The impact of concussion on cardiac autonomic function: A systematic review

Tracy A Blake*
Sport Injury Prevention Research Centre, Faculty of Kinesiology, University of Calgary; Calgary, Alberta, Canada
2500 University Drive NW, Calgary, Alberta, Canada T2N 1N4

Carly D McKay
Department for Health, University of Bath; Bath, Somerset, UK
Sport Injury Prevention Research Centre, Faculty of Kinesiology, University of Calgary; Calgary, Alberta, Canada

Willem H Meeuwisse
Sport Injury Prevention Research Centre, Faculty of Kinesiology, University of Calgary; Calgary, Alberta, Canada

Carolyn A Emery
Sport Injury Prevention Research Centre, Faculty of Kinesiology, University of Calgary; Department of Pediatrics, Alberta Children's Hospital Research Institute for Child and Maternal Health, Faculty of Medicine, University of Calgary; Department of Community Health Sciences, Faculty of Medicine, University of Calgary; Hotchkiss Brain Institute, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada

*** Corresponding author**

Abstract

Primary Objective: To evaluate the evidence regarding the effect of concussion on cardiac autonomic function (CAF).

Inclusion criteria: original research; available in English; included participants with concussion or mild traumatic brain injury (mTBI) and a comparison group; included measures of heart rate (HR) and/or heart rate variability (HRV) as outcomes. Studies of humans (greater than 6 years old) and animals were included.

Critical Appraisal Tools: The Downs and Black (DB) criteria and Structured Effectiveness Quality Evaluation Scale (SEQES). Results: Nine full-length articles and four abstracts were identified. There is conflicting evidence regarding CAF at rest following concussion. There is evidence of elevated HR and reduced HRV with low-intensity, steady-state exercise up to 10 days following concussion. There was no significant difference in HRV during isometric handgrip testing or HR while performing cognitive tasks following concussion. The validity of current literature is limited by small sample sizes, lack of female or pediatric participants, methodological heterogeneity, and lack of follow-up.

Conclusions: While there is some evidence to suggest CAF is altered during physical activity following concussion, methodological limitations highlight the need for further research. Understanding the effect of concussion on CAF will contribute to the development of more comprehensive concussion management strategies.

Abstract Word Count: 200

Insert Table 1 about here.

A concussion in a biomechanically induced injury that results in pathophysiological alterations to the brain, with a clinical presentation more reflective of a functional disturbance than a structural injury.[1] To date, concussion research has been heavily focused on epidemiology, clinical and neuropsychological outcomes and return to play (RTP) guidelines.[1-6] Little is known about the physiological impact of concussion, but given the potential for physiological changes to provide objective, quantifiable measures of concussion incidence as well as recovery, there is a need for additional research in this area.[7]

The autonomic nervous system is responsible for maintaining homeostasis in the human body.[8] It comprises the parasympathetic (PNS) and sympathetic nervous systems (SNS), the combined activities of which influence the function of several organs, including the heart.[9] Heart rate (HR) is a product of the interaction of the PNS and SNS on the heart.[9] Heart rate variability (HRV) is defined as "the oscillation in the interval between consecutive heart beats (i.e. RR interval) as well as the oscillations between consecutive instantaneous heart rates".[10] HRV has been established as a valid and reliable non-invasive tool for the exploration of cardiovascular autonomic function,[11-19] and can be measured using time domain or frequency domain methods.[10] Time domain methods determine HRV at a given point in time and the "intervals between adjacent QRS complexes resulting from sinus node depolarization" (i.e., the RR intervals).[10] Frequency domain methodology uses power spectral analysis to "describe how HRV distributes as a function of frequency".[10] Parasympathetic nervous system activation is thought to slow HR and increase HRV, while sympathetic nervous system activation results in increased HR with decreased HRV.[20]

Cardiac autonomic function can reflect the connection between psychological and physiological processes,[20,21] making it an ideal construct with which to assess the impact of concussion.

Changes in cardiac autonomic function such as significantly elevated HR and significantly reduced HRV have been observed following moderate and severe traumatic brain injury.[22-26] It is believed that the autonomic nervous system and the cardiovascular system become increasingly uncoupled as the severity of brain injury increases.[26]

Current post-concussion return-to-play guidelines include recommendations for graduated physical exertion, measuring activity intensity via percentage of maximum heart rate.[4,5] Yet, without an evidence-based understanding of the relationship between concussion and cardiac autonomic function, there can only be limited understanding of whether the use of heart rate as a measure of activity intensity is appropriate. Therefore, the primary objective of this review is to evaluate the evidence regarding the effect of concussion on cardiac autonomic function.

The importance of critical appraisal in evidence-based medicine is reflected in the burgeoning number of critical appraisal tools available for use.[27] There is significant diversity in these tools, and even those purporting to address similar study designs or methodological concepts may score the same publication quite differently.[28] Furthermore, there is a paucity of research evaluating how the choice of tool influences interpretation of evidence quality.[29] The secondary objective of this review is therefore to compare how study quality assessment is affected by the use of two different appraisal tools.

Methods

The PRISMA guidelines were used in the development of this review.[30]

Publication Identification

A comprehensive list of search terms related to cardiac autonomic function and concussion were synthesized into search strategies and utilized in 11 databases: CINHAL (Cumulative Index of Allied Health Literature; 1982-present), the Cochrane Central Register of Controlled Trials (1975-present), Embase (Excerpta Medicus; 1974-present), HealthSTAR (1966-present), Medline (1966-present), PsycINFO (1806-present), SportDiscus (1980-present), PubMed, Web of Science, ProQuest Dissertations and Theses, and Google Scholar. In addition, manual citation searches of the references of each included publication were conducted. All searches were initially completed between August 15, 2013 and September 12, 2013, then repeated on June 25, 2014, by one investigator (TB). The title and abstracts for all new citations were reviewed (TB) to identify potentially relevant publications. The full text was retrieved for these publications and independently reviewed for inclusion by two reviewers (TB, CM).

Publication Inclusion

The *a priori* publication inclusion criteria were: (1) the use of primary, original data; (2) publication (abstract or full-length) in a peer-reviewed journal; (3) being available in English; (4) including HR or HRV as an outcome; (5), including a population or subpopulation of participants who sustained a concussion or mild traumatic brain injury (mTBI); (6) including a comparison group. Due to the paucity of tools and guidelines that address the specific needs of a pediatric population, only studies with participants that were the equivalent of at least six human years old were included.[1, 31] Reviews, case-series, case studies without pre- and post-injury data, and opinion-based publications were excluded.

Data extraction and analysis

Characteristics extracted from each publication included study design, population (age, sex, sample size), outcomes, and key findings related to cardiac autonomic function (i.e., HR, HRV). Each publication was assigned a level of evidence based on the Oxford Centre for Evidence-Based Medicine Levels of Evidence for differential diagnosis/symptom prevalence studies[32], which was modified to include cross-sectional studies and case studies under level four.

Two appraisers (XX, YY) independently evaluated each publication using two critical appraisal tools, the Downs and Black criteria (DB), and the Systematic Evaluation of Quality of Evidence Scale (SEQES).[33,34]

The DB critical appraisal tool was first published in 1998.[33] It was developed in order to address limitations in appraisal tools relating to non-randomized trials as well as "a paucity of subscales profiling the methodological strengths and weaknesses of publications".[33] It is comprised of 27 items that are predominantly scored using a binary system, with the exception of one question scored on a three-point scale, and one question scored on a six-point scale, for a total score out of 32 points.[33] The items are organized into five categories: reporting, external validity, bias, confounding, and power.[33] The instructions require that items that are not applicable to non-intervention studies receive a score of zero.[33]

The SEQES was first published in 2004.[34] This 24-item appraisal tool uses a three-point scale, for a total of 48 points.[34] It was developed to facilitate critical appraisal skills in clinicians.[34] The questions are organized into seven categories: study question, study design, subjects, intervention, outcomes, analysis, and recommendations.[33] A detailed

description of the requirements for the scoring of each item is included as an appendix in the original publication.[34]

Each item from both tools was presented and discussed between the two appraisers; if scores were not in agreement, they were discussed until consensus could be reached. If there was no consensus, a third rater (CE), was consulted. The inter-rater agreement for each publication was assessed using kappa based on each rater's original scoring of each publication. The tool-specific scores for each publication were based on the final consensus scores, which were then converted into percentages of total score in order to facilitate comparison between tools. Between-tool differences in the rankings of the publications were evaluated using a Wilcoxon Rank-Sum test ($\alpha<0.05$).

Data Synthesis

Extracted data, level of evidence, and study quality were summarized for each publication. The dearth of literature, as well as the heterogeneity of outcomes, settings, and methodologies precluded meta-analysis for the primary objective of this review. The evidence quality category scores for each appraisal tool were collated and are presented as medians and ranges, based on the final consensus scores.

Results

Systematic Review

Publication Identification

The study identification process yielded nine manuscripts and four abstracts for appraisal (figure 1).

Insert figure 1 about here.

Publication Characteristics

Publication characteristics are summarized in table 2.

Insert table 2 about here.

Ten publications included participants with concussions (n=155) and healthy controls (n=143).[35-44] Two studies compared groups of participants who sustained concussions that were categorized based on their response to exercise (n=205).[45] One publication collected pre- and post-injury information on one case; thus the participant acted as his/her own control.[46] Finally, one publication utilized an animal model, where rats underwent either a surgery to induce mTBI via fluid percussion (n=22) or a sham injury (n=19), and a group that was placed under anesthetic only (n=22).[47]

Two studies explicitly reported and referenced their operational definition of concussion.[40,43] Three other studies provided references for operational definitions of concussion that were published elsewhere.[37-39] The remaining seven studies did not report or reference an operational definition of concussion or mild traumatic brain injury.[36,41,42,44-47] Seven studies reported HR as an outcome measure.[38,39,41,43,45-47] Nine publications employed parameters of HRV.[35-37,40,41,43,44] The publications evaluated the impact of concussion on cardiac autonomic function at rest (n=12), during 'stressful conditions' (n=1), during cognitive testing (n=1), and during physical activity (n=3).

Inter-rater Agreement

The inter-rater agreement for the DB criteria items ranged from 0.80 to 1.00. The inter-rater agreement for the SEQES criteria ranged from 0.63 to 1.00. Consensus was achieved for all items between the two raters, thus the third rater was not utilized. The itemized DB and SEQES scores can be found in the supplementary materials online. The

median SEQES score was 21/48 (range: 10-27). The median DB score was 9/32 (range: 3-13). The median scores and ranges for the DB and SEQES criteria categories are described in table 3.

Insert table 3 about here.

Synthesis of Results

There is a paucity of evidence in this area of research. Summaries of the quantity, quality and level of evidence of studies evaluating the impact of concussion/mTBI on HR (table 4), time domain measures of HRV (table 5), frequency domain measures of HRV (table 6), and miscellaneous measures of HRV (table 7) are available as supplementary online content.

There is conflicting evidence regarding the impact of concussion on HR/HRV at rest[37,38,42], but there is limited evidence to suggest those with self-reported history of mTBI had significantly higher HR during stressful conditions (i.e., doing mental arithmetic with 85dB white noise, bright lights, and environmental interrupters) than those without a self-reported history of mTBI.[39] There is no evidence of significant differences in HR while performing cognitive tasks between participants with concussions and healthy controls.[39]

There is no evidence of significant differences in HRV measures during isometric handgrip between participants with concussions and healthy control.[41] There is limited evidence that elevated HR and reduced HRV occur during steady-state low intensity aerobic exercise in participants up to 10 days post-concussion.[37,38] There is also some evidence to indicate that participants with post-concussion syndrome who abort submaximal exercise due to symptom exacerbation have lower HR than participants with post-concussion syndrome who exercised to exhaustion without symptoms.[45] However, no

significant differences in HR/HRV were demonstrated during high intensity, interval aerobic exercise 5 and 10 days following concussion.[37,38] In the sole publication utilizing an animal model, rats with mTBI who participated in voluntary or forced exercise had significantly elevated HR when compared to healthy, uninjured rats seven days following injury.

Critical Appraisal Tool Comparison

Inter-Tool Agreement

The ranking of the included studies by percentage of total score for the SEQES criteria (i.e., out of 48 points), and the DB criteria (i.e., out of 32 points) are illustrated in figure 2. The DB and SEQES criteria were significantly different with respect to how they ranked the methodological quality of the publications($p=0.007$).

Insert figure 2 about here.

Discussion

Systematic Review

There was a paucity of literature related to the relationship between cardiac autonomic function and concussion/mTBI. There were also significant limitations within the available research with respect to study design, sample size, setting, outcome measures and analysis.

The inclusion of only one study using animal participants[47] is indicative of the paucity of translational research being conducted in this area. There are also questions regarding the validity of the techniques utilized to induce concussion.[48,49] Building

translational research capacity via novel techniques with improved biomechanical validity[49] would facilitate our understanding of concussion and cardiac autonomic function.

Seven studies utilized a prospective cohort design, which is ideal for establishing temporality.[36-38, 40, 41, 46, 47] Temporality ensures that the exposure (i.e., sustaining a concussion) preceded the outcome (i.e., cardiac autonomic function measures), and is a central tenet of causation.[50] There was, however, a lack of substantial follow-up, with no study evaluation occurring past 14 days post-concussion.[40, 41] Studies that include a more substantial follow up period will be valuable in improving our understanding of the natural history of any post-concussion cardiac autonomic function changes and in the development of future clinical research and management strategies.

Providing operational definitions for key terms, particularly those related to the dependent and independent variables of interest, supports the internal and external validity of a study's results by allowing the 'truth' of the measure to be taken into consideration when interpreting the results, and facilitating the study's generalizability and reproducibility.[50] Nearly 54% of studies included in this review did not report or reference their definition of concussion/mild traumatic brain injury, nor provide any diagnostic criteria for the condition.[36,41,42,44-47] Moreover, two other studies referenced material that is no longer available, therefore cannot be accessed by individuals looking to reproduce their results.[37, 38] In contrast, all but one publication utilizing HRV outcome measures were consistent with the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology recommendations regarding which measures are appropriate for short-term HRV recordings.[10] There was, however, a significant amount of detail missing with respect to how these outcomes were measured.

Frequency domain measures, which were examined in seven of the 13 included publications, are highly sensitive to factors such as ectopic beats and noise.[10] The 1996 Task Force recommends the explicit detailing of the data recording, extraction and cleaning of frequency domain measures. [10] None of the studies included in this review provided the recommended level of detail, limiting the internal validity, as well as the reproducibility of the results.

The external validity the evidence available on concussion and cardiac autonomic function is also limited by the wide variety of outcome measures and settings that were employed. Fifteen different outcome measures were taken in the 13 included publications. Data collection was conducted prior to and/or during six different dosages of exercise/physical activity. Resting measures of several outcomes were collected in 12 of 13 included publications, but several failed to note the position in which it was measured. For example, resting LFnu was measured in five studies, but body position is unknown for three of them. Similarly, resting SDNN was evaluated in four publications, but only had position descriptions for two. Several measures of HRV are known to respond to changes in body position.[10] The diversity of outcomes as well as the lack of detail and consistency in how the outcome measures were collected further reduces the generalizability of the results. Future studies should provide more detail regarding key variables, including the operational definitions of concussion and cardiac autonomic function, information on participant position during the measurement, and data acquisition and data cleaning protocols in order to facilitate the generalizability and reproducibility of their results.

The majority of publications included in this review were rated 3b (i.e., prospective cohort study with a very limited population).[32] None of the publications provided a

quantitative or qualitative rationale for their sample size. This limitation is particularly significant in light of the evidence illustrating large within-subject and between-subject variation in many HRV measures.[11,15,16] Small sample sizes with large amounts of random variability would impede the ability to detect significant differences in the outcomes, increasing the probability of Type II error. Studies will larger, more representative sample populations are needed to increase the internal and eternal validity of future research.

Inadequate sample size would also attenuate the ability to evaluate potential confounding and effect modifying covariables. There is evidence to indicate that cardiac autonomic function and concussion outcomes are influenced by age and sex.[1, 51, 52] Six studies controlled for these variables by recruiting extremely homogenous populations.[37, 38, 40, 41, 46, 47] Three studies reported using age-and sex-matched controls, but provided descriptive data that suggested the matching was unsuccessful[36, 43], or did not verify the matching at all.[42] One study used age- and sex-corrected normative values in the analysis.[35] The remaining three studies did not account for age or sex at all.[39,44,45] In addition to established factors such as age and sex, emerging research has provided new information on variables that may influence the relationship between concussion and cardiac autonomic function. Headache and neck pain are two of the most common symptoms following concussion, with reported prevalence of up to 85.1%and 37.1%, respectively.[53-56] There is also emerging evidence to suggest that people who suffer from neck pain, headaches or migraines have altered cardiac autonomic function.[57-59] None of the studies included in this review addressed headache, migraines, or neck pain in the inclusion/exclusion criteria. Two studies provided descriptive statistics on the presence of headaches and/or neck pain in their respective populations, but did not adjust for them as

potential confounders or effect measure modifiers in the analysis.[39, 40] Future research must clearly report how they account for confounding and effect measure modification of known factors associated with concussion and cardiac autonomic function in order to increase the internal and external validity of their findings.

Critical Appraisal Tool Comparison

While the critical appraisal of evidence has long been acknowledged as an important tenet of evidence-based medicine, few studies have compared how the use of different tools influences how publications may be ranked. The inter-rater agreement was excellent (i.e., kappa greater than 0.8) for the DB criteria, while the SEQES criteria agreement ranged from substantial to excellent (i.e., kappa from 0.6 to 0.8).[50, 60] The differences in scoring between the tools may have contributed to this variation. All of the items in the SEQES criteria have three scoring options, whereas the DB criteria items predominantly have only two. The increased number of options provided increased opportunities for scoring diversity between the two raters.[49] Differences in the reviewers' familiarity between the two tools may also have been a factor in scoring variation. Both reviewers had at least 3 years of experience with the DB criteria, while only one had previously used the SEQES criteria. Despite the instructions provided, it was not until actually using the tool that systematic issues in scoring certain items became apparent. While consensus was attained on how to resolve these issues, the initial independent scores were varied, negatively impacting the inter-rater agreement. Despite these issues, full consensus was attained between the initial two raters for all items, suggesting that dialogue between the two reviewers was enough to facilitate a mutual understanding of both the item and the appropriate score for a given publication.

The DB and SEQES tools yielded significantly different rankings of the included publications. This may have been influenced by the differences in scoring, as well as item organization. To illustrate, the organization of the SEQES is such that there is an opportunity for partial points on every question, but the highest possible point allocation is two. As a result, there was only one item out of 24 (4.2%) in which none of the publications received even partial scores. In contrast, the predominantly binary nature of the DB criteria resulted in eight out of 27 items (29.6%) in which none of the publications received any points. This may have significantly impacted the total scores, and thus, the final rankings of the publications. Another related issue is in regards to the weighting of certain items. In the SEQES criteria, all the items are of equal weight, whereas the DB criteria have two items that are weighted differently than the rest. For example, both appraisal tools include items appraising study power. These items comprised 4.2% of total points on the SEQES, whereas similar items on the DB criteria accounted for 15.6% of the total points. Such a significant difference demonstrates how the weighting of items could play an influential role in altering how publications are ranked.

The largest between-tool differences in scoring were seen in the abstracts. The DB criteria utilized scoring categories more related to the methodological content, which would place the abstracts at a disadvantage due to the stringent word count restrictions they must abide by. In contrast, the SEQES criteria categories are quite similar to the components in most structured abstracts, providing the abstracts included in this review with a greater opportunity to garner points than the DB criteria. Four of the 13 publications reviewed were abstracts (30.8%). Given how small the body of literature on cardiac autonomic function and concussion/mTBI is, it was felt that information from full length

and abstract publications must be included. A sensitivity analysis found the significant difference in the inter-tool ranking of the full-text publications persisted even when abstracts were not included.

Conclusion

There is limited evidence to suggest that concussion/mTBI can impact HR and HRV at rest (in acute and chronic post-injury stages) as well as during steady state, low-intensity aerobic exercise (in the acute post-injury stage). Addressing limitations in the existing body of literature, however, would help to clarify the nature of these relationships and provide the opportunity for discovery and innovation in concussion research. First, key terms must be operationalized within study reports, and appropriate references should be provided. The use of novel models of injury in translational research is an opportunity to help build research capacity and inform decision-making in the development of studies including human participants. Validity and reliability studies in adult and pediatric populations are needed to improve our understanding of the role of factors such as time of day, raters, and technology on the variability associated with cardiac autonomic function outcomes. Prospective cohort studies need to be conducted, with sample sizes and analyses that account for factors known to be associated with between-subject variance in cardiac autonomic function (e.g., sex, age, body position during evaluation, presence of neck pain or headaches). Longer follow-up periods following concussion would facilitate our understanding of the natural history of cardiac autonomic function post-concussion. While both tools highlighted methodological areas of improvement in research evaluating post-concussion cardiac autonomic function, the significant difference in the ranking of the publications using the DB and SEQES criteria illustrates the importance of understanding

how a critical appraisal tool itself can impact one's interpretations of the methodological quality of a publication. Future research developing and evaluating the quality and utility of critical appraisal tools will help to standardize the critical appraisal process. This will, in turn, galvanize the methodological foundation upon which emerging areas of research such as post-concussion cardiac autonomic function are built, increasing the validity of future research findings, and facilitating their contribution to the development of evidence-based concussion prevention, clinical evaluation and management.

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Declaration of Interest

The authors report no declaration of interest.

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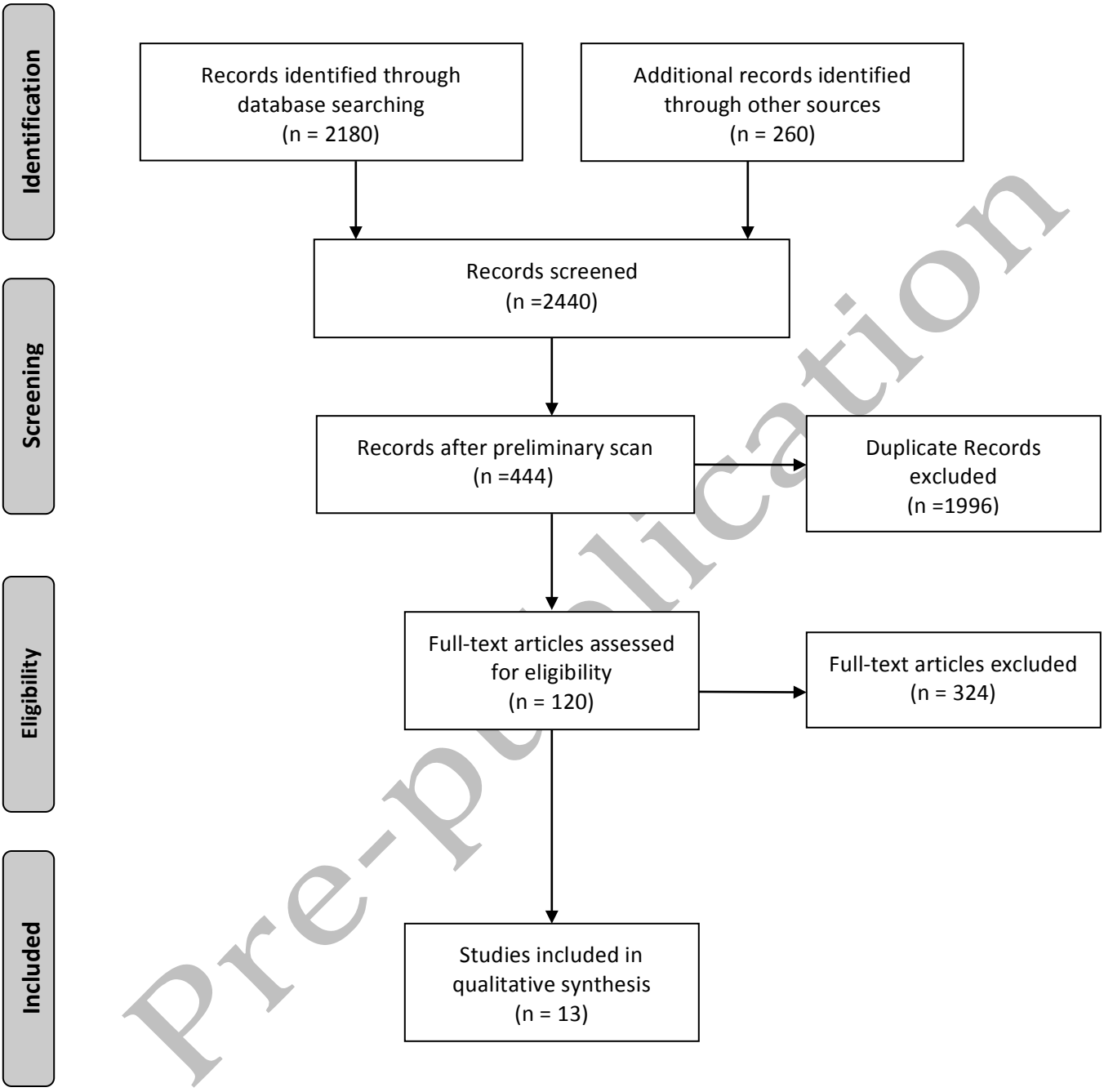
Figure 1. Search Strategy Flow Chart (adapted from PRISMA, 2009)



582 Table 1: Cardiac Autonomic Function Outcomes[10]

OUTCOME	MEASUREMENT	DESCRIPTION
Heart Rate (HR)	Beats per minute (bpm)	Mean number of heartbeats per minute
HEART RATE VARIABILITY: TIME DOMAIN MEASURES		
Mean RR Interval (RR)	Milliseconds (ms)	The average time interval between consecutive heartbeats, as measured from R-wave to R-wave[10]
SDNN	Milliseconds (ms)	Standard deviation of all RR intervals[10]
RMSSD	Milliseconds (ms)	The square root of the mean of the sum of the squares of differences between adjacent RR intervals[10]
NN50	count	The number of pairs of RR intervals differing by more than 50ms in a recording[10]
pNN50	Percentage (%)	The number of pairs of RR intervals differing by more than 50ms in a recording, divided by the total number of RR intervals[10]
HEART RATE VARIABILITY: FREQUENCY DOMAIN MEASURES		
Total Power	Milliseconds squared (ms^2)	The variance of all RR intervals[10]
LF	Milliseconds squared (ms^2)	Power in the low frequency range (i.e., 0.04-0.15Hz)[10]
LFnu	Normalized units (nu)	Power in the low frequency range divided by the difference between total power and very low frequency (i.e., ≤0.04Hz), multiplied by 100[10]
HF	Milliseconds squared (ms^2)	Power in the high frequency range (i.e., 0.15-0.4Hz)[10]
HFnu	Normalized units (nu)	Power in the high frequency range divided by the difference between total power and very low frequency (i.e., ≤0.04Hz), multiplied by 100[10]
LF:HF	Not applicable	The ratio of LF power to HF power[10]
HEART RATE VARIABILITY-OTHER MEASURES		
Approximate Entropy (ApEn)	Not applicable	The likelihood of regularity in the signal with more regularity yielding smaller values and less regularity yielding larger values.[40]
QT Interval Variability Index (QTVI)	Not applicable	The proportion of the respective variances of QT and RR intervals normalized to their means.[39]
Coefficient Variation of RR		

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586 Table 2: Publication Characteristics

REFERENCE	STUDY DESIGN	CARDIAC AUTONOMIC FUNCTION OUTCOMES	POPULATION	KEY FINDINGS	DB SCORE (/32)	SEQES SCORE (/48)	LEVEL OF EVIDENCE
Berkoff et al, 2008 (abstract)	Prospective cohort	Absolute values and percentage change from day 1 to 3, day 3 to 7 and day 1 to 7 in HRV (SDNN, RMSSD, pNN50, HF, LF, Total Power, LF:HF ratio)	10 concussed Division I athletes (4 females, mean age 19.7 years old) 9 non-concussed athletes (2 females, 19.5 years old)	Significant differences in absolute SDNN from day 1 (p=0.02) to day 3 (p=0.02). Significant differences in absolute RMSSD day 3 (p=0.01) and day 7 (p=0.046). No significant differences in the percentage change in any of the other HRV measurements from day 1-3, day 3-7, nor day 1-7.	9	23	3b
Gall et al, 2004a	Prospective cohort	HR	Concussed male junior hockey players with time loss (n=9; mean age 17.8±0.5 years old) and matched controls (n=8; mean age 18.7±0.4 years old) Concussed male junior hockey players with no time loss (n=5; mean age 18.8±0.8 years old) and matched controls (n=4; mean age 19.0±0.8 years old) Loss to follow up: one concussed athlete with time	No significant difference between concussed athletes and matched controls in the number of exercise bouts completed. No significant difference between concussed athletes and matched controls in symptoms associated with exercise. No significant difference in blood lactate between concussed athletes and matched controls. Concussed athletes who missed playing time had significantly higher HR during steady state exercise than matched controls. 5 days following injury (p<0.05), 10 days following injury (p<0.05), and on	13	27	3b

			loss in blood lactate test; one time loss matched control in heart rate; one concussed athlete with no time loss in heart rate.	average 126±3.4 beats per minute vs. 116.0±1.9 beats per minute). There was no significant difference in maximum HR between concussed athletes with no time loss and their matched controls.			
Gall et al, 2004b	Prospecti ve cohort	HRV (Mean RR, SDRR, LF, HF, HF, LF:HF, LFnu, HFnu, Total Power)	14 male junior hockey players who sustained concussions (mean age 18.1±0.4 years old). 14 male junior hockey players matched for age body stature, position, and playing time that did not sustain a concussion (mean age 18.8±0.4 years old).	No significant differences between concussed athletes and matched controls in HRV parameters at rest at 2-3 days or 7 days following concussion. Concussed athletes had a significantly lower mean RR interval than their matched controls ~5 days following injury (466.3ms ±7.4 vs. 504.1ms ±7.8) and ~10 days following injury (466.12ms ±13.6 vs. 512ms ±13.7) during low-to-moderate intensity steady state exercise. Concussed athletes had significantly lower LF than their matched controls ~5 days following concussion ($17.4ms^2$±2.9 vs. $35.1ms^2$±7.1) and ~10 days following injury ($14.4ms^2$±5.0 vs. $24.5ms^2$±4.4) during low-to-moderate steady state exercise. Concussed athletes had significantly lower HF than their matched controls ~5 days following concussion ($1.9ms^2$±0.3 vs. $3.9ms^2$±0.8) and ~10 days following injury ($1.9ms^2$±0.6 vs. $3.2ms^2$±0.3) during low-to-moderate steady state exercise. There was no significant difference in SDRR, LFnu, HF	12	24	3b

				nu, LH/HF ratio or total power between concussed athletes and their matched controls (p>0.05).			
Griesbach et al, 2013	Prospecti ve Cohort	HR	19 male rats who underwent sham injury 22 male rats who had an mTBI induced by fluid percussion injury 22 control rats (anesthesia only)	Lower HR during dark cycle for injured rats vs. control (p<0.05). During light cycle, significantly HR lower in voluntarily exercising injured rats than voluntarily exercising control rats on the day of surgery (p<0.05), and significantly lower by post-injury day 10 (p<0.05). Significantly elevated HR in injured rats during voluntary exercise compared to controls doing voluntary exercise (p<0.05). Significantly elevated HR in injured rats during forced exercise compared to controls doing voluntary exercise (p<0.05). The elevations in HR were higher in voluntary exercising injured rats than in forced exercising injured rats (p<0.05).	10	26	3b
Hanna-Pladdy et al, 2013	Cross-sectional	HR	44 participants with self-reported history of mTBI (24 female) who reported symptoms (n=22; mean age 22.77 years, SD=4.27) and did not report symptoms (n=22; mean age 23.87, SD=7.34). 44 participants with no self-reported history of mTBI (32 female) who	Participants with a self-reported history of mTBI reported the highest HR during the stress condition.	11	23	4

			reported symptoms (n=22; mean age 20.41, SD=4.79) and did not report symptoms (n=22; mean age 21.64, SD=3.01).				
Hilz et al, 2011	Cross-sectional	HR, HRV (mean RR, SDNN, Coefficient of variation of RR intervals, RMSSD, 30:15 ratio, LF, HF, LFnorm, HFnorm, LF:HF ratio)	20 participants (3 women, means age 37±13 years) who sustained mild TBI 5-43 months prior to examination, 20 age- and sex-matched controls (5 women, means age 26±9 years)	Supine mean RR (p=0.006), SDNN (p=0.043), RMSSD (p=0.005), HF (p=0.02), HFnu (p=0.000) and BRSgain (p=0.04) were significantly lower in participants who had sustained mTBIs vs. controls. Supine LFnu (p=0.000) and LF:HF ratio (p=0.000)was significantly higher in participants who had sustained mTBIs vs. controls. Standing SDNN (p=0.013) the coefficient of variation of RR (p=0.008), and LF (p=0.013) were significantly lower in participants who had sustained mTBIs vs. controls. 30:15 upon standing was significantly lower in participants who had sustained mTBIs vs. controls (p=0.014). There were no significant differences in respiratory frequency or blood pressure in supine or standing.	12	22	4
LaFountaine et al, 2009	Prospective cohort	HR, HRV (HF, LF, LF:HF ratio), heart rate complexity	3 concussed participants (one female; man age 19±2 years) 3 control participants matched for age, gender, height, weight, sport *and position* (one female; man age	No significant differences in HRV were found at rest or during isometric handgrip test 48 hours or two weeks following concussion. No significant differences in hear rate complexity was found at rest 48 hours or two weeks following concussion.	8	17	3b

			19±2 years) *where possible	Heart rate complexity was significant reduced in concussed participants vs. controls 48 hours following concussion ($p<0.05$), and returned to control group levels by 2 weeks following concussion.			
LaFountaine et al, 2011	Prospecti ve cohort	QT interval variability	3 concussed participants (one female; man age 19±2 years) 3 control participants matched for age, gender, height, weight, sport and position (one female; man age 19±2 years)	The QT interval variability in concussed (-1.7ms±0.4) participants was significantly higher than in control participants (-0.4ms±0.4) 48 hours following concussion ($p=0.016$). There was no significant difference in QT interval variability between concussed and control participants one week and two weeks following concussion.	9	22	3b
Leddy et al, 2013 (abstract)	Retrospec tive cohort	HR	Concussed individuals who: Had submaximal exertion induced symptom exacerbation (n=39) Exercised to exhaustion without symptoms (n=25) Exercised to exhaustion with cervicogenic symptoms (n=101) Exercised to exhaustion with vestibular/ocular /	Concussed individuals with submaximal exertion induced symptom exacerbation had significantly lower HR during exertion and significantly higher RPE than concussed individuals who exercised to exhaustion ($P<0.05$).	3	10	2b

			Migraine-related symptoms (n=40)				
Senthinathan et al, 2014a (abstract)	Case study with pre-/post-injury measures	HR, HRV (mean RR, SDNN, NN50, pNN50, LFnorm, HFnorm)	18-year old female varsity athlete tested 3 times in one month prior to injury then retested at 72 hours post-concussion, at the beginning of exercise progression once asymptomatic and one week following medical clearance to return to play	Signficiant elevation in HR and LFnu, and significant decrease in HFnu 72 hours post-concussion ($p<0.05$). Significant increase in HR, at the start of exercise progression when asymptomatic ($p<0.05$). Decrease in mean RR, SDNN, NN50 and pNN50 at start of exercise progression.	5	13	4
Senthinathan et al, 2014b (abstract)	Prospecti ve cohort	HFnu, LFnu	11 concussed varsity athletes, 11 matched controls	Concussed athletes had increased LFnu and decreased HFnu in sitting vs. controls 72 hours post-concussion.	8	13	2b
Su et al, 2005	Cross-sectional	LF, HF, LF:HF, LFnu, HFnu	90 concussed participants classified upon hospital admission: Group I: "mild head concussion"; GCS=15 (n=18; ages 13-42 years) Group II: GCS=9-14; no pupil dilation (n=29; ages 17-84 years) Group III: GCS=4-8; no pupil dilation (n=17; ages 27-78 years) Group IV: GCS I=4-8; unilateral or bilateral pupil dilation without reaching criteria for brain death (n=12; ages 18-82	There was no significant difference in LF, HF, LFnu or LF:HF between concussed participants and normal participants ($p>0.05$).	11	17	4

			years) Group V: GCS=3; brain dead (n=14; ages 4-67 years) 17 "normal" participants; ages 18-42 years				
Tan et al, 2009	Cross-sectional	SDNN	18 war veterans medically diagnosed with mTBI (all male, ages 24-52)** 10 war veterans with no medical diagnosis of mTBI (two female, 24-48)** ** groups aggregated to compare to sex and age-corrected normative data	Significantly decreased SDNN as compared to sex- and age-corrected normative data. A mean numeric pain rating of greater than 3 over 30 days prior to evaluation, as well as medically diagnosed of mTBI and PTSD had a significant negative correlation with decreased SDNN ($r=-0.373$, $p<0.05$).	9	14	4

DB=Downs and Black; SEQES=Systematic Evaluation of Quality of Evidence Scale. HR=heart rate; HRV=heart rate variability; SDNN=Standard deviation of all RR intervals; RMSSD=the square root of the mean of the sum of the squares of differences between adjacent RR intervals; NN50=the number of pairs of RR intervals differing by more than 50ms in a recording; pNN50 the number of pairs of RR intervals differing by more than 50ms in a recording, divided by the total number of RR intervals; LF=low frequency; HF= high frequency; nu=normalized units.[10]

596 Table 3: Appraisal Category Score Summary

APPRAISAL TOOL	CATEGORY	MEDIAN SCORE (RANGE)
DOWNS and BLACK	Reporting (/11)	1 (1-7)
	External Validity (/3)	0 (0)
	Internal Validity-Bias (/7)	3 (1-5)
	Internal Validity-Confounding (/6)	1 (0-3)
	Power (/5)	0 (0)
SEQES	Study Question (/2)	1 (0-2)
	Study Design (/14)	7 (3-10)
	Subjects (/8)	3(0-3)
	Intervention (/6)	3 (1-4)
	Outcomes (/6)	2 (1-4)
	Analysis (/10)	3 (1-6)
	Recommendations (/2)	1 (1-2)

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599 Table 4: Summary of Quantity, Quality and Level of Evidence-Heart Rate (HR)

			LEVEL OF EVIDENCE																	TOTAL STUDIES
			1				2			3			4						5	
			a: Systematic review of prospective cohort studies	b: Prospective cohort with god follow up	c: All-or-none case series	a: Systematic review of 2b and better studies	b: Retrospective cohort		c: Ecological study	a: Systematic review of 3B and better studies	b: Non-consecutive cohort study/cohort study with very limited population		Case Series	Cross-Sectional		Case Study		Studies with superceded reference standards	Expert opinion	
							SIG	nSIG			SIG	nSIG		SIG	nSIG	SIG	nSIG			
OUTCOME MEASURES & ENVIRONMENTS	Rest	Sitting										1 **(8)** *(17)*								1
		Position Unknown										1 **(13)** *(27)*				1 **(5)** *(13)*				2
	Exercise	Steady state, low intensity aerobic exercise									1 **(13)** *(27)*									1
		High intensity interval aerobic exercise										1 **(13)** *(27)*								1
		Voluntary aerobic exercise *										1 **(10)** *(26)*								1
		Forced aerobic exercise *									1 **(10)** *(26)*									1
		Submaximal aerobic exercise intervals to exhaustion					1 **(3)** *(10)*													1
	NP	Paced													1					1

	Tasks	Auditory Serial Addition Task-Revised													**(1 1)** *(23)*				
		Short Category test													1 **(1 1)** *(23)*				1
		Rey Osterrieth Complex Figure, copy and memory													1 **(1 1)** *(23)*				1
		Rey Auditory Verbal Learning test													1 **(1 1)** *(23)*				1
		Symbol Digit Modalities test													1 **(1 1)** *(23)*				1
	Under stressful conditions**														1 **(1 1)** *(23)*				1

SIG=significant finding; NSIG=non-significant finding; NP Tasks=neuropsychological tasks. *=animal model study; **= doing mental arithmetic with 85dB white noise, bright lights, and environmental interrupters) The top number in each cell is the number of publications for each outcome; the bold number in parentheses is the range in the Downs and Black (DB) criteria scores for each outcome; the italicized number in parentheses is the range in Systematic Evaluation of Quality of Evidence Scale (SEQES) criteria scores for each outcome.

609 Table 5: Summary of Quantity, Quality and Level of Evidence-Heart Rate Variability (HRV),
610 Time Domain Measures
611

				LEVEL OF EVIDENCE															TOTAL STUDIES
				1				2		3			4					5	
				a: Systematic review of prospective cohort studies	b: Prospective cohort with good follow-up	c: All-or-none case series	a: Systematic review of 2b and better studies	b: Retrospective cohort	c: Ecological study	a: Systematic review of 3B and better studies	b: Non-consecutive cohort study/cohort study with very limited population		Case Series	Cross-Sectional		Case Study		Studies with superceded reference standards	Expert opinion	
											SIG	nSIG		SIG	nSIG	SIG	nSIG			
mean RR	Rest	Standing													1 **(12)** *(22)*					1
		Supine												1 **(12)** *(22)*						1
		Position Unknown										1 **(12)** *(24)*					1 **(5)** *(13)*			2
	Exercise	Steady state, low intensity aerobic exercise									1 **(12)** *(24)*									1
RMSSD	Rest	Standing													1 **(12)** *(22)*					1
		Supine										1 **(9)** *23*		1 **(12)** *(22)*						2
SDNN	Rest	Sitting													1 **(9)** *(14)*					1
		Standing												1 **(12)** *(22)*						1

			Supine								1 **(9)** *23*		1 **(12)** *(22)*						2
			Position Unknown								1 **(12)** *(24)*					1 **(5)** *(13)*			2
		Exercise	Steady state, low intensity aerobic exercise								1 **(12)** *(24)*								1
	NN50	Rest	Position Unknown													1 **(5)** *(13)*			1
	PNN 50	Rest	Supine								1 **(9)** *(23)*								1
			Position Unknown													1 **(5)** *(13)*			1

SIG=significant finding; NSIG=non-significant finding. RMSSD= the square root of the mean of the sum of the squares of differences between adjacent RR intervals; SDNN=standard deviation of all RR intervals; NN50= The number of pairs of RR intervals differing by more than 50ms in a recording, divided by the total number of RR intervals; PNN50= the number of pairs of RR intervals differing by more than 50ms in a recording, divided by the total number of RR intervals.[10] The top number in each cell is the number of publications for each outcome; the bolded number in parentheses is the range in the Downs and Black (DB) criteria scores for each outcome; the italicized number in parentheses is the range in Systematic Evaluation of Quality of Evidence Scale (SEQES) criteria scores for each outcome.

625 Table 6: Summary of Quantity, Quality and Level of Evidence: Heart Rate Variability (HRV),
626 Frequency Domain Measures
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LEVEL OF EVIDENCE				LEVEL OF EVIDENCE																TOTAL STUDIES
				1				2		3			4						5	
				a: Systematic review of prospective cohort studies	b: Prospective cohort with good follow up	c: All-or-none case series	a: Systematic review of 2b and better studies	b: Retrospective cohort	c: Ecological study	a: Systematic review of 3B and better studies	b: Non-consecutive cohort study/cohort study with very limited population		Case Series	Cross-Sectional		Case Study		Studies with superceded reference standards	Expert opinion	
											SIG	nSIG		SIG	nSIG	SIG	nSIG			
OUTCOME MEASURES & ENVIRONMENTS	LF Power	Rest	Standing											1 **(12)** *(22)*						1
			Supine									1 **(9)** *(23)*								1
			Position Unknown									1 **(12)** *(24)*			1 **(11)** *(17)*					2
		Exercise	Steady state, low intensity aerobic exercise								1 **(12)** *(24)*									1
	HF Power	Rest	Standing												1 **(12)** *(22)*					1
			Supine									1 **(9)** *(23)*		1 **(12)** *(22)*						2
			Position Unknown									1 **(12)** *(24)*			1 **(11)** *(17)*					2
		Exercise	Steady state,								1 **(1**									1

			low intensity aerobic exercise							**2)** *(24)*									
	LFnu	Rest	Sitting							1 **(8)** *(21)*									1
			Supine										1 **(12)** *(22)*						1
			Position Unknown								1 **(12)** *(24)*			1 **(11)** *(17)*		1 **(5)** *(13)*			3
			Difference between sitting and standing							1 **(8)** *(21)*									1
		Exercise	Steady state, low intensity aerobic exercise							1 **(12)** *(24)*									1
	HFnu	Rest	Sitting							1 **(8)** *(21)*									1
			Supine										1 **(12)** *(22)*						1
			Position Unknown								1 **(12)** *(24)*					1 **(5)** *(13)*			2
			Difference between sitting and standing							1 **(8)** *(21)*									1

		Exercise	Steady state, low intensity aerobic exercise									1 **(12)** *(24)*								1
	LF:HF Ratio	Rest	Sitting									1 **(8)** *(17)*								1
			Supine									1 **(9)** *(23)*								1
			Position Unknown									1 **(12)** *(24)*			1 **(11)** *(17)*					2
		Exercise	Isometric Handgrip									1 **(8)** *(17)*								1
			Steady state, low intensity aerobic exercise									1 **(12)** *(24)*								1
	Total Power	Rest	Supine									1 **(9)** *(23)*								1
			Position Unknown									1 **(12)** *(24)*								1

SIG=significant finding; NSIG=non-significant finding. LF=low frequency; HF=high frequency; nu=normalized units.[10] The top number in each cell is the number of publications for each outcome; the bold number in parentheses is the range in the Downs and Black (DB) criteria scores for each outcome; the italicized number in parentheses is the range in Systematic Evaluation of Quality of Evidence Scale (SEQES) criteria scores for each outcome.

Table 7: Summary of Quantity, Quality and Level of Evidence-Heart Rate Variability (HRV), Miscellaneous

				LEVEL OF EVIDENCE															TOTAL STUDIES
				1			2			3			4					5	
				a: Systematic review of prospective cohort studies	b: Prospective cohort with god follow up	c: All-or-none case series	a: Systematic review of 2b and better studies	b: Retrospective cohort	c: Ecological study	a: Systematic review of 3B and better studies	b: Non-consecutive cohort study/cohort study with very limited population		Case Series	Cross-Sectional		Case Study	Studies with superceded reference standards	Expert opinion	
											SIG	nSIG		SIG	nSIG				
OUTCOME MEASURES & ENVIRONMENTS	Approximate Entropy	Rest	Sitting	EXCLUDED	NO DATA ANALYSIS	EXCLUDED	EXCLUDED	NO DATA AVAILABLE	NO DATA AVAILABLE	EXCLUDED		1 **(8)** *(17)*				NO DATA AVAILABLE	NO DATA AVILABLE	EXCLUDED	1
		Exercise	Isometric Hand grip								1 **(8)** *(17)*								1
	QT Interval Variability	Rest	Standing								1 **(9)** *(20)*								1
	Coefficient variation of RR	Rest	Standing											1 **(12)** *(22)*					1
			Supine												1 **(12)** *(22)*				1

SIG=significant finding; NSIG=non-significant finding. The top number in each cell is the number of publications for each outcome; the bold number in parentheses is the range in the Downs and Black (DB) criteria scores for each outcome; the italicized number in parentheses is the range in Systematic Evaluation of Quality of Evidence Scale (SEQES) criteria scores for each outcome.

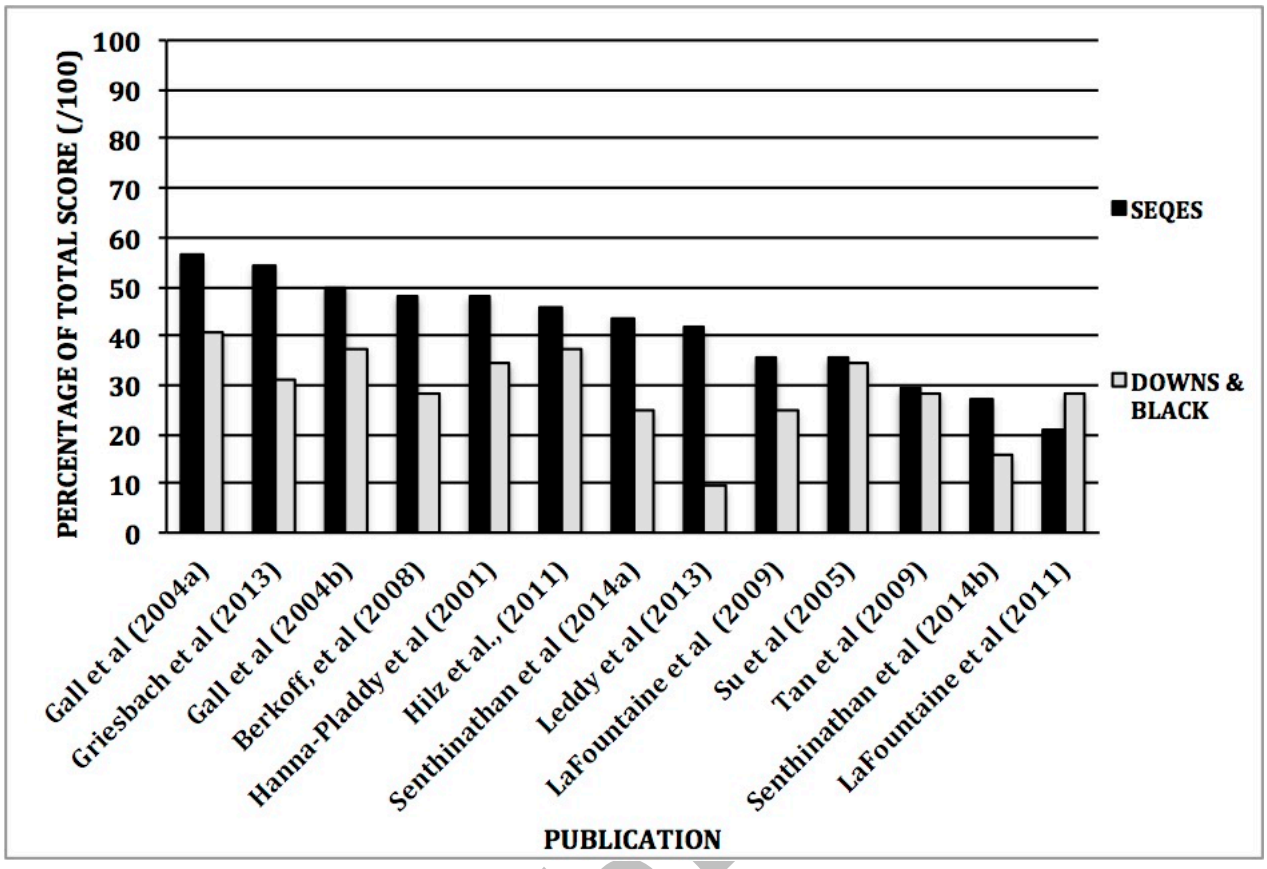

Figure 2. Ranking of included studies by percentage of total score for the SEQES criteria (/48 points) and the DB criteria (/32 points).