). The fact that only three of the studies reported that none of their controls had a concussion history is particularly concerning, especially considering the potential for long-term asymptomatic ANS dysfunction following concussion.

Other physiological systems affected by concussion may also indirectly influence the cardiac ANS. For example, vestibular dysfunction can impact ANS regulation during postural changes (57), whilst hormonal dysfunction, particularly related to cortisol and thyroid hormones may alter the autonomic tone (58). Future studies should use a combination of strict exclusion criteria, stratified analyses, and targeted investigation of these systems to help decipher the factors influencing ANS changes.

Previous systematic reviews focused on adults (14,33) or used broad age ranges of individuals aged over 6 years old (34), with an average age of 13–40 (36) or of any age (35). The majority also found possible ANS dysfunction post-concussion, but like this review, the poor methodological quality of the articles involved limited their ability to draw definitive conclusions (14,33,34). Mercier et al. (14) similarly found that ANS dysfunction is more apparent under exertion, whilst Blake et al. (34) and Charron et al. (33) did not offer verdicts on this, perhaps since they contained only five and three studies that assessed the ANS under exertion, respectively. Pertab et al. (35) concluded that it is likely that concussion causes ANS dysfunction, but they did this despite finding no Class I studies, which are studies deemed to have a low risk of bias, which puts the strength of their conclusion into question. The meta-analysis of Wesolowski et al. (36) found that MeanNN and RMSSD at rest were significantly different between those who had sustained a concussion more than 4 months ago and those without a concussion history, but SDNN wasnot. Of these metrics, in our review significant findings at rest were only seen for RMSSD, which partially aligns with the findings of Wesolowski et al. (36). The difference regarding MeanNN could be due to the neurological plasticity of adolescents; with key regions in ANS regulation, like the hypothalamus, still undergoing significant refinement, adolescents could be able to regain their ANS function sooner than adults. Alternatively, the difference may be because only one study evaluated MeanNN at rest in our review. Interestingly, Wesolowski et al. (36) only included studies in which the controls had no concussion history. This may explain why they found significant findings for the metric and condition combination (resting HRV) that had the lowest percentage of significant results in this systematic review. The finding of significant differences even beyond the acutely concussed phase highlights the potential long-term autonomic dysfunction that results from concussion and illustrates the limitations of using controls with a concussion history.

Whilst all of the previous systematic reviews acknowledged age, sex and time since concussion as relevant factors, only Charron et al. (33) explored these variables in detail. They reported that HRV generally decreases with age and shows consistent sex-based variation. This contrasts with the inconsistent sex-related findings in this review, which may reflect the variable pubertal status of our participants or the limitations of the studies exploring sex differences. Charron et al. (33) also found that ANS disturbances persisted for many months post-injury even in asymptomatic individuals, which aligns with our findings and further demonstrates the importance of using controls with no concussion history.

This systematic review has several limiting factors. Like all systematic reviews, it is affected by publication bias, which may have led to studies that did not show significant results not being published. Furthermore, the limited number of high-quality studies found fitting the inclusion criteria limits the ability of this review to make confident assertions. Elements of the inclusion criteria, such as only including interaction analyses that included 'group' as a factor, may be considered too stringent; however, this was to ensure the systematic review focused on its main aim of determining whether cardiac ANS dysfunction is present in adolescents following concussion. It may be considered an oversight to limit the outcomes of HR, BP, and HRV and not include additional metrics, such as mean arterial pressure and baroreflex sensitivity. However, this selection of outcomes allowed the study the greatest chance of the study being applicable to clinical practice since these are common, easily measured metrics, which provide a reliable reflection of the cardiac ANS. HRV is a widely recognized, sensitive, and specific indicator of autonomic function. HR and BP are less sensitive, and so findings based solely on their results should be interpreted with greater caution.

However, their prevalence in the literature and widespread use in clinical practice necessitated their inclusion in this review. The differing sensitivity of these metrics may partially explain the variation in findings across studies, although inconsistencies were also present between studies assessing the same metrics, suggesting that other factors, such as methodological variability, are a more likely cause. Additionally, by only selecting three outcomes, each one could be thoroughly explored. The calculation of percentage of significant results is not a completely fair comparison as it does not account for the different methodologies of the studies, including the range of statistical tests used; however, its inclusion provides an overall measure of each metric's consistency.

Conclusion

This is the first systematic review to look at how concussion affects the cardiac ANS of adolescents. It is vital that adolescents are explored, since they are undergoing a crucial period of neurological development, with maturation of their ANS. As such, adolescents cannot be expected to respond identically to concussions to adults; their recovery patterns are likely to be unique, and the potential for long-term impacts is substantial. Due to limitations within the existing literature, this review is unable to reach definitive conclusions; for these to be drawn, it is vital that future research works to control confounding factors, particularly the concussion history of adolescents. Furthermore, a longer-term follow-up period would allow us to see how the ANS is affected over time. There is also limited evidence on the effect of sex and different exercise intensities on the ANS of adolescents, and these are also important areas to explore. More research is required to fully elucidate the mechanism through which concussions may cause ANS dysfunction in adolescents, since current models are primarily based on adult research. This review suggests that ANS dysfunction may be present in some adolescents following concussion; this may be apparent many months post-injury, irrespective of symptoms, and is more likely to be present during exertion. However, whilst in the future ANS testing may assist in identifying and managing concussion, current evidence is insufficient to support its use in routine clinical care.

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ORCID

Simon M Walker http://orcid.org/0000-0002-6997-3981

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