TECHNICAL COMMENTARY

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POST-TRAUMATIC STRESS DISORDER LIBRARY

Heart disease

Introduction

People with mental disorders often show increased rates of co-occurring physical conditions such as heart disease. An increased risk of heart disease in people with PTSD may be a consequence of the disorder itself as PTSD is associated with dysfunction of the immunological system and excess inflammation, which in turn is associated with significant cardiovascular health problems. Unhealthy lifestyle factors such as smoking and poor diet may also contribute to any increased risk of heart disease and these factors are also prevalent in people with PTSD.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with PTSD. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. When multiple copies of reviews were found, only the most recent version was included. We prioritised reviews with pooled data for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items checked have been excluded from the library. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found four systematic reviews that met our inclusion criteria[3-6].

- High quality evidence finds a small increased risk of coronary heart disease in people with PTSD (with or without comorbid depression) compared to people without PTSD.
- Moderate quality evidence finds large effects of lower high-frequency and RMSSD (root mean square of the successive differences) heart rate variability in people with PTSD. These effects were largest in clinical populations. There was also a small increased risk of lower resting respiratory sinus arrhythmia. There was no change in low-frequency heart rate variability. The results remained regardless of medication status, year of publication, study quality score, study methodology, or participant age or sex.
- Moderate to high quality evidence finds a small association between increased PTSD symptoms and increased cardio-respiratory symptoms in general.

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Akosile W, Colquhoun D, Young R, Lawford B, Voisey J

The association between post-traumatic stress disorder and coronary artery disease: a meta-analysis

Australasian Psychiatry 2018; 26: 524-30

View review abstract online

Comparison	**Risk of coronary heart disease in people with PTSD compared to people without PTSD.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) finds a small increased risk of coronary heart disease in people with PTSD with or without comorbid depression.**
Coronary heart disease	
Significant, small effect of increased rates of coronary heart disease in people with PTSD; 9 prospective studies, N = 150,507, HR = 1.61, 95%CI 1.47 to 1.77, $p < 0.0001$, $I^2 = 0\%$ Results were similar in the analysis where depression was controlled for. All samples were free of cardiovascular disease at baseline and the diagnosis of PTSD preceded the diagnosis of coronary heart disease.	
Consistency in results‡	Consistent
Precision in results§	Precise
Directness of results‖	Direct

Campbell AA, Wisco BE, Silvia PJ, Gay NG

Resting respiratory sinus arrhythmia and posttraumatic stress disorder: A meta-analysis

Biological Psychology 2019; 144: 125-35

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Comparison	**Resting respiratory sinus arrhythmia in people with PTSD vs. controls (various).** **Respiratory sinus arrhythmia refers to the naturally occurring variability in the length of time between heart beats that is coordinated with the respiratory cycle. It is often used as an index of parasympathetic control of heart rate, with high**

	respiratory sinus arrhythmia indicating a healthy parasympathetic nervous system.
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, precise, indirect) finds a small effect of lower resting respiratory sinus arrhythmia in people with PTSD.**
Resting respiratory sinus arrhythmia	
Significant, small effect of decreased resting respiratory sinus arrhythmia in people with PTSD; All controls: 55 studies, N = 6,689, g = -0.26, 95%CI -0.35 to -0.16, $p < 0.001$, I^2 = 56%, $p < 0.001$ Healthy controls: 18 studies, g = -0.44, 95%CI -0.62 to -0.25, $p < 0.05$ Trauma-exposed controls: 18 studies, g = -0.20, 95%CI -0.41 to -0.01, $p < 0.05$ Other mental health controls: 10 studies, g = -0.30, 95%CI -0.55 to -0.05, $p < 0.05$ The effects were larger in adults than in children, in studies using DSM-5 PTSD measures and in studies using pNN50 (proportion of beat-to-beat intervals that differ by more than 50 ms) and SDNN (standard deviation of beat-to-beat intervals) measures of resting respiratory sinus arrhythmia.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Some indirectness (mixed controls).

Ge F, Yuan M, Li Y, Zhang W

Posttraumatic stress disorder and alterations in resting heart rate variability: A systematic review and meta-analysis

Psychiatry Investigation 2020; 17: 9-20

View review abstract online

Comparison	**Heart rate variability in people with PTSD vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) finds large effects of lower high-frequency and RMSSD (root mean square of the successive differences) heart rate variability in people with PTSD. These effects were largest in clinical populations. There were no differences in low-frequency heart rate variability. There were no moderating effects of medication status, year of publication, study quality score, study methodology, or participant age or sex.**
Heart rate variability	

Significant, large effect of lower high-frequency heart rate variability in people with PTSD; 14 studies, N = 1,375, *g* = -1.58, 95%CI -2.32 to -0.84, *p* < 0.0001, I^2 = 96% This effect was largest in clinical populations. The effect was not significant in studies conducted in America or in studies that used long-term recording of heart rate variability. *Significant, large effect of lower RMSSD (root mean square of the successive differences) heart rate variability in people with PTSD;* 9 studies, N = 629, *g* = -1.96, 95%CI -2.76 to -1.16, *p* < 0.00001, I^2 = 94% This effect was largest in clinical populations. *There were no significant differences in low-frequency heart rate variability;* 12 studies, N = 1,318, *g* = -0.63, 95%CI -1.49 to 0.24, *p* = 0.15, I^2 = 97% There were no moderating effects of medication status, year of publication, study quality score, study methodology, or participant age or sex on any outcome variable.

Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Pacella ML, Hruska B, Delahanty DL

The physical health consequences of PTSD and PTSD symptoms: a meta-analytic review

Journal of Anxiety Disorders 2013; 27: 33-46

View review abstract online

Comparison	**Associations between PTSD and cardio-respiratory symptoms.**
Summary of evidence	**Moderate to high quality evidence (unclear sample size, consistent, precise, direct) finds a small association between increased PTSD symptoms and increased cardio-respiratory symptoms.**
Cardio-respiratory symptoms	
Significant, small association between increased PTSD symptoms and increased cardio-respiratory symptoms; 21 studies, N not reported, *r* = 0.17, 95%CI 0.12 to 0.22, *p* < 0.001, Q*p* > 0.05	
Consistency in results	Consistent

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Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, *g* = Hedges g, standardised mean difference between groups, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, *p* = statistical probability of obtaining that result, Q = test for heterogeneity, vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[7].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[7].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[8]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship

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between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[7];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[9].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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