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A meta-analysis investigating the outcomes and correlation between heart rate variability biofeedback training on depressive symptoms and heart rate variability outcomes versus standard treatment in comorbid adult populations

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Abstract. *Background and Aim:* Heart rate variability biofeedback (HRVB) has previously been used to ameliorate depressive symptoms but its uses for tackling depressive symptoms in an array of comorbid adult patients is less established. This meta-analysis aims to evaluate whether HRVB is a useful tool to reduce depressive symptoms and improve HRV relative to standard treatment in adult comorbid populations, while also attempting to establish the association between the two outcomes. *Methods:* An extensive literature review was conducted using several databases including PubMed, Cinahl, Medline, Web of science and clinical.gov/UK register. A total of 149 studies were identified with 9 studies, totalling 428 participants were analysed using a random effects model. *Results:* Depressive outcomes yielded a mean effect size g=0.478 (CI 95% 0.212, 0.743) with HRV outcomes, yielding a mean effect size of g=0.223 (95% CI 0.036 to 0.411). Total heterogeneity was non-significant for depressive outcomes (Q= 13.77, p=0.088 I^=42.86%) and HRV (Q= 1.598, p=0.991, I^=0.000%) which indicates that little variance existed for the included studies. *Conclusions:* In summary, the outcomes demonstrate that HRVB can improve both clinically relevant depressive symptoms and physiological HRV outcomes in various comorbid conditions in adult populations, while the correlation between the two was moderately negative, but non-significant. (www.actabiomedica.it)

Key words: HRVB, depressive, symptoms, meta-analysis, adult populations

Depression represents the most common mental health condition (1) and is recognised globally as the leading cause of disability (2) which is proposed to affect 265 million people of various ages (2). This is exacerbated by the bidirectional relationship between chronic diseases and depressive symptoms (3), where research has demonstrated an association between comorbid states of depressive symptoms and worsened prognosis (4). This has profound implications for clinical practice since depressive symptoms in patients include anhedonia or loss of interest (5), attenuated energy levels and reduced cognition (6), altered appetite (7), fatigue, low productivity, and irritability (8).

Depression has been strongly associated with increased prevalence of diseases including metabolic disorders (9) and cardiac disease (10), with the later perhaps best documented due to the heart and brains bidirectional communication strategy (11; 12). Several interventions have been put forward to treat such conditions, including pharmacological interventions (13), and various psychological treatments including cognitive behavioural therapy (CBT) (14) and psychotherapy (15).

While older research deemed pharmacological treatment to be the gold standard (16), recent research in the form of a meta-analysis contests this stance as RCTs showed no difference between antidepressant

medication versus psychotherapy in depressive outcome measures such as the beck depression inventory 11 (BDI-11) (15). This indicates that better techniques must be sought to address depressive symptoms in comorbid patients.

A potential solution to such limitations is to use heart rate variability (HRV) as an outcome measure. HRV represents a powerful biomarker (17) of the autonomic nervous system (ANS) (18; 19) which is sensitive to physiological, psychological conditions (20) and emotional regulation (21). HRV time domain data measure is the temporal variation between adjacent heartbeats, known as the R-R interval (18) while frequency domain readings can quantify the absolute signal intensity of each component band (22). These component readings measure the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) dynamics (22), with a non-linear R-R interval variation reflecting higher HRV (22; 23) that has in turn been linked to improvements in psychosocial outcomes and depression (24). Meanwhile, higher frequency of certain bands such as high frequency (HF) corresponds to better PNS (25) and vagal nerve activation (26). This has resulted in growing consensus that identifies HRV as a powerful diagnostic tool (27) beyond its traditional use in cardiology (28) as HRV outcomes are now deemed a predictive marker for depression (23).

Due to such discoveries, the use of HRV has extended beyond its diagnostic use as it is now considered as a valid biofeedback (HRVB) tool to ameliorate depressive symptoms (27; 1). Performing HRVB at the resonant frequency (which is individually specified breathing at a slow rate, usually 4.5 to 7 breaths per minute, that maximises Respiratory Sinus Arrhythmia; RSA) is proposed to further activate the PNS due to greater HF signalling (29). This offers the advantage of being non-invasive (1) while offering real time feedback (27) that is considered engaging and straightforward to use (30). Furthermore, it is now considered a cost-effective method for clinical practice due to the growing availability of portable HRVB devices (17). Research has also shown that the more accessible versions of HRVB are highly efficacious since certain polar heart rate monitors have demonstrated correlation coefficients as high as 0.996 and 0.995 for time and frequency domain readings, respectively (31). This means that accessible field based HRVB is comparable to gold standard ECG (31).

Given that low PNS activation and vagal nerve tone are considered two deficient physiological changes associated with depression (23), it is deemed important for depressed participants to breathe at a frequency that has the potential to activate their parasympathetic system in the best way. This physiological mechanism might explain the improvement in clinical depressive symptoms due to the link between heart and brain as outlined by the neurovisceral integration model (11). This is best shown by Steffen and colleagues (32) who noticed that breathing at the resonant frequency improved systolic blood pressure, HRV LF/HF ratio, and mood versus the control group, while breathing at just one breathe above the resonant frequency resulted in non-significant change compared to the control.

Lehrer et al. (30) provided support for the use of HRVB use as a complementary therapeutic aid. Their meta-analysis showed that HRVB conducted at the resonant frequency to be effective for improving depressive symptoms in a variety of physical, behavioural, and cognitive conditions. A recent systematic review by Blasé et al. (33) demonstrated that HRV biofeedback (HRVB) improved BDI-11 score by 78% which outperformed the treatment as usual (TAU) group by 34%. Another meta-analysis by Pizzoli and colleagues (1) examined the link between HRVB and depressive symptoms in adult populations with comorbidities. However, the same study (1) didn't examine HRV outcomes or the relationship between HRV physiological outcomes and subjective depressive outcome measures.

This is an important distinction since improving physiological readings might help establish field-based treatments that could potentially assist in the improvement of depressive outcomes. Conversely, a lack of HRV response might suggest that adaptations elsewhere are responsible for clinical improvements which is plausible when linked to the neurovisceral integration model (11). Either way, HRVB might represent a practical method to address the underlying pathophysiology of depression to improve clinical outcomes (31; 33; 34).

Therefore, the aim of the current study is to expand on the work of Pizzoli et al. (1) by conducting a meta-analysis to establish whether HRVB is superior to current standard treatments for ameliorating depressive symptoms and improving HRV outcomes in populations that are suffering from comorbidity or depressive states. Finally, the study intends to assess the relationship between the two variables by establishing whether HRVB training improves depressive outcomes in adult comorbid populations relative to TAU groups.

Methods

The research was conducted and completed in June 2022. There were no publication data limitations.

Database selection

Based on relevant recommendations (35) the following databases were searched: Pubmed, Cinahl, Medline and Web of Science, Proquest, Psyche-info, Sports discus, Magonline library, Sage, Amed, Wiley online library, and Cochrane. Finally, the clinical trials.gov register was searched (see Table 1, PRISMA checklist).

The use of search strings was performed accordingly: The research question was compartmentalised into each key concept using the PICO method (population, issue, comparison intervention, and outcome) (36). The search criteria was as follows; Variable one (P)= Depression or major depressive disorder or MDD or depressive disorder or depressive symptoms, AND Variable two (I)= HRV Biofeedback or HRV or heart rate variability biofeedback training or heart rate variability training AND Variable three {C}= randomised controlled trial or RCT AND Variable four (O) = outcome measures or HRV.

For the clinicaltrials.gov search, variable one (P) was used for "condition or disease", variable two (I) interventional studies (clinical trials), variable three (C) completed trials sought involving adult populations, intervention/treatment, and variable four consisting of outcome measures (O). Funder type remained open and required further investigation to account for conflict of interests.

The inclusion criteria were: 1) a randomised interventional study, 2) containing a HRVB intervention group compared to control which involved standard treatment/TAU, 3) including both a psychometric and HRV outcome measure, 4) in English language, 5) investigating depressive symptoms in relation to other psychopathological and medical comorbidities including stress related disorders, and 6) performed on adults.

The following studies were excluded based on the following criteria: 1) not a randomised study, 2) no HRVB intervention, 3) no Psychometric outcome measure, 4) no HRV outcome measure, 5) HRVB combined with exercise or antidepressants, 6) review article, 7) studies reporting acute response to single HRVB session, 8) not peer reviewed, 9) articles not in English language, and 10) other confounding factors included in HRVB protocol such as Religious Practice.

The McMasters critical appraisal tool was used for consistency (37) as it is well used in healthcare and clinical research (37) to establish strengths and limitations of studies (38). The Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines (Figure 1) were also applied (39). This was also performed to establish a paper's strengths and limitations to ensure that included studies are of a high quality (38).

Effect size calculation

Both depressive symptoms and HRV outcomes versus a standard treatment were measured using comprehensive meta-analysis software (CMA) (40). Hedges g was the effect size selected as it represents a standardised mean difference of the sample population for each study (41). This also allows for comparability across studies and can be used to standardise different outcome scales (42). Studies with three intervention groups led to the exclusion of the control group as the aim of the meta-analysis is to compare the effects of HRVB against conventional approaches or TAU groups in clinical practice. Effect sizes for both groups were measured at post intervention using sample size, mean and standard deviation for both psychometric and HRV outcome since pre-post measurements is proposed to inflate bias and lack of reliability (43).

Table 1. PRISMA Checklist.

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	A meta-analysis investigating the outcomes and correlation between heart rate variability biofeedback training on depressive symptoms and heart rate variability outcomes versus standard treatment in comorbid adult populations	Yes
BACKGROUND			
Objectives	2	The objectives are to establish whether HRVB (heart rate variability biofeedback) is superior to current standard treatments for ameliorating depressive symptoms and improving HRV (heart rate variability) outcomes in populations that are suffering from comorbidity or depressive states.	Yes
METHODS			
Eligibility criteria	3	Inclusion criteria: 1) a randomised interventional study, 2) containing a HRVB intervention group compared to control which involved standard treatment/TAU, 3) included both a psychometric and HRV outcome measure, 4) in English language, 5) investigating depressive symptoms in relation to other psychopathological and medical comorbidities including stress related disorders, and 6) performed on adults. Exclusion criteria: 1) not a randomised study, 2) no HRVB intervention, 3) no Psychometric outcome measure, 4) no HRV outcome measure, 5) HRVB combined with exercise or antidepressants, 6) review article, 7) studies reporting acute response to single HRVB session, 8) not peer reviewed, 9) articles not in English language, and 10) other confounding factors included in HRVB protocol such as Religious Practice.	Yes
Information sources	4	Pubmed, Cinahl, Medline, Web of Science, Proquest, Psyche-info, Sports discus, Magonline library, Sage, Amed, Wiley online library, Cochrane and clinical trials.gov (Date of last search for above: July 2022)	Yes
Risk of bias	5	Assessing risk of bias was based on the Cochrane risk of Bias (ROB) tool	Yes
Synthesis of results	6	Comprehensive meta-analysis software was used to present and synthesise the figures. Microsoft word was also used to present data in table form.	Yes No
RESULTS			
Included studies	7	The studies included in the meta-analysis were published from 2009 to 2020 with the meta- analysis being comprised of studies from the following countries: three from USA, two from Taiwan and Germany, one from Sweden, and Austria. The studies were conducted on remitted cancer patients, depressed inpatient cohorts and outpatient major depressive disorder, alcohol substance abuse/dependence, acute ischemic stroke, coronary artery disease, heart failure, stress related neck pain and non-clinical populations experiencing stressful symptoms. Six studies utilised the Beck depression inventory-11 outcome measure, two used Hospital Anxiety depression scale, and one used Center for Epidemiologic Studies Depression scale.	Yes

Section and Topic	Item #	Checklist item	Reported (Yes/No)
Synthesis of results	8	Total number of included studies = 9 Total number of participants = 428 subjects that were divided into the experimental HRVB groups: (Number, 224 Weighted mean age and standard deviation = 52.56, 13.31, 62.05% males and 37.95% females) and control group (Number, 204, Weighted mean age and standard deviation = 52.56, 11, 53, 73% males and 46.27% females). Hedges G effect size of 0.478 (95% CI 0.212,0.743) and prediction intervals = (-0.204 to 1.160) were found which corresponded to a small effect. This signified that HRVB represents a better intervention modality than treatment as usual groups for improving depressive symptoms in comorbid populations. The hedges G effect size of 0.223 (95% CI 0.036 to 0.411) and prediction intervals = (-0.003 to 0.449) were found which corresponded to a small effect. This signified that HRVB represents a better intervention modality than treatment as usual groups for improving HRV in comorbid populations. A moderate correlation was found between the improvement in HRV and depressive outcomes.	Yes
DISCUSSION			
Limitations of evidence	9	A potential limitation of the meta-analysis is failing to measure these outcomes relative to a specific condition which might limit specificity in clinical practice. Furthermore, differences in HRVB protocols means that it is difficult to establish a gold standard HRV intervention. Finally, marked differences in volume between HRVB and standard care might lead to difficulty in establishing the most time efficient strategy for clinical practice.	Yes
Interpretation	10	The outcomes registered in this meta-analysis indicate that HRVB represents a superior method to conventional psychotherapeutic interventions when attempting to ameliorate depressive symptoms and improve HRV in comorbid adult populations.	Yes
OTHER			
Funding	11	None	Yes
Registration	12	The review was not registered	No

Risk of bias

Assessing risk of bias was based on the Cochrane Risk of Bias (ROB; Table 2 for a complete list of abbreviations) tool to ensure a consistent approach to establishing bias (44; 45). The ROB was classified as low, high or unclear (44) (Table 3) and included an overall ROB based on Cochrane's ROB by Higgins et al. (44) (Figure 2).

Data analysis

Socio-demographic information from the participant characteristic section of the results in each respective paper (46) was used to document weighted age and standard deviation, the percentage of males versus females, participant pathology, as well as study location of study and range of sample size. The CMA random effects model was performed twice to assess

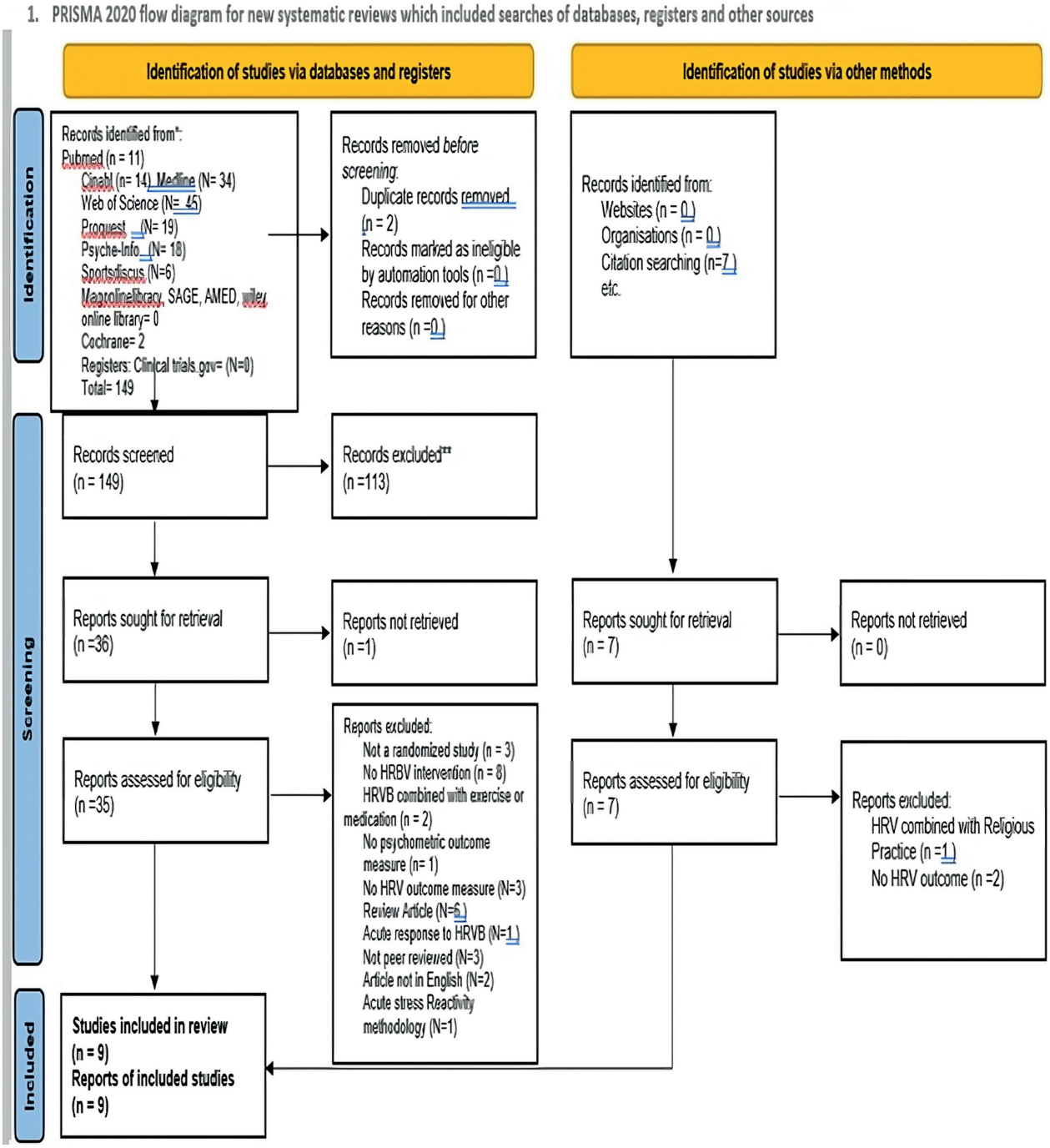

Figure 1: Prisma Flow Chart.

the effect of HRVB versus control for depressive and HRV outcomes as outlined in the effect size section.

HRV outcomes were also assigned a positive direction since higher levels of time and frequency domain included in the study represented better vagal nerve or PNS activity (22) with the same forest plot interpretation. A larger positive effect size number therefore corresponds to a larger effect for HRVB on HRV outcomes. RMSSD was the HRV variable sought in each study as it is considered a valid and

Table 2. Abbreviations.

Abbreviation	Full term
ANS	Autonomic Nervous System
BDI-11	Beck Depression Inventory Two
CBT	Cognitive Behavioural Therapy
EBP	Evidence Based Practice
HAMD	Hamilton Depression Rating Scale
HF	High Frequency
HRV	Heart Rate Variability
HRVB	Heart Rate Variability Biofeedback
LF	Low Frequency
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta Analysis
PNS	Parasympathetic Nervous System
RMSSD	Root Mean Squared Standard Deviation
ROB	Risk Of Bias
RSA	Respiratory Sinus Arrhythmia
SD	Standard Deviation
SDNN	Standard Deviation of normal beats intervals (NN interval)
SE	Standard Error
SNS	Sympathetic Nervous System
TAU	Treatment As Usual
WHO	World Health Organization

Table 3. Overall Risk of Bias Assessment.

Combinations ROB	Overall ROB Classification
All low risk with exception of participant blinding	Low Risk
One unclear ROB with 2 high ROB	High Risk
One unclear with one high ROB	Unclear
Two or more ROB	High Risk

reliable method to capture PNS and vagal nerve activity (22) while also representing powerful statistical properties (47). However, when RMSSD was unavailable, frequency domain measurement in the form of HF were utilised due to research stating that greater HF power corresponds better to vagal nerve and overall PNS activity (22).

To ascertain whether the included studies were suitable for a meta-analysis, an inter-study assessment of heterogeneity assessment was performed using a q-test, I-squared test for depressive and HRV outcomes (48). Publication bias was evaluated using both the trim and fill method and by plotting observed and imputed values into a funnel plots (49) which can indicate if studies are absent from the meta-analysis (49). The Egger's test was also conducted to explore the correlation between effect size and sampling variances which can be illustrated by a asymmetrical funnel plot (50).

Correlational analysis

The difference in means between HRVB and control for both depressive and HRV outcomes was calculated by pooled SD to convert them to Hedges G effect size to factor in the weighting of the sample size and subsequent standard deviation (51) to ensure that studies are accurately interpreted regarding their significance (52). Depressive outcomes were assigned a negative value in this instance to factor in the scale's true clinical interpretation (53) and to ensure correct correlational interpretation relative to HRV outcomes. Hedges G was then converted to fishers Z score (54) which is considered useful for minimising bias and for studies with small sample sizes (55).

Post hoc analysis

A post hoc analysis was conducted in CMA which involved the removal of studies that registered higher level of variance to see whether this altered the overall outcome and effect size (56).

Results

A total of 9 studies were included in the meta-analysis (Figure 3) with sample sizes ranging from 20 to 134 on a total of 428 subjects which were divided into the experimental HRVB (Number, 224 Weighted mean age and standard deviation = 52.56, 13.31, 62.05% males and 37.95% females) and control (Number, 204, Weighted mean age and standard deviation = 52.56, 11, 53, 73% males and 46.27% females).

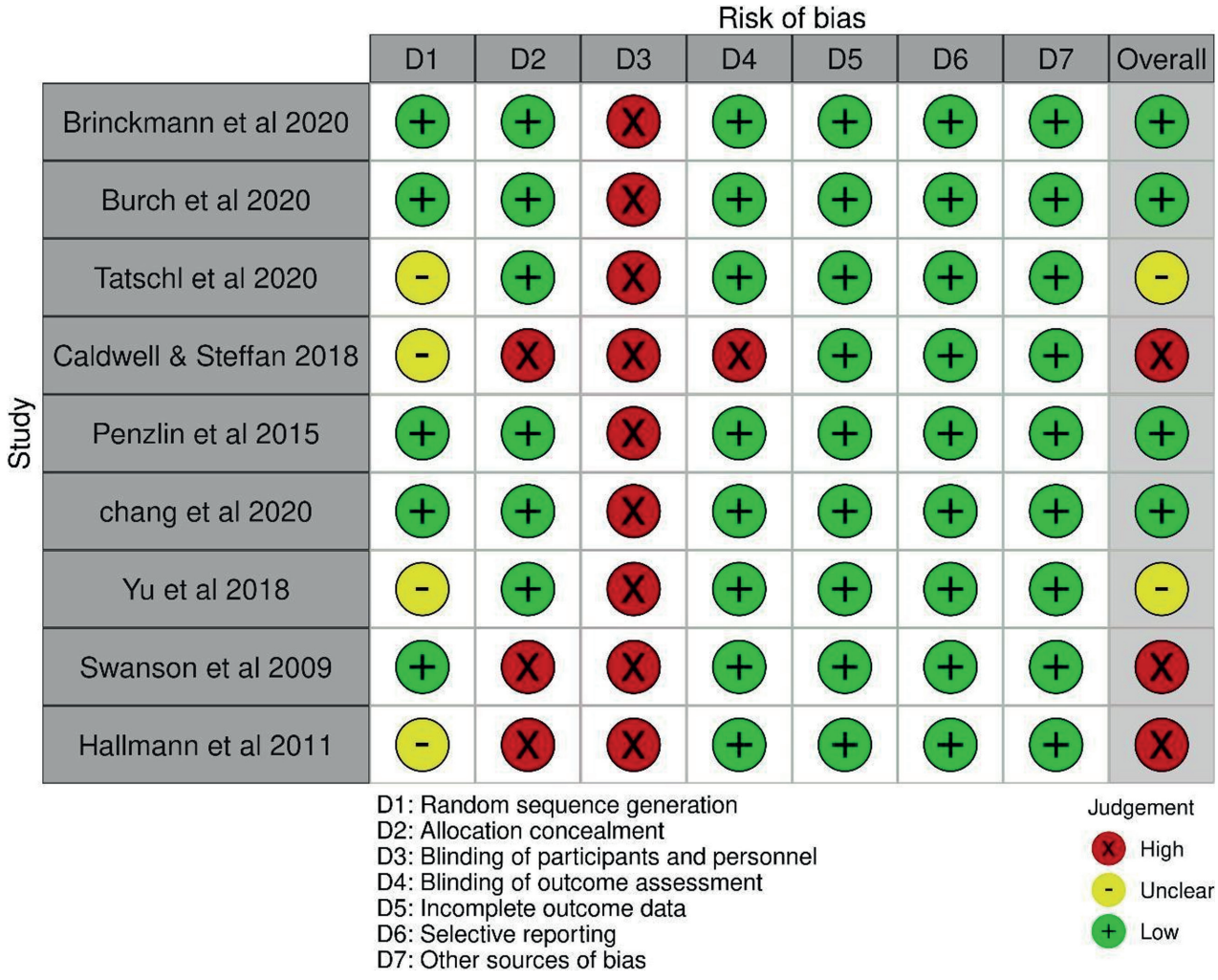

Figure 2. Risk of Bias Outcomes.

The studies included in the meta-analysis were published from 2009 to 2020 with the meta-analysis being comprised of studies from the following countries; three from USA (57; 25; 58), two from Taiwan (59; 60) and Germany (61; 62), one from Sweden (63), and Austria (64). The studies were conducted on remitted cancer patients (57), depressed inpatient cohorts (64) and outpatient major depressive disorder (25), alcohol substance abuse/dependence (62), acute ischemic stroke (59), coronary artery disease (60), heart failure (58), stress related neck pain (63) and non-clinical populations experiencing stressful symptoms (61). Six studies utilised BDI-11 outcome measure (61; 57; 25; 62; 64; 60), two used the Hospital Anxiety and Depression Scale (HADS) (59; 63), and one used the Center for Epidemiologic Studies Depression Scale (CES-D) (58). As per the inclusion criteria, each study outcome was gathered immediately post intervention, with intervention length from pre to post ranging from 2 weeks (59), 6 weeks (61; 57) to ten weekly sessions over 10 weeks (63). HRV outcomes included in the analysis was RMSSD (61; 57; 59; 64; 60) with the remaining articles involving HF data (25; 63; 62). The sample size of each studied ranged from 23 to 134 which is reflected by their respective weights in the forest plots (Figure 3 and 6).

Risk of bias

Figure 2 presents the risk of bias assessment. No information was withheld when reporting results as

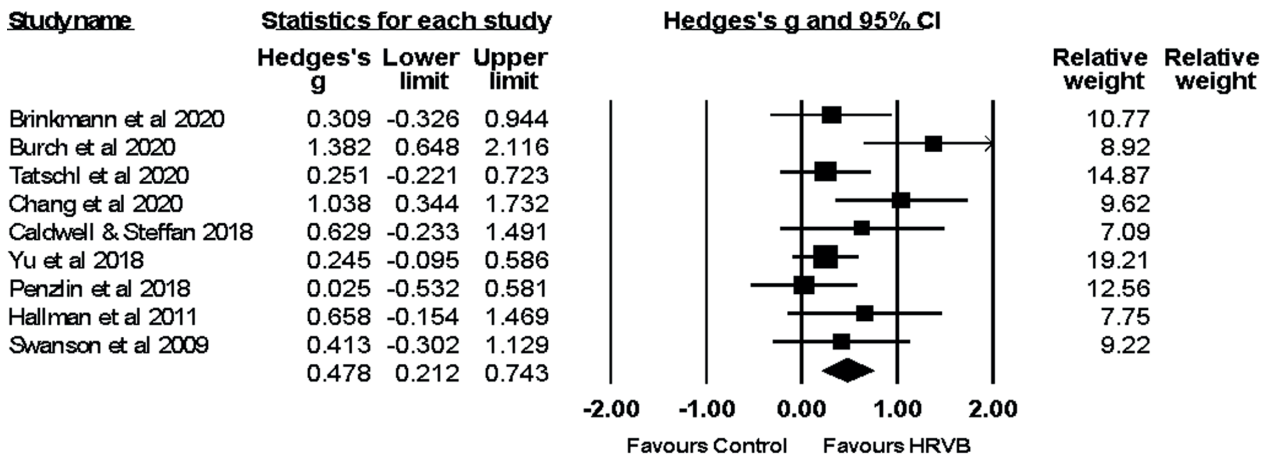

Figure 3. Forest Plot for HRVB versus control for Depressive Outcomes

demonstrated during analysis of included participants at baseline and participants finishing each trial. All included studies clearly accounted for incomplete data and reasons for participants drop out was clearly stated. Four studies did not clearly outline the random sequence generation and no studies blinded participants since this is not possible for biofeedback techniques (33). Only one study failed to blind outcome assessors (25). Overall, four studies were considered to present a low ROB, 3 studies were considered high while two studies were considered uncertain due to methodological uncertainty (70).

Depressive outcomes

The random effects meta-analysis (N=9) generated a combined Hedges G effect size of 0.478 (95% CI 0.212,0.743) (Figure 3) with prediction intervals = -0.204 to 1.160) (Table 4), with Z= 3.528 and p = 0.000**.** The hedges G effect size corresponded to a small effect with the outcome registered as a negative value which signifies that HRVB is a better intervention modality than TAU groups. Heterogeneity outcomes were non-significant as Q value = 13.76, p = 0.088 and I Squared= 41.86% (Table 5) which indicates that there was moderate between study variance (65).

The funnel plot imputed values showed no missing studies (Figure 4). The Duval and Tweedie's trim and fill (Table 6) indicate that under the random effects model, the combined effect size hedges g and associated confidence intervals remain at 0.478 (95% CI 0.212 to 0.743) indicating low overall bias (49) with the classic fail-safe N (Table 7) showing that 45 non-significant studies would be required to nullify the alternative hypothesis and accept the null hypothesis for depressive outcomes. The leave one out sensitivity analysis showed that the overall effect remained unaltered when each study was systematically excluded (Figure 5). There were no studies missing from the analysis as depicted by the trim and fill outcome (Table 6) which resulted in unaltered outcomes. The Egger's regression intercept (Table 8) presented non-significant outcomes regarding publication bias (t-value= 2.012, p=0.084).

Table 4. Prediction Intervals for HRVB on Depressive Outcomes.

Mean	0.478
Prediction Interval (95%) lower limit	-0.204
Prediction Interval (85%) Upper Limit	1.160

Table 5. Heterogeneity for HRVB for Depressive outcomes.

Q-value	P-Value	I squared
13.760	0.088	41.860

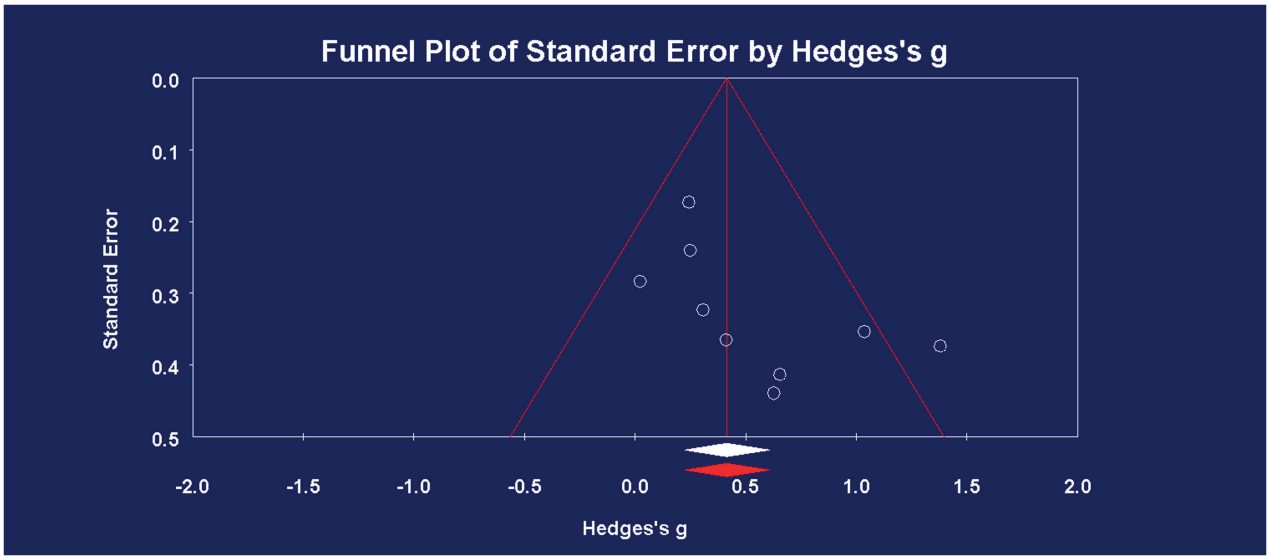

Figure 4. Funnel Plot of Standard Error by Hedge's g with Imputed Values (Depressive Outcomes).

Table 6. Duval and Tweedie's trim and fill for random effect model for Depressive Outcomes.

	Point Estimate	Lower Limit	Upper Limit	Q VALUE
Observed values	0.478	0.212	0.743	13.759
Adjusted values	0.478	0.212	0.743	13.759

Table 7. Classic fail-safe N for Depressive Outcomes.

Z value for observed studies	4.757 (3dp)
P-value for observed studies	0.000 (3dp)
Alpha	0.050 (3dp)
Tails	2.00
Z for alpha	1.966 (3dp)
Number of observed studies	9.0
Number of missing studies that would bring p-value to > alpha	45.000

Table 8. Egger's Regression Intercept for Depressive Outcomes.

Intercept	2.483
Standard Error	1.234
95% lower limit (2-tailed)	-0.435
95% upper limit (2-tailed)	5.401
t-value	2.012
df	7.000
P-value (1-tailed)	0.042
P-value (2-tailed)	0.084

HRV outcomes

The random effects meta-analysis (N=9) generated a combined Hedges G effect size of 0.223 (95% CI 0.036 to 0.411) (Figure 6) prediction intervals= -0.003 to 0.449) (Table 9) with Z=2.331 and p = 0.020.

The hedges G effect size corresponded to a small effect size with HRVB registering better outcomes than control groups. Heterogeneity outcomes were non-significant as Q value = 1.598, p= 0.991 and I Squared= 0.000 (Table 10) which indicated that there was little between study variance (65). The funnel plot imputed values (Figure 7) showed that three studies may be absent from the analysis which might indicate publication bias.

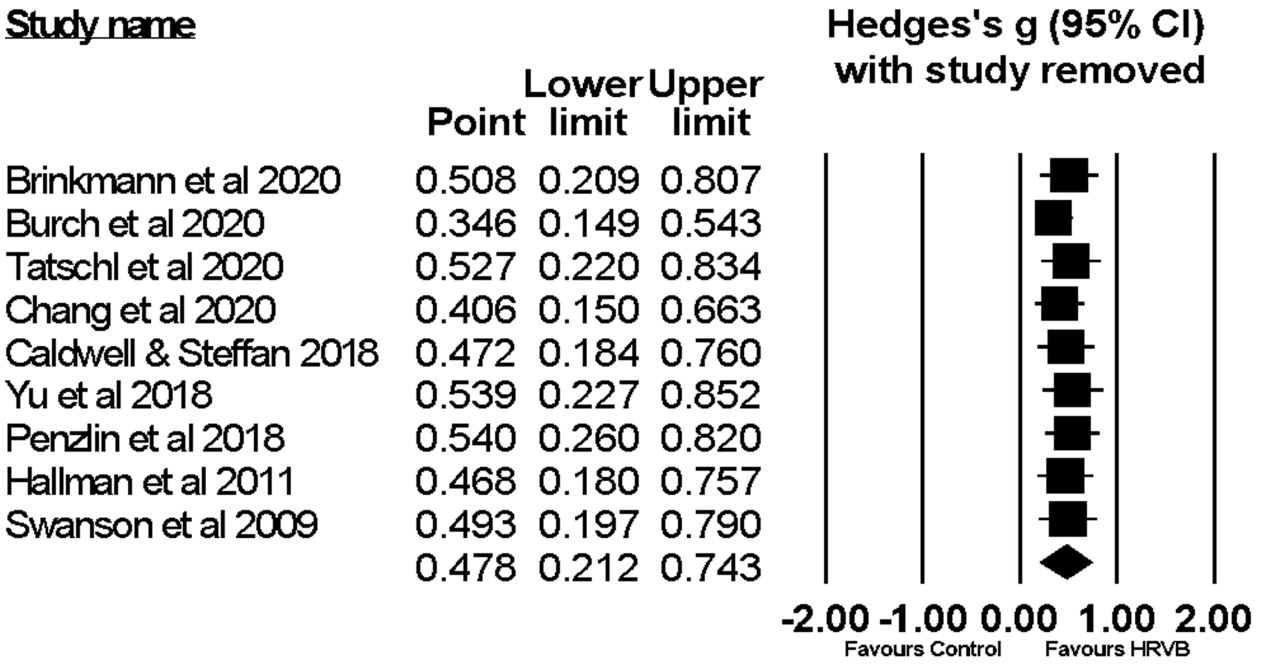

Figure 5. HRVB versus control for Depressive Outcomes leave 1 out sensitivity analysis.

Discussion

Nine peer reviewed studies were included in the meta-analysis. The sum of participants was 428 and were divided into 224 for HRVB and 204 for control which compared the effect of HRVB versus control on depressive symptoms, HRV outcomes and correlation between the two outcomes. To the authors knowledge, this represents the first meta-analysis to investigate all three of these variables. Overall, the results indicate that the effects of HRVB for depressive outcomes are significant, classified as small and close to medium (Figure 3). This outcome is comparable to Pizzoli et al. (1) who also investigated the impact of HRVB on depressive outcomes in adult populations with comorbidity.

The outcomes reported here and Pizzoli et al. (1) appear to suggest that the effect size could exceed both moderate and large values of 0.5 and 0.8 based on prediction intervals (Riley et al., 2015). This finding is further supported by Lehrer et al. (30) who reported a similar effect size of 0.37 and a prediction interval of 0.29 to 1.03. This appears to be a recurring finding and appears to indicate that the true effect might be larger than the effect size reported in this paper (0.478). Conversely, it is equally plausible that the true effect of greater populations is towards the lower limit prediction interval (-0.204). Regardless, future research is needed to elucidate the true effect (66) as this would influence the perception of HRVB efficacy within the clinical domain in relation to using it as a tool to ameliorate depressive symptoms in an array of comorbid conditions.

As the inclusion criteria clearly stated, HRVB was compared to a control which consisted of a current active treatment standard. However, the included studies presented large differences in HRVB delivery, contributing to difficult methodological comparisons (57; 62). The lack of clarity complicates the ability to draw accurate comparisons (45) regarding overall

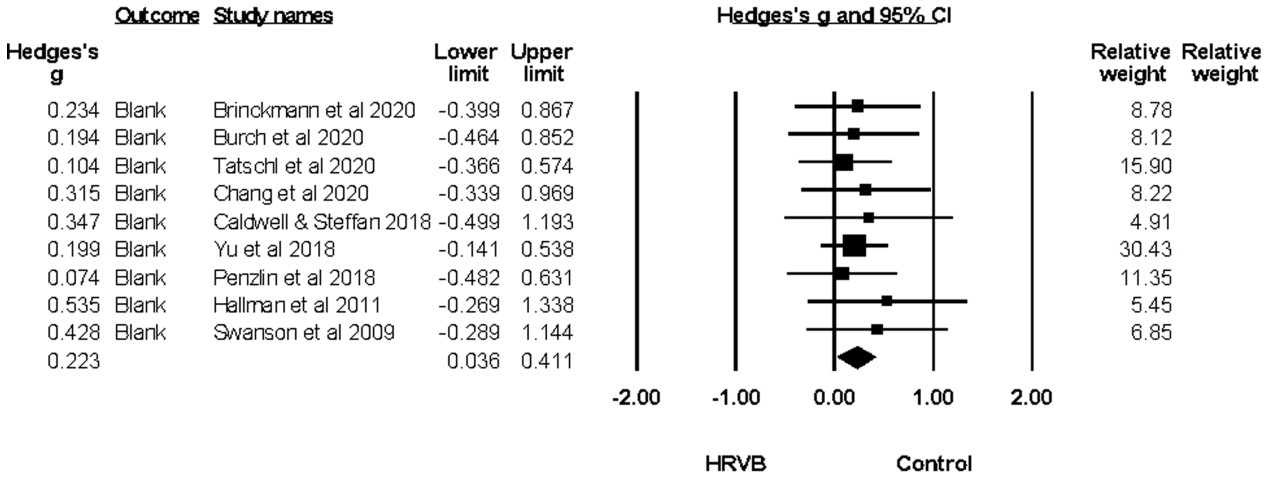

Figure 6. Forest Plot for HRVB versus control for HRV Outcomes.

Table 9. Prediction Intervals for HRVB for HRV Outcomes.

Mean	0.233
Prediction Interval (95%) lower limit	-0.003
Prediction Interval (95%) Upper Limit	0.449

Table 10. Heterogeneity for HRVB for HRV outcomes.

Q-value	P-Value	I squared
1.598	0.991	0.000

volume and techniques between the compared groups in the included studies of the current meta-analysis.

Unfortunately, this meta-analysis did not measure the relationship between variables such as the personnel delivering HRVB, duration, frequency, and total volume (67). Before this is possible however, primary research studies should explicitly declare such training variables in both the HRVB and standard treatment groups. While the effect size presented in this paper suggests that HRVB is a superior method to current psychotherapeutic methods, more detailed methodological content (45) would help clarify whether HRVB should replace contemporary techniques seen throughout the control groups, or whether it should be considered a complementary therapy to standard approaches (33).

While the studies by Pizzoli et al. (1), Lehrer et al. (30) and Blase et al (33) showed similar effect sizes for HRVB influence on depressive symptoms, neither study included HRV physiological outcome measures. While some sections of research might be more interested in patient reported outcome measures for better BPS insights (68), techniques to address the underlying mechanism may enhance understanding and assist in the treatment of clinical symptoms of depression in morbid patients. The results reported in this meta-analysis for HRVB on HRV outcomes indicate that HRVB is an effective biofeedback tool to improve HRV outcomes compared with control (Figure 6). However, a more detailed examination reveals a small effect size of 0.223 which is some way off being classified as medium (69).

The results reported by Schumann et al. (70) dichotomised the above conclusion as to whether their data supports or refutes the HRV outcomes. The use of different metrics for HRV effects (SDNN vs. RMSSD; 69; 71), impacted the accuracy of comparisons and again reinforces the need for researchers to clearly report all HRV metrics and methodology to allow accurate comparisons (63).

Therefore, establishing which HRV variable is being measured and for what purpose is essential to better

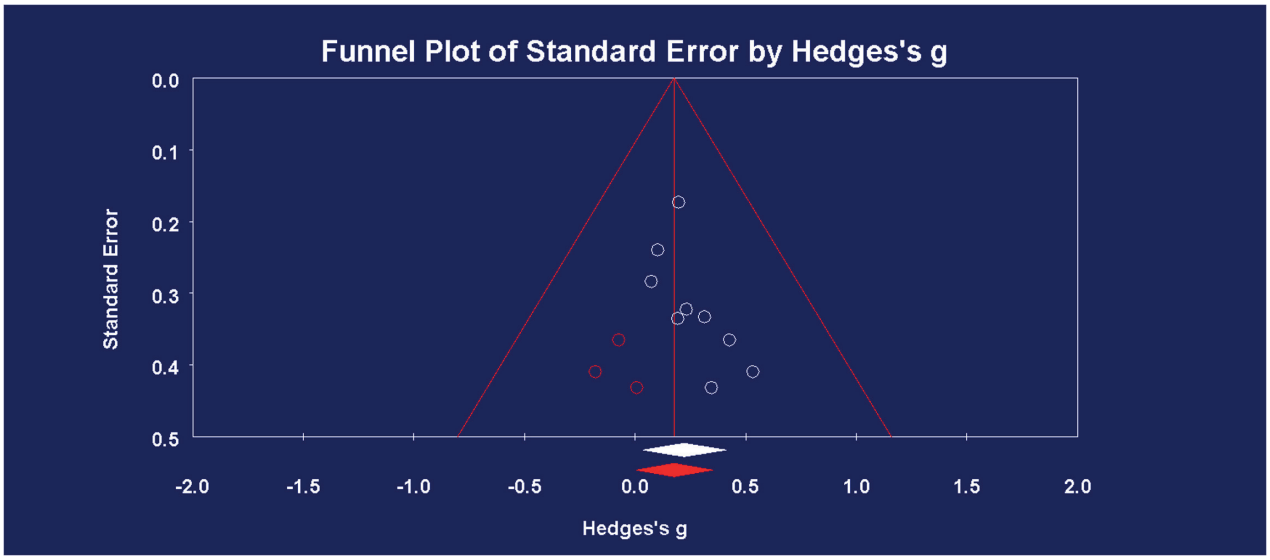

Figure 7. Funnel Plot of Standard Error by Hedge's G with Imputed Values.

inform clinical practice. The current meta-analysis included data from RMSSD and HF due its vagal nerve and PNS activity (22) which is strongly associated with depression (23), while SDNN is described as better reflecting the dynamic relationship between SNS and PNS and is more suited to identifying cardiac pathology (22). This potentially signifies that SDNN should be measured in conjunction with RMSSD for a more comprehensive comparison of autonomic function (22).

While outside the scope of this review, these are important considerations for clinical practice since the exact HRV index used might be dependent on the type of comorbidity and specific patient presentation (22). This potentially explains why the three studies involving patients with cardiac comorbidities all included SDNN for HRV outcomes (59; 58; 60) while one study involving alcohol dependent subjects did not (62). Again, the results need to be contextualised relative to the clinical environment, and future research might benefit from investigating HRVB relative to a particular disease or pathology (22).

For example, a potential explanation behind the lack of change in HF HRV reported by Penzlin et al. (62) is the ethyl toxic damage of vasomotor and autonomic nerve fibres which results in neurovascular dysfunction and poor HRV. Different pathologies may influence the malleability of certain HRV parameters in response to HRVB, since the same authors presented contrasting findings and confirm that each HRV parameter is not interchangeable (22) as they did report improvement in the coefficient of R-R intervals.

These results also imply that environmental factors need to be considered when performing HRVB and especially when measuring HF HRV measurements as this reading is supposedly greater during the evening (72; 22). Only the study by Chang et al. (59) included the time of measurement so it is possible that HF frequency domain measurement included by Penzlin et al. (62) was under-estimated. The inability to specify times may have attenuated the scientific veracity, reliability, and reproducibility (73) of outcomes since cardiac vagal activity (72) is altered by circadian factors (73). It is possible that this occurred here since HF data was used where RMSSD was not available in 3 out of the 9 included studies (25; 63; 62) and this might have reduced the overall effect size. These considerations should be considered in clinical practice to ensure that outcomes are robust and reliable (73).

Research could also build on this by complementing the correlational analysis with a regression analysis to enter the realm of prediction which might better inform its place in clinical practice (74) and add comparative data to the prediction intervals. Currently, the evidence appears to indicate that HRVB represents a useful tool to ameliorate depressive symptoms and improve HRV in an array of comorbid conditions, but

there is insufficient data to suggest that the two outcomes are strongly correlated with each other. Due to the moderate correlation seen here, supported by the moderate effect size in HRV, it is questionable whether the changes in depressive symptoms are explained by physiological changes occurring elsewhere. A reasonable suggestion, due to the bidirectional relationship between the heart and the brain, is the possibility that HRVB induces neuroplastic changes in key faculties of the brain. This means that HRVB might exert influence in areas of the brain which influence emotive (75) and executive regions (i.e. functional connectivity in the insula, amygdala, middle cingulate cortex and lateral prefrontal region was correlated with SDNN HRV in response to HRVB versus control; 70). Similar effects can assist in disinhibiting the dis-connection between the cingulate cortex and the amygdala which is proposed to occur in those experiencing depressive symptoms (76).

Another clinically important outcome of HRVB interventions in general was the absence of any negative side effects which means that it is safe to utilise and upholds key ethical principles (77). The strengths of this meta-analysis include the reliability of the results due to rigorous testing and adjustment for publication bias. Several tests were utilised and included the Duval and Tweedle trim and fill method, Eggers test, funnel plot and classic fail safe N. Outcomes suggested that the results were minimally impacted by publication bias, despite the low number included in the analysis.

The outcomes reported in the study provide significant information for the clinical environment since the results are aligned with other research outcomes (43; 1; 70). Moreover, the inclusion of prediction intervals provides a wider perspective of the true effect size which strengthens the case for further research. This, along with the positive treatment effects concluded here, indicates that HRVB represents a useful tool to induce positive physiological and clinical outcomes to address the growing prevalence of depressive symptoms in an array of comorbidities.

A potential limitation of the meta-analysis is failing to measure these outcomes relative to a specific condition which might limit specificity in clinical practice. Methodological differences between protocols also means that no gold standard HRVB intervention can be established. Additionally, marked differences in volume between HRVB and standard care might lead to difficulty in establishing the most time efficient strategy for clinical practice.

The outcomes registered in this meta-analysis indicate that HRVB represents a superior method to conventional psychotherapeutic interventions when attempting to ameliorate depressive symptoms and improve HRV in comorbid adult populations. The outcomes also documented a moderate negative correlation between the two variables that might help inform clinical practice. Further research on the variables measured in the current review is warranted, and this could even be expanded on by elucidating its link to the neurovisceral model which might also explain physiological changes behind clinical improvements.

Finally, a greater breadth of studies might offer the potential to explore these variables relative to a specific condition. Regardless of the condition under investigation, more rigorous methodological approaches are certainly required, which includes the type of HRV outcome index and rationale, while clearly outlining the personnel credentials, treatment duration, frequency, and HRVB protocol used. Similarly, it would also be useful to delineate the exact make up of standard care in order to converge on more accurate comparisons and conclusions when comparing HRVB to TAU groups. Such insights will not only serve to enlighten clinicians regarding the optimal intervention choice, but intervention variables will help establish its potency and feasibility for clinical practice.

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