Review

When Heart Beats Differently in Depression: Review of Nonlinear Heart Rate Variability Measures

Milena Čukić[1], PhD; Danka Savić[2], PhD; Julia Sidorova[3], PhD

[1]Empa Materials Science and Technology, Empa Swiss Federal Institute, St Gallen, Switzerland

[2]Vinča Institute for Nuclear Physics, Laboratory of Theoretical and Condensed Matter Physics 020/2, Vinca Institute, University of Belgrade, Belgrade, Serbia

[3]Bioinformatics Platform, Hospital Clínic, Barcelona, Spain

Corresponding Author:
Milena Čukić, PhD
Empa Materials Science and Technology
Empa Swiss Federal Institute
Lerchenfeldstrasse 5
St Gallen, 9014
Switzerland
Phone: 41 +41587657070
Fax: 41 +41587657070
Email: milena.cukic@gmail.com

Abstract

Background: Disturbed heart dynamics in depression seriously increases mortality risk. Heart rate variability (HRV) is a rich source of information for studying this dynamics. This paper is a meta-analytic review with methodological commentary of the application of nonlinear analysis of HRV and its possibility to address cardiovascular diseases in depression.

Objective: This paper aimed to appeal for the introduction of cardiological screening to patients with depression, because it is still far from established practice. The other (main) objective of the paper was to show that nonlinear methods in HRV analysis give better results than standard ones.

Methods: We systematically searched on the web for papers on nonlinear analyses of HRV in depression, in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 framework recommendations. We scrutinized the chosen publications and performed random-effects meta-analysis, using the *esci* module in jamovi software where standardized effect sizes (ESs) are corrected to yield the proof of the practical utility of their results.

Results: In all, 26 publications on the connection of nonlinear HRV measures and depression meeting our inclusion criteria were selected, examining a total of 1537 patients diagnosed with depression and 1041 healthy controls (N=2578). The overall ES (unbiased) was 1.03 (95% CI 0.703-1.35; diamond ratio 3.60). We performed 3 more meta-analytic comparisons, demonstrating the overall effectiveness of 3 groups of nonlinear analysis: detrended fluctuation analysis (overall ES 0.364, 95% CI 0.237-0.491), entropy-based measures (overall ES 1.05, 95% CI 0.572-1.52), and all other nonlinear measures (overall ES 0.702, 95% CI 0.422-0.982). The effectiveness of the applied methods of electrocardiogram analysis was compared and discussed in the light of detection and prevention of depression-related cardiovascular risk.

Conclusions: We compared the ESs of nonlinear and conventional time and spectral methods (found in the literature) and demonstrated that those of the former are larger, which recommends their use for the early screening of cardiovascular abnormalities in patients with depression to prevent possible deleterious events.

(JMIR Ment Health 2023;10:e40342) doi: 10.2196/40342

KEYWORDS

heart rate variability; HRV; electrocardiogram; ECG; depression; autonomous nervous system; ANS; nonlinear measures; cardiac risk; cardiovascular; mortality; heart dynamics; ECG analysis; analysis; online

Introduction

Cardiovascular diseases (CVDs) are the number one cause of death globally according to the World Health Organization [1,2]. Depression is the number one mental health–related contributors to the global burden of disease [3]. When combined, these 2 diseases can lead to increased mortality risk [4-6]. Recently, the European Society of Cardiology published a position paper about the mechanisms linking depression and CVD, based on abundant evidence from literature [7]. Although this connection was discovered a long time ago [8-10], the CVD screening of patients with depression is still far from routine.

In nearly 70% of patients with depression, somatic symptoms, such as lack of energy, sleep disturbance, lack of appetite, decreased sex drive, general pains, etc, dominate the clinical picture [11]. These symptoms are due to autonomous nervous system (ANS) dysfunction. Heart rate variability (HRV) is regulated by the ANS, and its disturbance is a marker of CVD. The relation between HRV and depression has been well understood [7,12-15]. We registered at least 14 reviews that meta-analytically compared conventional methods of analysis of this relation [16-28].

Medical professionals interested in the detection of depression may be uninformed of the knowledge and methods offering additional insights into a patient's condition, with the knowledge coming from theoretical research—mathematical analysis, complex systems dynamic theory, and information theory. These methods can be used to extract information embedded in electrophysiological signals, represented as time series—electrocardiogram (ECG), electroencephalogram, electromyogram, etc. Current view of what electrophysiological signals can yield is quite obsolete and limited by a reductionist approach established in clinical practice, because most devices for recording physiological signals have built-in algorithms based on Fourier analysis [29]. These standard (time and frequency) methods of electrical signal analysis are designed for (predictable) electro-mechanical systems and are not well suited for (complex) physiological systems. A number of review studies [16-27] offer very detailed comparative analyses of time and frequency measures of HRV related to depression. They rely on the assumption that the dynamics of the system may be linearized, where valuable information is lost in the case of electrophysiological signals.

Physiological systems are complex. Complex systems are composed of multiple subunits that interact in a nonlinear fashion producing unpredictable behaviors [29,30]. Although homeostasis is usually perceived as a still condition, "healthy heartbeat displays highly complex, apparently unpredictable fluctuations even under steady-state conditions" [29], whereas heart failure, for example, shows "slow periodic oscillations that correlate with Cheyne-Stokes breathing" [31]. The theory of complex dynamic systems applies to such a system. Its behavior can be predicted at best for short intervals, and it is characterized by long-range correlations and organized variability.

In information theory, the rate at which a system is producing information is described by Shannon entropy (ShanEn)—a quantity reflecting the number of possible states a system can occur in, that is, the level of uncertainty (unpredictability). Pincus et al [32,33] adapted the ShanEn for cardiology research and devised the approximate entropy (ApEn) algorithm, a statistic quantifying serial irregularity. Further, Richman and Moorman [34] refined this measure into sample entropy (SampEn), which was later improved by Costa et al [35], proposing the multiscale entropy (MSE) algorithm that calculates irregularity changes on multiple scales [35]. Costa et al [36] performed a series of studies focusing on methods of analysis of ECG, and their work was a significant step in the acceptance of nonlinear methodology. Translated to signals, the higher the entropy, the higher the irregularity of a signal, which is most often interpreted as higher complexity. This "awkward fact," as Vargas et al [30] noted, is paradoxical as complexity assumes a structure that is highly ordered. Glass and Mackey [37] stated that "Random outputs result from degraded control mechanisms and/or breakdown of the coupling among them," that is, from the loss of complexity. Nevertheless, as much as this confusion makes the insights into control mechanisms more difficult, the measures of complexity or irregularity differ between health and disease rendering them suitable for nonspecific markers of ill-health.

Neural control mechanisms, which demonstrate fractal properties, generate "organized variability" (previously thought to be the "noise" in the signal) characteristic of a healthy physiological system [38]. Physiological systems are scale-free; self-similar fluctuations are observed on different time scales. From one moment to the next, the fluctuations detected in the same signal are quite variable [31,32]. A system that is fractal can demonstrate irregularity across a wide range of scales, but the type of "disorder" or "roughness" on different scales is statistically similar [39-41]. Goldberger et al [31] stated that "organized variability is an inevitable consequence of fractal self-organization." According to the number of publications (in cardiology), the most popular fractal-based methods in use for analyzing HRV is detrended fluctuation analysis (DFA), which is based on correlation properties and uses random walk [42].

In interpreting the results and choosing the measures to be used, the physical meaning of the applied nonlinear analysis and the physiological context of a particular disease have to be kept in mind. Beside entropy- and fractal-based measures, there are other families of nonlinear measures that are methodologically very different. Poincaré plots are among the most accurate measures applied in cardiology [43], and being a graphical representation, they are very convenient for clinical application. Largest Lyapunov exponents (LLE) [44], which were used often in the beginning of the field, detect the level of chaos in a signal. Lempel-Ziv complexity (coming from information theory) quantifies the uncertainty contained in time-series data and is still among the frequently used measures in physiology [45]. Several correlation-based measures also showed promising results, but to describe even the basic methodology for all of them is out of the scope of this manuscript.

The fundamental difference between irregularity statistics and conventional variability measures is that the conventional approach is focusing on tasks of quantifying the degree of spread around the central value while the order of the input data is

irrelevant; whereas in irregularity statistics, nonlinear measures track changes from random to very regular and the order of samples is essential to the algorithm [40]. Nonlinear measures have been shown to be very effective in detecting the slightest differences between healthy and ill heart dynamics—even when time series of the compared states are varying around almost the same mean values [29,41]. An impressive example of the advantage of nonlinear methods is the case of detecting sudden infant death syndrome based on entropy measures calculated from ECG; the standard method was not able to detect any difference between healthy and babies under a serious risk [41].

This study is a random-effects meta-analysis of the most important studies that used nonlinear methods to confirm the connection between HRV (as a marker of CVD) and depression. We calculated effect sizes (ESs) from these studies and compared them with the ESs of standard (conventional) methods found in the literature. The aim of this work was to help convince clinicians to (1) introduce cardiological screening to patients with depression, since depression is confirmed to bear a risk for CVD [10,16,22,46-48] and (2) apply nonlinear methods to HRV analysis for more accurate and reliable screening results.

Methods

Overview

Since there are a considerable number of recently published meta-analytic studies [16-27] regarding the classical (spectral or conventional) approach to analyzing HRV, we decided to include only those studies that performed any nonlinear method of analysis or had mixed analytic approaches (applying both standard and nonlinear methods of analysis of heart rhythm to compare the effectiveness of analytics). This meta-analysis was performed in agreement with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines [49] with the main aim to present an integrated, realistic ES of the nonlinear measures in distinguishing between major depressive disorder (MDD) and controls, in comparison to conventionally used measures reported in previously published meta-analytic studies. Our work does not compare effects of interventions; thus, it was not preregistered (ie, the review protocol registration does not exist).

Only case-control studies or longitudinal studies that used ECG recordings or measurements of heart rate or any automated ECG diagnosis (for example, including early arrhythmia detection) and successive nonlinear analyses were included in our pool. Our query was kept as broad as possible to retrieve as many relevant papers as possible. We searched web resources, such as Springer, Wiley, Elsevier, IEEE, National Institute of Mental Health, Frontiers, PlosOne, Hindawi, Web of Science, PubMed, Cochrane Library, Scopus, and National Center for Biotechnology Information, with sets of keywords: (“depression” OR “Major depressive disorder” OR “bipolar depression”) AND (“ECG” OR “electrocardiography” OR “HRV” OR “heart rate variability”) AND (“Nonlinear analysis” OR “Fractal analysis” OR “entropy”).

We then scrutinized the abstracts and full texts (in English) and discarded those that were purely theoretical considerations of the connection of HRV and depression without the quantification of HRV measures (even when they included keywords from all 3 sets); papers on mood disorders without separate data on depression; studies where samples comprised solely of healthy subjects or subjects under the age of 18 years; studies without age-matched controls; animal studies; and papers without peer review.

Depression was diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (DSM; DSM-III-R, DSM-IV-TR, and DSM-5), International Classification of Diseases 10th Revision, Mini-International Neuropsychiatric Interview, Beck Depression Inventory, or Montgomery-Åsberg Depression Rating Scale. Some studies, found as references through hand searching of citation lists in review papers, were downloaded from the ResearchGate platform or were included even if nonretrievable as full text. Papers with standard analyses of ECG, added for comparison, were found in part via web-based search, from reference lists of review papers, and from the authors who were kind to send us full texts. The web search was performed in February and March 2021. Our screening was finalized in October 2021.

During the process (after removing the duplicates), we kept the working sheet (updated by all authors) with the basic data extracted from every paper included in the study (the first author’s name and the year of publication as an identifier, sample size, the mean and SD calculated for groups, the measures used in the research, the effect detected, and specific observations about the accuracies of applied analyses). Where we were unable to extract the data, we used WebPlotDigitizer software [50]. After coding all the data from the included papers, ES estimates were transformed into the same metric to be compared (Cohen’s d_s was corrected, hence having the same value as Hedges’ g). We used the *esci* module in jamovi exploratory software (open-source statistical software written in R) [50] to calculate overall ESs (correction of Cohen’s d) and 95% CIs and to generate forest plots [51]. The forest plots were used to visually display the individual and overall ESs.

ES is a quantitative description of the strength of evidence about a phenomenon. Cohen’s d describes the standardized mean difference of an effect [52-55]. In between 2 groups of independent observations, Cohen’s d_s is:

$$d_s = \frac{M_1 - M_2}{\sqrt{\frac{(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2}{n_1 + n_2 - 2}}}$$

where M_1 and M_2 are the variable means of the 2 groups (patients and controls); in the denominator, the pooled SD is the Bessel correction for bias in the estimation of population variance (based on the least squares estimator [54,55]); SD_1 and SD_2 are the respective SDs; and n_1 and n_2 are the sample sizes of the groups. Cohen’s d_s is also directly related to the t test:

$$d_s = t\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$$

where t is the t statistic, and n_1 and n_2 are as above. This is a direct relation between the ES and statistical significance. Here, statistical significance is expressed regardless of whether the 95% CI around Cohen's d_s includes 0 or not. Hedges and Olkin [54] showed that the formula for Cohen's d based on sample averages gives a biased estimate of the population ES (especially for smaller sample sizes, n<20). The Cohen's d that we calculated is actually Cohen's d_s, described in Lakens [55] (where SDs are pooled as in the formula above, not a single average of both SDs from samples 1 and 2). Thus, it is the Cohen's d of a sample, d_s. Further to be corrected for biases, according to Hedges and Olkin [54], it must be multiplied by another Bessel correction (1 – 3 / 4(N1 + N2) – 9) [55]. After calculating the corrected Cohen's d_s for all the included studies, by applying pooled SD in the process, we confirmed that what is calculated as a correction (for biases) in the *esci* module in jamovi software is actually Hedges' g. The authors of the software also describe that the product of their calculation (included in forest plot that the program is generating) is equal to Hedges' g [51,56]. In several studies that reported t values, we calculated Cohen's d_s according to the second formula. This interpretation was done based on previous literature [51-56].

Ethical Considerations

Since all the studies included in our review have already received prior approvals from their local ethics committees, and we did not use nor collect any additional data from the patients and only reanalyzed already published data, we do not report any ethic approval for this particular study.

Results

Our initial search (based on the logical formula given in *Methods*) in the abovementioned web services yielded 867 papers. The elimination was performed through phases shown in the flow chart (Figure 1) showing the identification, screening, eligibility check, and inclusion of studies in accordance with PRISMA 2020 [49]. The chosen 26 papers originated from the following databases: Elsevier (n=10), PubMed (n=8), Frontiers (n=2), Web of Science (n=4), Springer (n=1), and IEEE (n=1). They encompassed a total of 1537 patients diagnosed with depression and 1041 healthy controls. The studies included those that used nonlinear analyses or both nonlinear and standard analyses.

Direct quantitative comparisons could not have been made, as studies varied in methodologies, as well as in research questions—detecting biomarkers or predictors of depression, CVD mortality risk estimation or risk analysis, effects of different therapies, etc. Therapies included those exploring medication effects or spillover on HRV and psychological or psychiatric interventions; some examined inflammation or other important physiological markers, but some also used historical medical data (for example, from Medicare archives in the United States, see [57-59]). As the effects of therapies are not the topic of this paper, we compared the studies grouped by family of measures used (in nonlinear analysis) and summarized their results and conclusions concerning only the detection of the relation between depression and CVD mortality risk.

Figure 2 shows the information about the studies' methodologies (the majority [19/26, 73%] used more than one; only 7 [27%] studies were based on one nonlinear measure) and their conclusions. After initial random-effects meta-analysis of overall ESs of all included studies, we identified 3 distinct (methodological) groups of research and performed 3 additional meta-analyses. The first group used DFA (8 studies) with reported Cohen's d_s (corrected for biases) and 95% CIs. The second group of studies used methods from the large family of entropy measures: ApEn in 5 studies, SampEn in 5 studies, MSE in 3 studies, and ShanEn, Renyi entropy and refined composite multiscale entropy, and multilag tone-entropy, each in one study. The third group comprised various nonlinear analyses: Poincaré plots (n=4), LLE (n=2), symbolic measures (n=2), Lempel-Ziv complexity (n=1), complex variability, mutual information, autonomic information flow, beat decay NN, logarithmic respiratory sinus arrhythmia, recurrence plot analysis, Complex Correlation Measure, correlation dimension, and Katz fractal dimension. This group also demonstrates a historical order in which nonlinear measures entered cardiology, and some of them are still very popular in health applications (for example, LLE or Poincaré plots). Besides, this "historical" group demonstrated an average ES more than 2 times higher than any prior conventional approach, to the best of our knowledge.

The forest plot (and the table with Cohen's d_s corrected and 95% CIs) is used to visualize those meta-analytic comparisons of the ESs. Figure 2 represents the overall meta-analytic comparison of the best ESs of the 26 included studies. Figure 3 represents meta-analysis of the DFA group (with 8 studies compared, with an overall ES of 0.364, 95% CI 0.237-0.491). Figure 4 represents meta-analysis of the entropy group (15 studies compared, with an overall strong ES of 1.05, 95% CI 0.572-1.52). Figure 5 represents all other nonlinear methods used in the examined studies (13 studies compared, with an overall ES of 0.702, 95% CI 0.422-0.982). All mentioned comparisons yielded P<.01 (as shown the tables in all the figures). As the majority of studies applied several types of nonlinear analysis, we did multiple comparisons of corrected ESs that we separately calculated for each method. The best ES (d_s=7.7, 95% CI 6.4193-8.997) was obtained for the study [60] that used 4 entropy algorithms (ApEn, SampEn, ShanEn, and fuzzy entropy). When calculating ESs for each entropy method separately, ShanEn performed the best, and fuzzy entropy did not yield a significant result.

From overall meta-analytic comparison of ESs, out of 26 studies included, 11 were shown to be statistically insignificant [59-70], and one paper [71] had the lower CI touching the zero line, implying border significance. Thus, 15 (58%) out of 26 studies were statistically significant, with the overall ES of corrected Cohen's d_s=1.03 (elsewhere also reported as Hedges' g), which is a large ES [52] and can be translated to more than 1 SD [55].

Figure 1. Flow chart representing the procedure of choosing 26 studies included for this review. ECG: electrocardiogram; HC: healthy controls; HRV: heart rate variability.

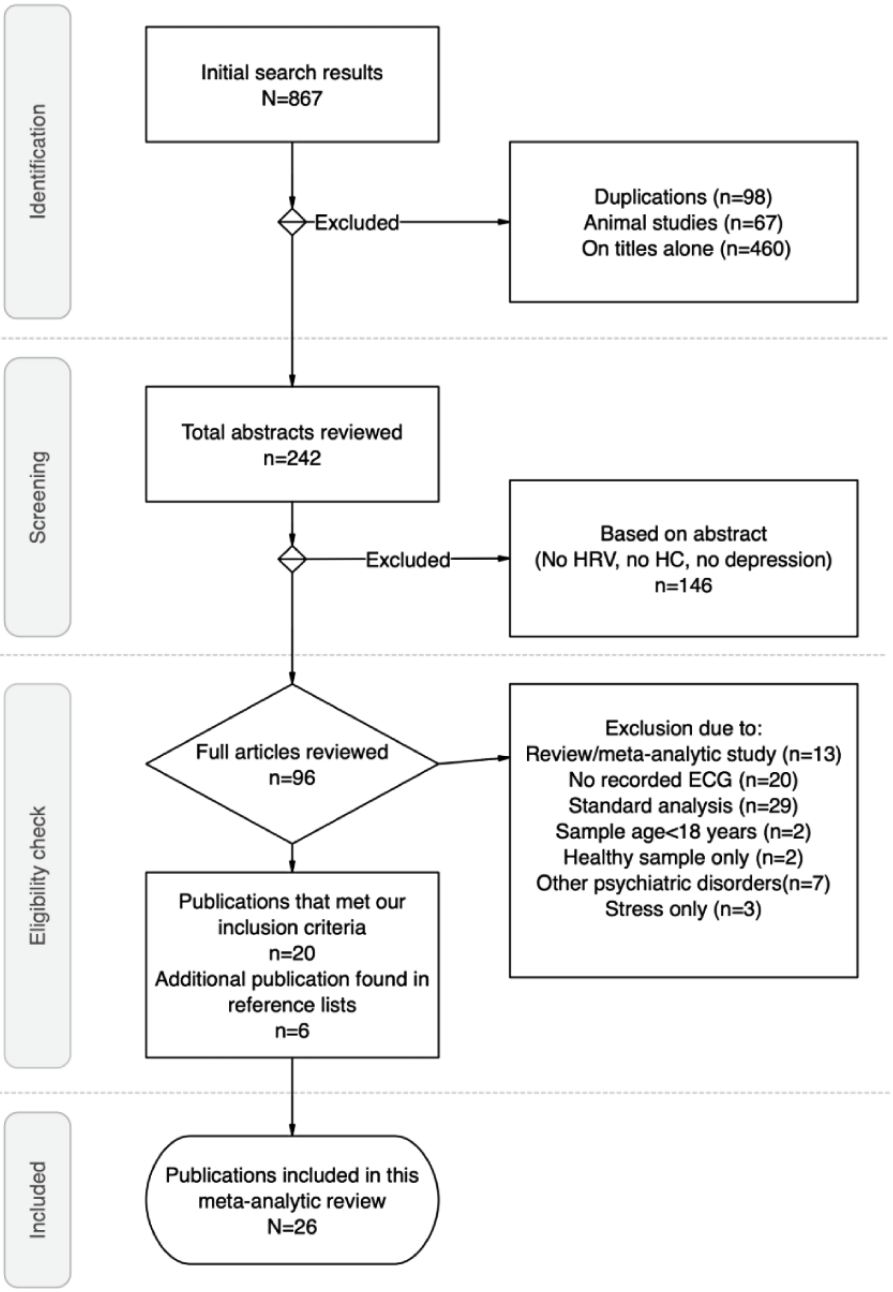


Figure 2. Forest plot and the table of random-effects meta-analysis showing the corrected effect size and CIs, as well as both sample sizes (N1: patients diagnosed with depression; N2: controls). For each study performing more than one method of nonlinear HRV analysis, we presented the largest effect size. Both table and forest plot are generated by the esci module in jamovi software. In all, 15 (58%) out of 26 included studies were shown to have statistically significant results. The overall effect size (unbiased/corrected) is 1.03 (diamond ratio 3.60). HRV: heart rate variability. [14,44,45,57-79].

Meta-Analysis Results

		95 % CI				95 % CI	
Label	Cohen's d	Lower	Upper	p	Diamond Ratio	Lower	Upper
Overall	1.03	0.703	1.35	<.001	3.60	2.70	5.47

Table of Studies

		95 % CI			
Label	Cohen's d	Lower	Upper	N1	N2
Moser 1998	0.1379	-0.40635	0.682	26	26
YeraganiRao 2002	1.3842	0.60779	2.161	14	18
Yeragani 2002a	0.5194	-1.47331	2.512	2	2
Kop 2010	0.2578	0.06007	0.455	776	113
Vigo 2004	0.9958	0.39976	1.592	19	33
Iverson 2005	1.2115	0.61407	1.809	30	22
Pincus 2008	0.5600	-0.41079	1.531	9	8
Boettger 2008	0.6649	-0.00624	1.336	18	18
Bob 2009	0.7918	0.32075	1.263	40	35
Baumert 2009	0.4386	-0.46622	1.344	12	8
Schulz 2010	0.5900	0.21498	0.965	57	57
Jelinek 2011	0.6968	0.38128	1.012	73	93
Voss 2011	0.4155	-0.05144	0.882	36	36
Yang 2011	0.2725	-0.07180	0.617	52	88
Leistedt 2011	1.3754	0.72238	2.028	25	20
Kemp 2012	0.5176	0.20687	0.828	73	94
Berger 2012	0.9348	0.24668	1.623	18	18
Migliorini 2012	0.2123	-0.99092	1.416	4	8
Moon 2013	0.2271	-0.27977	0.734	34	27
Kemp 2014	0.5574	0.24468	0.870	72	94
Khandoker 2017	7.1886	5.58294	8.794	16	29
Valenza 2017	0.0436	-0.35648	0.444	48	48
Chen 2017	0.3130	-0.12798	0.754	40	40
Greco 2017	3.5108	2.69758	4.324	36	24
Byun 2019	7.7079	6.41931	8.997	37	41
Byun 2019a	0.4467	-0.04181	0.935	33	33

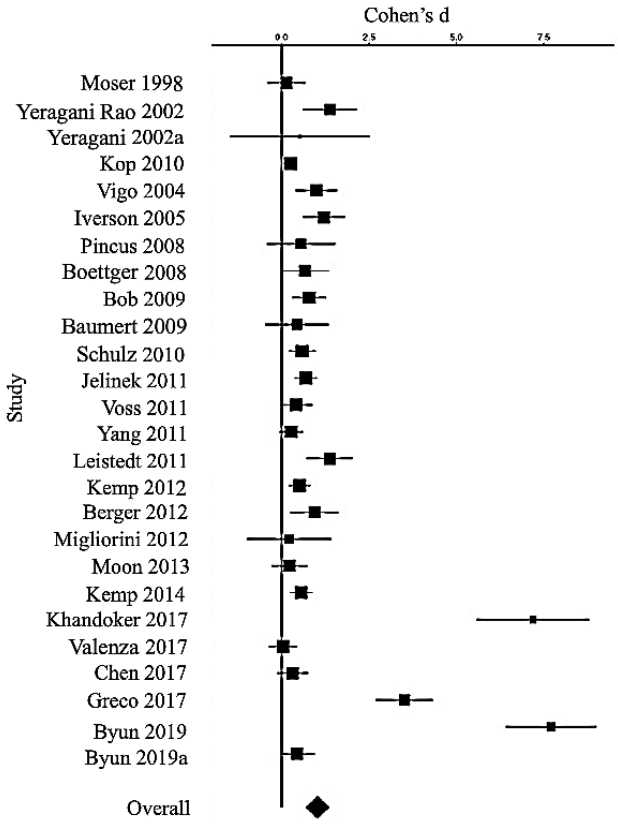


Figure 3. Forest plot (and table) showing the random-effects meta-analysis of a group of selected papers (8 publications [45,58,59,64,73,74,77,79]) that used detrended fluctuation analysis generated by the esci module in jamovi software. In all, 4 out of 8 studies were shown to have statistically nonsignificant results, with the overall effect size (biases corrected) being 0.364 (between small and medium effect, closer to medium, according to Cohen [52]), and the diamond ratio is 1.

Meta-Analysis Results

		95 % CI				95 % CI	
Label	Cohen's d	Lower	Upper	p	Diamond Ratio	Lower	Upper
Overall	0.364	0.237	0.491	<.001	1.00	1.00	8.82

Table of Studies

		95 % CI			
Label	Cohen's d	Lower	Upper	N1	N2
Vigo 2004	0.7288	0.1473	1.310	19	33
Baumert 2009	0.1714	-0.7247	1.068	12	8
Migliorini 2012	0.0277	-1.1726	1.228	4	8
Greco 2017	0.2452	-0.2732	0.764	24	36
Jelinek 2011	0.4977	0.1866	0.809	73	93
Kemp 2012	0.5176	0.2069	0.828	73	94
Kop 2010	0.2578	0.0601	0.455	776	113
Schulz 2010	0.3079	-0.0614	0.677	57	57

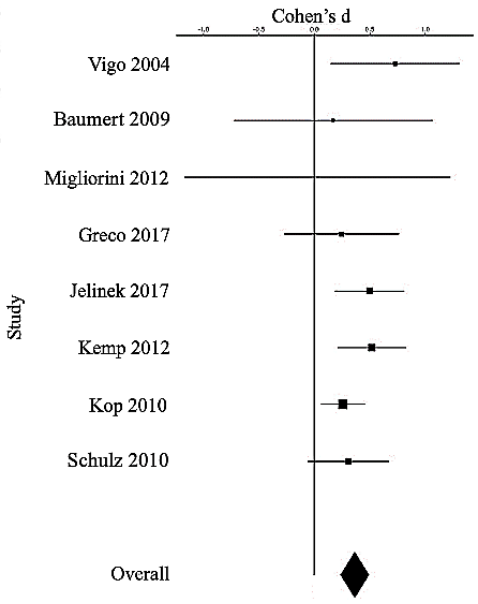


Figure 4. Forest plot (and table) showing the random-effects meta-analysis of a group of selected papers (15 publications [45,57,60,63-67,69,70,72,73,77-79]) that used entropy measures: approximate entropy (ApEn), logarithmic ApEn, sample entropy, fuzzy entropy, Shannon entropy, cross entropy, Renyi entropy, multiscale entropy, and improved refined composite multiscale entropy, generated by the esci module in jamovi software. The overall effect size for this group is 1.05 (which is very large, according to Cohen [52]). In all, 10 out of 18 studies were shown to have statistically nonsignificant results. Interestingly, Byun et al [60] calculated 4 entropy measures and demonstrated that only Shannon entropy yielded a highly useful effect size of 7.7 (which is the best result detected in this entire pool of publications, followed by Khandoker et al [72] with a corrected effect size of 7.3).

Meta-Analysis Results

		95 % CI				95 % CI	
Label	Cohen's d	Lower	Upper	p	Diamond Ratio	Lower	Upper
Overall	1.05	0.572	1.52	<.001	3.62	2.67	5.69

Table of Studies

		95 % CI			
Label	Cohen's d	Lower	Upper	N1	N2
Vigo 2004	0.9958	0.3998	1.592	19	33
Baumert 2009	0.4386	-0.4662	1.344	12	8
Migliorini 2012	0.2123	-0.9909	1.416	4	8
Moon 2013	0.2271	-0.2798	0.734	34	27
Berger 2012	0.9348	0.2467	1.623	18	18
Greco 2017	0.5438	0.0183	1.069	36	24
Byun 2019	7.7079	6.4193	8.997	37	41
Byun 2019a	0.4467	-0.0418	0.935	33	33
Byun 2019a	0.3666	-0.1199	0.853	33	33
Byun 2019a	0.4299	-0.0582	0.918	33	33
Shulz 2010	0.3278	-0.0418	0.697	57	57
Voss 2011	0.4155	-0.0514	0.882	36	36
Pincus 2008	0.0180	-0.9344	0.970	9	8
Pincus 2008	0.3388	-0.6203	1.298	9	8
Yang 2011	0.2725	-0.0718	0.617	52	88
Leistedt 2011	1.3754	0.7224	2.028	25	20
Chen 2017	0.3130	-0.1280	0.754	40	40
Khandoker 2017	7.1886	5.5829	8.794	16	29

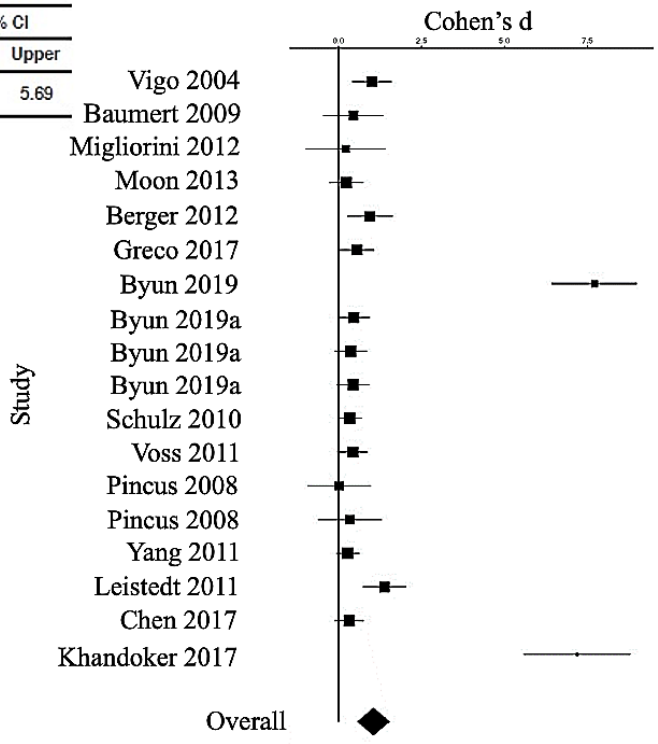


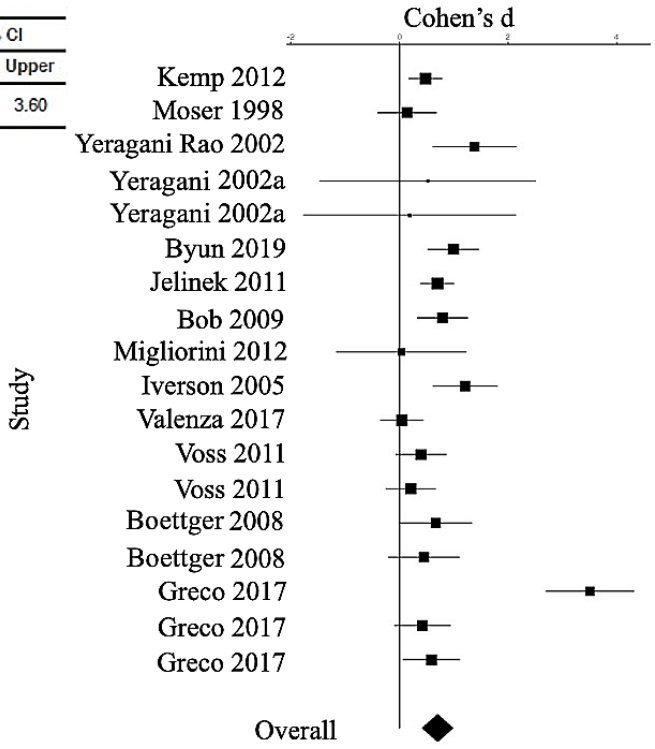
Figure 5. Forest plot (and table) showing the random-effects meta-analysis of group of selected papers that used a number of different nonlinear analyses of HRV in depression, excluding entropy and detrended fluctuation analysis measures. Those are Poincaré plots (SD1 and SD2), largest Lyapunov exponents, symbolic measures, Katz fractal dimension, correlation dimension, Complex Correlated Measure, mutual information, logarithmic respiratory sinus arrhythmia, heart rate turbulence, Lempel-Ziv complexity, recurrence plot analysis (determinism and recurrent rate are the most prominent result in Greco et al [73], ds=3.5), autonomic information flow, and beat decay NN. The plot and table are generated by the esci module in jamovi software. The overall effect size of studies included in this group is 0.7 (diamond ratio 2.3), which is considered large. Eight studies from this group were shown to have practically meaningful results: Kemp et al [74], Yeragani, Rao et al [44], Byun et al [70], Iverson et al [75], Jelinek et al [59], Bob et al [76], and Greco et al [73] (2 out of the 3 applied measures included and represented in this group). [44,45,59,61,62,65,68,70,71,73-76].

Meta-Analysis Results

Label	Cohen's d	95 % CI Lower	95 % CI Upper	p	Diamond Ratio	95 % CI Lower	95 % CI Upper
Overall	0.702	0.422	0.982	<.001	2.30	1.71	3.60

Table of Studies

Label	Cohen's d	95 % CI Lower	95 % CI Upper	N1	N2
Kemp 2012	0.4778	0.16779	0.788	94	73
Moser 1998	0.1379	-0.40635	0.682	26	26
YeraganiRao 2002	1.3842	0.60779	2.161	18	14
Yeragani 2002a	0.5194	-1.47331	2.512	2	2
Yeragani 2002a	0.1880	-1.77629	2.152	2	2
Byun 2019	0.9931	0.52211	1.464	41	37
Jelinek 2011	0.6968	0.38128	1.012	93	73
Bob 2009	0.7918	0.32075	1.263	35	40
Migliorini 2012	0.0369	-1.16340	1.237	8	4
Iverson 2005	1.2115	0.61407	1.809	22	30
Valenza 2017	0.0436	-0.35648	0.444	48	48
Voss 2011	0.3957	-0.07077	0.862	36	36
Voss 2011	0.2077	-0.25547	0.671	36	36
Boettger 2008	0.6649	-0.00624	1.336	18	18
Boettger 2008	0.4498	-0.21175	1.111	18	18
Greco 2017	3.5108	2.69758	4.324	24	36
Greco 2017	0.4213	-0.10071	0.943	24	36
Greco 2017	0.5863	0.05925	1.113	24	36



Discussion

Our results show that the overall standardized ES of nonlinear measures of HRV in depression overperforms the ESs of conventional measures of HRV reported in the literature. Although the overall ES in our comparison (all 26 studies) was 1.03, the best entropy-based group ES was 1.05, the DFA group ES was 0.36, and the third, miscellaneous group yielded an ES of 0.70. In the latest standard HRV measures-based study [28] (which is very similar to ours by the number of included studies), the ESs of several conventional measures varied up to 0.46. The meta-analysis by Rottenberg [13] reports a small ES (d~0.2), which explains only about 2% of the overall variance for conventional measures. Many of the published papers reported nonsignificant and mild-to-moderate ESs, whereas we found much larger effects: for example, the best ES in our research reached the value of 7.7 [60], and several others demonstrated higher ESs than those reported in conventional analyses (eg, the ES in Khandoker et al [72] was 7.3, which is very large according to Cohen [52]; in Greco et al [73], the ES was 3.5; and several others reached an ES around 1).

As commented in *Results*, almost half of the included studies did not have a significant effect in discriminating patients with depression from controls. This might be because not all patients with depression have disturbed heart function and because of the modest sample sizes. Indeed, the majority of those authors concluded that their initial results were promising but required replication. Later studies (2010 onward) show that researchers started using larger data sets or at least existing databases [58]. In the last 10 years, studies not only started using nonlinear measures but also combining them with some forms of machine learning to discern MDD [60,72,73,77,81,82]. We consider this methodological combination promising, especially since our previous work based on depression detection from electroencephalogram yielded good results [83-86].

Through the list of nonlinear methods presented in *Results*, we can follow the evolution of the understanding of how to interpret the results of nonlinear analysis. First, it was LLE, but since Lyapunov exponents mainly serve to detect chaos in signals, they can hardly be used for the precise delineation of groups. Then, in several papers, symbolic methods were used and reported as being successful, but again, their interpretation was problematic for which they were practically abandoned. The most promising family of nonlinear measures is the one based on entropy, in particular, ShanEn, then SampEn and ApEn (maybe also logarithmic ApEn); MSE seems a little more difficult to interpret. Irregular signals have higher entropies. Increased irregularity can point to a degradation of internal control mechanisms, or as Goldberger [29] puts it, decomplexification that is characteristic of aging and disease. Additionally, DFA, as a fractal method (as well as several other methods of calculating fractal dimension and correlation

dimension) makes sense, since neural control mechanisms are shown to have a fractal nature. In fact, all spectral measures calculated from ECG are a function of RR intervals length and are correlated; they do decrease with aging, but in disease that change is much more pronounced, and the function is lost [87-89]. In that sense, DFA is accurately detecting short- and long-term correlation that are important for healthy heart dynamics but also its synchronization with breathing [82,90]. Among other measures, the Complex Correlated Measure applied by Jelinek et al [59] performed quite well. Some recurrence plot analyses (Poincaré plot analysis and generalized Poincaré analysis) that quantify self-similarity in the processes were also used with good results [91]. In the reviewed literature, there are also combinations and alterations of the mentioned methods of analysis, such as combining the Poincaré analysis with DFA, applying Pearson coefficients on prior Poincaré analysis, or choosing the most prominent coefficients from several analyses and combining them as successful features for classification.

Nonlinear HRV analysis might be used as an aid in differential diagnosing or in indicating comorbidities [14,20,43,92]. For example, Chang et al [82] succeeded in distinguishing between bipolar II depression and unipolar depression, based on SampEn analysis of the HRV of 707 subjects. Kemp et al [14] found that anxiety disorders comorbid to MDD, most of all generalized anxiety disorder, contributed to the reduction of HRV. They elaborated on how nonvagal components of heart rate might further distinguish between subtypes of the disorder [20,43,92].

Cardiac vagal control (CVC) is associated with both physical and mental health. Low CVC is considered to be an indicator of risk of cardiac disease, including myocardial infarction and congestive heart failure [10,93]. Since variability in heart rate that is gated by the respiratory cycle [13,43] reflects the extent of CVC, it is logical to analyze its nonlinear dynamics and its aberrations to detect and treat depression. It could be a link between the polyvagal theory of Porges [94] and the physiological complexity (decomplexification and stereotypy of disease) of Goldberger [95]. In parallel to the polyvagal theory, there is also the neurovisceral integration model [96], both emphasizing the importance of taking into account ANS aberrations, along with the existing need to improve psychiatric nosology.

Important insights about healthy heart dynamics and how it changes with aging and disease were published in the 90s and served well the detection of several pathological entities [41,90,97]. We have learned that the mechanisms of neural control are fractal in nature (scale-free) and that they generate the so-called complex variability (once believed to be a background noise to the signal), which is a characteristic of healthy heart dynamics. In pathological states, one can observe a characteristic loss of complexity (decomplexification) that leads to recognizable oscillatory (predictable) behavior of a complex system, reduced to a single scale or frequency. The aberrated dynamics can be precisely quantified by fractal and nonlinear measures. The standard idea of comparison of healthy and ill organism pertains to the calculation of traditional mean values, SDs and the like, from electrophysiological signal (here ECG). When one compares the recording of a healthy heart with one of a patient diagnosed with congestive heart failure, their calculated means are within the same SD. However, it can be seen even with a naked eye that those signals are different (in dynamics and structure). Traditional methods do not show a significant difference here. The stereotypy of disease, as Goldberger explained [31], is connected with the decomplexification of a dynamical system's output, observed in early complexity studies. Complexity analysis can complement this clinical heuristic with adequate mathematical tools to quantify the changes in a patient's state.

Too aggressive preprocessing of the data can contribute to misleading results due to the loss of the exact order of samples. The history of the system is important in knowing its dynamics: earlier samples—the values of a physical phenomenon we measure (here in microvolts)—affect the later values, and if you shuffle the order, you lose the internal nonlinear structure that is contained in the sequence of those samples; this is called the historicity of data. Thus, it is necessary to analyze raw sequences of the records (broadband signal is the most information rich). This might be the reason why the nonlinear methods are superior to conventional ones.

The data can be easily obtained by novel portable ECG monitoring devices that are approved as medical-grade signal quality equivalent to a Holter monitor but are much more practical and comfortable to use by the patient herself or himself, taking only a couple of minutes. The data can then be processed by a combination of nonlinear analytics and advanced statistical procedures (to control, for example, for comorbidities and other confounding factors or for feature selection for further machine learning). Even better, the analysis can be empowered by machine learning applications that are widely in use due to the high power of computation and cloud computing [83-86,97].

To conclude, the ESs of nonlinear methods are larger than those of standard methods in HRV analysis. Measuring ECG and applying nonlinear analysis of HRV should enter the routine clinical practice for patients with depression. Although Porges [94] states that psychiatrists and psychologists seem not to be sufficiently interested in the use of objective biomarkers in their daily diagnostic work with patients with depression, the real question here is how ethical it is to keep this status quo and apply trial and error protocols in depression treatment without prior objective screening for CVD risks.

Acknowledgments

Part of this work has been supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (DS). MC and JS did not receive any funding support for this work.

Authors' Contributions

MC contributed to conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing–original draft, and writing–review and editing. DS contributed to data curation, investigation, methodology, and writing–review and editing. JS contributed to data curation, investigation, and writing–review and editing.

Conflicts of Interest

None declared.

References

1. The global burden of disease: 2004 update. World Health Organization. 2008. URL: https://apps.who.int/iris/bitstream/handle/10665/43942/9789241563710_eng.pdf?sequence=1&isAllowed=y [accessed 2023-01-05]
2. Depression and other common mental disorders: global health estimates. World Health Organization. 2017. URL: http://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf;jsession [accessed 2023-01-05]
3. Herrman H, Kieling C, McGorry P, Horton R, Sargent J, Patel V. Reducing the global burden of depression: a Lancet-World Psychiatric Association Commission. Lancet 2019 Jun 15;393(10189):e42-e43. [doi: 10.1016/S0140-6736(18)32408-5] [Medline: 30482607]
4. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. Eur Heart J 2006 Dec;27(23):2763-2774. [doi: 10.1093/eurheartj/ehl338] [Medline: 17082208]
5. Lange-Asschenfeldt C, Lederbogen F. Antidepressant therapy in coronary artery disease. Article in German. Nervenarzt 2011 May;82(5):657-64; quiz 665. [doi: 10.1007/s00115-010-3181-7] [Medline: 21109992]
6. Lett HS, Blumenthal JA, Babyak MA, Sherwood A, Strauman T, Robins C, et al. Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. Psychosom Med 2004;66(3):305-315. [doi: 10.1097/01.psy.0000126207.43307.c0] [Medline: 15184688]
7. Vaccarino V, Badimon L, Bremner JD, Cenko E, Cubedo J, Dorobantu M, ESC Scientific Document Group Reviewers. Depression and coronary heart disease: 2018 position paper of the ESC working group on coronary pathophysiology and microcirculation. Eur Heart J 2020 May 01;41(17):1687-1696 [FREE Full text] [doi: 10.1093/eurheartj/ehy913] [Medline: 30698764]
8. Malzberg B. Mortality among patients with involution melancholia. Am J Psychiatry 1937 Mar;93(5):1231-1238. [doi: 10.1176/ajp.93.5.1231]
9. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. Arch Gen Psychiatry 1998 Jul 01;55(7):580-592. [doi: 10.1001/archpsyc.55.7.580] [Medline: 9672048]
10. Dhar AK, Barton DA. Depression and the link with cardiovascular disease. Front Psychiatry 2016 Mar 21;7:33 [FREE Full text] [doi: 10.3389/fpsyt.2016.00033] [Medline: 27047396]
11. Tylee A, Gandhi P. The importance of somatic symptoms in depression in primary care. Prim Care Companion J Clin Psychiatry 2005 Aug 15;7(4):167-176 [FREE Full text] [doi: 10.4088/pcc.v07n0405] [Medline: 16163400]
12. Messerotti Benvenuti S, Buodo G, Mennella R, Palomba D. Somatic, but not cognitive-affective, symptoms are associated with reduced heart rate variability in individuals with dysphoria. Front Psychol 2015 May 07;6:599 [FREE Full text] [doi: 10.3389/fpsyg.2015.00599] [Medline: 25999905]
13. Rottenberg J. Cardiac vagal control in depression: a critical analysis. Biol Psychol 2007 Feb;74(2):200-211. [doi: 10.1016/j.biopsycho.2005.08.010] [Medline: 17045728]
14. Kemp AH, Quintana DS, Quinn CR, Hopkinson P, Harris AWF. Major depressive disorder with melancholia displays robust alterations in resting state heart rate and its variability: implications for future morbidity and mortality. Front Psychol 2014 Nov 27;5:1387 [FREE Full text] [doi: 10.3389/fpsyg.2014.01387] [Medline: 25505893]
15. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. Front Public Health 2017 Sep 28;5:258 [FREE Full text] [doi: 10.3389/fpubh.2017.00258] [Medline: 29034226]
16. Rugulies R. Depression as a predictor for coronary heart disease. a review and meta-analysis. Am J Prev Med 2002 Jul;23(1):51-61. [doi: 10.1016/s0749-3797(02)00439-7] [Medline: 12093424]
17. van Zyl LT, Hasegawa T, Nagata K. Effects of antidepressant treatment on heart rate variability in major depression: a quantitative review. Biopsychosoc Med 2008 Jun 30;2(1):12 [FREE Full text] [doi: 10.1186/1751-0759-2-12] [Medline: 18590531]
18. Carney RM, Freedland KE. Depression and coronary heart disease. Nat Rev Cardiol 2017 Mar;14(3):145-155. [doi: 10.1038/nrcardio.2016.181] [Medline: 27853162]
19. Kemp AH, Quintana DS, Gray MA, Felmingham KL, Brown K, Gatt JM. Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. Biol Psychiatry 2010 Jun 01;67(11):1067-1074. [doi: 10.1016/j.biopsych.2009.12.012] [Medline: 20138254]

20. Taylor CB, Conrad A, Wilhelm FH, Strachowski D, Khaylis A, Neri E, et al. Does improving mood in depressed patients alter factors that may affect cardiovascular disease risk? J Psychiatr Res 2009 Dec;43(16):1246-1252 [FREE Full text] [doi: 10.1016/j.jpsychires.2009.05.006] [Medline: 19577757]
21. Nemeroff CB, Goldschmidt-Clermont PJ. Heartache and heartbreak--the link between depression and cardiovascular disease. Nat Rev Cardiol 2012 Sep 26;9(9):526-539. [doi: 10.1038/nrcardio.2012.91] [Medline: 22733213]
22. Bassett D. A literature review of heart rate variability in depressive and bipolar disorders. Aust N Z J Psychiatry 2016 Jun 23;50(6):511-519. [doi: 10.1177/0004867415622689] [Medline: 26698824]
23. Gan Y, Gong Y, Tong X, Sun H, Cong Y, Dong X, et al. Depression and the risk of coronary heart disease: a meta-analysis of prospective cohort studies. BMC Psychiatry 2014 Dec 24;14(1):371 [FREE Full text] [doi: 10.1186/s12888-014-0371-z] [Medline: 25540022]
24. de la Torre-Luque A, Bornas X, Balle M, Fiol-Veny A. Complexity and nonlinear biomarkers in emotional disorders: a meta-analytic study. Neurosci Biobehav Rev 2016 Sep;68:410-422. [doi: 10.1016/j.neubiorev.2016.05.023] [Medline: 27267791]
25. Carr O, Andreotti F, Saunders KEA, Bilderbeck AC, Goodwin GM, de Vos M. Linking changes in heart rate variability to mood changes in daily life. Computing Cardiol 2017;44:1-4. [doi: 10.22489/cinc.2017.319-334]
26. Brown L, Karmakar C, Gray R, Jindal R, Lim T, Bryant C. Heart rate variability alterations in late life depression: a meta-analysis. J Affect Disord 2018 Aug 01;235:456-466. [doi: 10.1016/j.jad.2018.04.071] [Medline: 29679898]
27. Koch C, Wilhelm M, Salzmann S, Rief W, Euteneuer F. A meta-analysis of heart rate variability in major depression. Psychol Med 2019 Sep;49(12):1948-1957. [doi: 10.1017/S0033291719001351] [Medline: 31239003]
28. Klonowski W. From conformons to human brains: an informal overview of nonlinear dynamics and its applications in biomedicine. Nonlinear Biomed Phys 2007 Jul 05;1(1):5 [FREE Full text] [doi: 10.1186/1753-4631-1-5] [Medline: 17908344]
29. Goldberger AL. Fractal variability versus pathologic periodicity: complexity loss and stereotypy in disease. Perspect Biol Med 1997;40(4):543-561. [doi: 10.1353/pbm.1997.0063] [Medline: 9269744]
30. Vargas B, Cuesta-Frau D, Ruiz-Esteban R, Cirugeda E, Varela M. What can biosignal entropy tell us about health and disease? applications in some clinical fields. Nonlinear Dynamics Psychol Life Sci 2015 Oct;19(4):419-436. [Medline: 26375934]
31. Goldberger AL, Peng CK, Lipsitz LA. What is physiologic complexity and how does it change with aging and disease? Neurobiol Aging 2002;23(1):23-26. [doi: 10.1016/s0197-4580(01)00266-4] [Medline: 11755014]
32. Pincus SM, Goldberger AL. Physiological time-series analysis: what does regularity quantify? Am J Physiol 1994 Apr;266(4 Pt 2):H1643-H1656. [doi: 10.1152/ajpheart.1994.266.4.H1643] [Medline: 8184944]
33. Pincus S, Singer BH. Randomness and degrees of irregularity. Proc Natl Acad Sci U S A 1996 Mar 05;93(5):2083-2088 [FREE Full text] [doi: 10.1073/pnas.93.5.2083] [Medline: 11607637]
34. Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. Am J Physiol Heart Circ Physiol 2000 Jun;278(6):H2039-H2049 [FREE Full text] [doi: 10.1152/ajpheart.2000.278.6.H2039] [Medline: 10843903]
35. Costa M, Goldberger AL, Peng CK. Multiscale entropy analysis of complex physiologic time series. Phys Rev Lett 2002 Aug 05;89(6):068102 [FREE Full text] [doi: 10.1103/PhysRevLett.89.068102] [Medline: 12190613]
36. Costa M, Cygankiewicz I, Zareba W, Lobodzinski S. Multiscale complexity analysis of heart rate dynamics in heart failure: preliminary findings from the music study. 2006 Presented at: 2006 Computers in Cardiology; September 17-20, 2006; Valencia, Spain p. 101-103 URL: https://ieeexplore.ieee.org/document/4511798
37. Glass L, Mackey M. From Clocks to Chaos: the Rhythms of Life. Princeton, NJ: Princeton University Press; 1988.
38. Goldberger A, Amaral LAN, Glass L, Hausdorff JM, Ivanov PC, Mark RG, et al. PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals. Circulation 2000 Jun 13;101(23):E215-E220. [doi: 10.1161/01.cir.101.23.e215] [Medline: 10851218]
39. Pincus SM, Gladstone IM, Ehrenkranz RA. A regularity statistic for medical data analysis. J Clin Monit 1991 Oct;7(4):335-345. [doi: 10.1007/BF01619355] [Medline: 1744678]
40. Pincus SM. Quantitative assessment strategies and issues for mood and other psychiatric serial study data. Bipolar Disord 2003 Aug;5(4):287-294. [doi: 10.1034/j.1399-5618.2003.00036.x] [Medline: 12895206]
41. Pincus SM, Cummins TR, Haddad GG. Heart rate control in normal and aborted-SIDS infants. Am J Physiol 1993 Mar;264(3 Pt 2):R638-R646. [doi: 10.1152/ajpregu.1993.264.3.R638] [Medline: 8457020]
42. Peng CK, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. Chaos 1995;5(1):82-87. [doi: 10.1063/1.166141] [Medline: 11538314]
43. Kemp AH, Quintana DS, Malhi GS. Effects of serotonin reuptake inhibitors on heart rate variability: methodological issues, medical comorbidity, and clinical relevance. Biol Psychiatry 2011 Apr 15;69(8):e25-6; author reply e27. [doi: 10.1016/j.biopsych.2010.10.035] [Medline: 21353666]
44. Yeragani VK, Rao KARK, Smitha MR, Pohl RB, Balon R, Srinivasan K. Diminished chaos of heart rate time series in patients with major depression. Biol Psychiatry 2002 May 01;51(9):733-744. [doi: 10.1016/s0006-3223(01)01347-6] [Medline: 11983187]

45. Migliorini M, Mendez MO, Bianchi AM. Study of heart rate variability in bipolar disorder: linear and non-linear parameters during sleep. Front Neuroeng 2012 Jan 10;4:22 [FREE Full text] [doi: 10.3389/fneng.2011.00022] [Medline: 22291638]
46. Schumann A, Andrack C, Bär KJ. Differences of sympathetic and parasympathetic modulation in major depression. Prog Neuropsychopharmacol Biol Psychiatry 2017 Oct 03;79(Pt B):324-331. [doi: 10.1016/j.pnpbp.2017.07.009] [Medline: 28710030]
47. Wagner CD, Persson PB. Chaos in the cardiovascular system: an update. Cardiovasc Res 1998 Nov;40(2):257-264. [doi: 10.1016/s0008-6363(98)00251-x] [Medline: 9893718]
48. Sgoifo A, Carnevali L, Alfonso ML, Amore M. Autonomic dysfunction and heart rate variability in depression. Stress 2015 May 25;18(3):343-352. [doi: 10.3109/10253890.2015.1045868] [Medline: 26004818]
49. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021 Mar 29;372:n160 [FREE Full text] [doi: 10.1136/bmj.n160] [Medline: 33781993]
50. Rohatgi A. WebPlotDigitalizer: HTML5 based online tool to extract numerical data from plot images. Version 4.1. arohatgi.info. URL: http://arohatgi.info/WebPlotDigitizer/app/2012 [accessed 2023-01-05]
51. esci in jamovi. The New Statistics. URL: https://thenewstatistics.com/itns/esci/jesci/ [accessed 2023-01-05]
52. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Hillsdale, NJ, England: Lawrence Erlbaum Associates; 1988.
53. McGrath RE, Meyer GJ. When effect sizes disagree: the case of r and d. Psychol Methods 2006 Dec;11(4):386-401. [doi: 10.1037/1082-989X.11.4.386] [Medline: 17154753]
54. Hedges LV, Olkin I. Statistical Methods for Meta-Analysis. San Diego, CA: Academic Press; 1985.
55. Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. Front Psychol 2013 Nov 26;4:863 [FREE Full text] [doi: 10.3389/fpsyg.2013.00863] [Medline: 24324449]
56. Cumming G. Understanding the New Statistics: Effect sizes, Confidence Intervals, and Meta-Analysis. New York, NY: Routledge; 2012.
57. Leistedt SJ, Linkowski P, Lanquart J, Mietus JE, Davis RB, Goldberger AL, et al. Decreased neuroautonomic complexity in men during an acute major depressive episode: analysis of heart rate dynamics. Transl Psychiatry 2011 Jul 26;1(7):e27 [FREE Full text] [doi: 10.1038/tp.2011.23] [Medline: 22832529]
58. Kop WJ, Stein PK, Tracy RP, Barzilay JI, Schulz R, Gottdiener JS. Autonomic nervous system dysfunction and inflammation contribute to the increased cardiovascular mortality risk associated with depression. Psychosom Med 2010 Sep;72(7):626-635 [FREE Full text] [doi: 10.1097/PSY.0b013e3181eadd2b] [Medline: 20639389]
59. Jelinek HF, Khandoker AH, Quintana DS, Imam MH, Kemp AH. Complex Correlation Measure as a sensitive indicator of risk for sudden cardiac death in patients with depression. 2011 Presented at: 2011 Computing in Cardiology; September 18-21, 2011; Hangzhou, China p. 809-812.
60. Byun S, Kim AY, Jang EH, Kim S, Choi KW, Yu HY, et al. Entropy analysis of heart rate variability and its application to recognize major depressive disorder: a pilot study. Technol Health Care 2019 Jun 18;27(S1):407-424 [FREE Full text] [doi: 10.3233/THC-199037] [Medline: 31045557]
61. Yeragani VK, Pesce V, Jayaraman A, Roose S. Major depression with ischemic heart disease: effects of paroxetine and nortriptyline on long-term heart rate variability measures. Biol Psychiatry 2002 Sep 01;52(5):418-429. [doi: 10.1016/s0006-3223(02)01394-x] [Medline: 12242058]
62. Moser M, Lehofer M, Hoehn-Saric R, McLeod DR, Hildebrandt G, Steinbrenner B, et al. Increased heart rate in depressed subjects in spite of unchanged autonomic balance? J Affect Disord 1998 Mar;48(2-3):115-124 [FREE Full text] [doi: 10.1016/s0165-0327(97)00164-x] [Medline: 9543200]
63. Pincus SM, Schmidt PJ, Palladino-Negro P, Rubinow DR. Differentiation of women with premenstrual dysphoric disorder, recurrent brief depression, and healthy controls by daily mood rating dynamics. J Psychiatr Res 2008 Apr;42(5):337-347. [doi: 10.1016/j.jpsychires.2007.01.001] [Medline: 17336329]
64. Baumert M, Lambert GW, Dawood T, Lambert EA, Esler MD, McGrane M, et al. Short-term heart rate variability and cardiac norepinephrine spillover in patients with depression and panic disorder. Am J Physiol Heart Circ Physiol 2009 Aug;297(2):H674-H679 [FREE Full text] [doi: 10.1152/ajpheart.00236.2009] [Medline: 19502559]
65. Voss A, Boettger MK, Schulz S, Gross K, Bär KJ. Gender-dependent impact of major depression on autonomic cardiovascular modulation. Prog Neuropsychopharmacol Biol Psychiatry 2011 Jun 01;35(4):1131-1138. [doi: 10.1016/j.pnpbp.2011.03.015] [Medline: 21453741]
66. Yang AC, Tsai S, Yang C, Kuo C, Chen T, Hong C. Reduced physiologic complexity is associated with poor sleep in patients with major depression and primary insomnia. J Affect Disord 2011 Jun;131(1-3):179-185. [doi: 10.1016/j.jad.2010.11.030] [Medline: 21195485]
67. Moon E, Lee SH, Kim DH, Hwang B. Comparative study of heart rate variability in patients with schizophrenia, bipolar disorder, post-traumatic stress disorder, or major depressive disorder. Clin Psychopharmacol Neurosci 2013 Dec 28;11(3):137-143 [FREE Full text] [doi: 10.9758/cpn.2013.11.3.137] [Medline: 24465250]
68. Valenza G, Citi L, Garcia RG, Taylor JN, Toschi N, Barbieri R. Complexity variability assessment of nonlinear time-varying cardiovascular control. Sci Rep 2017 Feb 20;7(1):42779 [FREE Full text] [doi: 10.1038/srep42779] [Medline: 28218249]

69. Chen X, Yang R, Kuang D, Zhang L, Lv R, Huang X, et al. Heart rate variability in patients with major depression disorder during a clinical autonomic test. Psychiatry Res 2017 Oct;256:207-211. [doi: 10.1016/j.psychres.2017.06.041] [Medline: 28646783]
70. Byun S, Kim AY, Jang E, Kim S, Choi K, Yu HY, et al. Detection of major depressive disorder from linear and nonlinear heart rate variability features during mental task protocol. Comput Biol Med 2019 Sep;112:103381 [FREE Full text] [doi: 10.1016/j.compbiomed.2019.103381] [Medline: 31404718]
71. Boettger S, Hoyer D, Falkenhahn K, Kaatz M, Yeragani VK, Bär KJ. Nonlinear broad band dynamics are less complex in major depression. Bipolar Disord 2008 Mar;10(2):276-284. [doi: 10.1111/j.1399-5618.2007.00503.x] [Medline: 18271907]
72. Khandoker AH, Luthra V, Abouallaban Y, Saha S, Ahmed KI, Mostafa R, et al. Predicting depressed patients with suicidal ideation from ECG recordings. Med Biol Eng Comput 2017 May 18;55(5):793-805. [doi: 10.1007/s11517-016-1557-y] [Medline: 27538398]
73. Greco A, Messerotti Benvenuti S, Gentili C, Palomba D, Scilingo EP, Valenza G. Assessment of linear and nonlinear/complex heartbeat dynamics in subclinical depression (dysphoria). Physiol Meas 2018 Mar 29;39(3):034004. [doi: 10.1088/1361-6579/aaaeac] [Medline: 29595146]
74. Kemp AH, Quintana DS, Felmingham KL, Matthews S, Jelinek HF. Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk. PLoS One 2012 Feb 15;7(2):e30777 [FREE Full text] [doi: 10.1371/journal.pone.0030777] [Medline: 22355326]
75. Iverson GL, Gaetz MB, Rzempoluck EJ, McLean P, Linden W, Remick R. A new potential marker for abnormal cardiac physiology in depression. J Behav Med 2005 Dec 13;28(6):507-511. [doi: 10.1007/s10865-005-9022-7] [Medline: 16222413]
76. Bob P, Susta M, Gregusova A, Jasova D. Dissociation, cognitive conflict and nonlinear patterns of heart rate dynamics in patients with unipolar depression. Prog Neuropsychopharmacol Biol Psychiatry 2009 Feb 01;33(1):141-145. [doi: 10.1016/j.pnpbp.2008.11.005] [Medline: 19041359]
77. Vigo D, Nicola Siri L, Ladrón de Guevara MS, Martínez-Martínez JA, Fahrer R, Cardinali DP, et al. Relation of depression to heart rate nonlinear dynamics in patients ≥60 years of age with recent unstable angina pectoris or acute myocardial infarction. Am J Cardiol 2004 Mar 15;93(6):756-760 [FREE Full text] [doi: 10.1016/j.amjcard.2003.11.056] [Medline: 15019886]
78. Berger S, Kliem A, Yeragani V, Bär KJ. Cardio-respiratory coupling in untreated patients with major depression. J Affect Disord 2012 Jul;139(2):166-171. [doi: 10.1016/j.jad.2012.01.035] [Medline: 22386048]
79. Schulz S, Koschke M, Bär KJ, Voss A. The altered complexity of cardiovascular regulation in depressed patients. Physiol Meas 2010 Mar;31(3):303-321. [doi: 10.1088/0967-3334/31/3/003] [Medline: 20086275]
80. Byun S, Kim AY, Jang E, Kim S, Choi K, Yu H, et al. Detection of major depressive disorder from linear and nonlinear heart rate variability features during mental task protocol. Comput Biol Med 2019 Sep;112:103381 [FREE Full text] [doi: 10.1016/j.compbiomed.2019.103381] [Medline: 31404718]
81. Kuang D, Yang R, Chen X, Lao G, Wu F, Huang X, et al. Depression recognition according to heart rate variability using Bayesian Networks. J Psychiatr Res 2017 Dec;95:282-287. [doi: 10.1016/j.jpsychires.2017.09.012] [Medline: 28926794]
82. Chang HA, Chang CC, Kuo TBJ, Huang SY. Distinguishing bipolar II depression from unipolar major depressive disorder: differences in heart rate variability. World J Biol Psychiatry 2015 Mar 24;16(5):351-360. [doi: 10.3109/15622975.2015.1017606] [Medline: 25800950]
83. Čukić M, Stokić M, Simić S, Pokrajac D. The successful discrimination of depression from EEG could be attributed to proper feature extraction and not to a particular classification method. Cogn Neurodyn 2020 Aug;14(4):443-455 [FREE Full text] [doi: 10.1007/s11571-020-09581-x] [Medline: 32655709]
84. Čukić M, Stokić M, Radenković S, Ljubisavljević M, Simić S, Savić D. Nonlinear analysis of EEG complexity in episode and remission phase of recurrent depression. Int J Methods Psychiatr Res 2020 Jun 09;29(2):e1816 [FREE Full text] [doi: 10.1002/mpr.1816] [Medline: 31820528]
85. Čukić M, López V, Pavón J. Classification of Depression Through Resting-State Electroencephalogram as a Novel Practice in Psychiatry: Review. J Med Internet Res 2020 Nov 03;22(11):e19548 [FREE Full text] [doi: 10.2196/19548] [Medline: 33141088]
86. Čukić M, Pokrajac D, Lopez D. On mistakes we made in prior computational psychiatry data driven approach projects and how they jeopardize translation of those findings in cinical practice. 2020 Aug 25 Presented at: IntelliSys 2020: Intelligent Systems and Applications; September 3-4, 2020; London, UK p. 493-510. [doi: 10.1007/978-3-030-55190-2_37]
87. Zeković J, Madžgalj Š, Platiša MM. Detrended fluctuation analysis of heart and respiratory rhythm in atrial fibrillation. 2018 Presented at: 2018 Computing in Cardiology Conference (CinC); September 23-26, 2018; Maastricht, the Netherlands p. 1-4. [doi: 10.22489/cinc.2018.300]
88. Platiša MM, Radovanović NN, Milašinović G, Pavlović SU. Sample entropy approach to the examination of cardio-respiratory coupling in response to cardiac resynchronization therapy. 2021 Presented at: Entropy 2021: The Scientific Tool of the 21st Century; May 5-7, 2021; Basel, Switzerland. [doi: 10.3390/entropy2021-09770]
89. Platisa MM, Gal V. Dependence of heart rate variability on heart period in disease and aging. Physiol Meas 2006 Oct;27(10):989-998. [doi: 10.1088/0967-3334/27/10/005] [Medline: 16951458]

90. Peng CK, Hausdorff JM, Goldberger AL. Fractal mechanisms in neural control: human heartbeat and gait dynamics in health and disease. In: Walleczek J, editor. Self-Organized Biological Dynamics and Nonlinear Control. Cambridge, MA: Cambridge University Press; Aug 14, 1999.
91. Kemp AH, Quintana DS, Malhi GS. Effects of serotonin reuptake inhibitors on heart rate variability: methodological issues, medical comorbidity, and clinical relevance. Biol Psychiatry 2011 Apr 15;69(8):e25-6; author reply e27. [doi: 10.1016/j.biopsych.2010.10.035] [Medline: 21353666]
92. Kemp A. Depression, antidepressant treatment and the cardiovascular system. Acta Neuropsychiatr 2014 Jun 24;23(2):82-83. [doi: 10.1111/j.1601-5215.2011.00535.x]
93. Tsuji H, Larson MG, Venditti FJ, Manders ES, Evans JC, Feldman CL, et al. Impact of reduced heart rate variability on risk for cardiac events: the Framingham Heart study. Circulation 1996 Dec;94(11):2850-2855. [doi: 10.1161/01.cir.94.11.2850]
94. Porges SW. The Polyvagal Theory: Neurophysiological Foundations of Emotions, Attachment, Communication, Self-Regulation. 1st ed. New York, NY: W.W. Norton & Company; 2011.
95. Goldberger AL, Amaral LAN, Hausdorff JM, Ivanov PC, Peng C, Stanley HE. Fractal dynamics in physiology: alterations with disease and aging. Proc Natl Acad Sci U S A 2002 Feb 19;99 Suppl 1(Suppl 1):2466-2472 [FREE Full text] [doi: 10.1073/pnas.012579499] [Medline: 11875196]
96. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord 2000 Dec;61(3):201-216. [doi: 10.1016/s0165-0327(00)00338-4] [Medline: 11163422]
97. Saad M, Ray LB, Bujaki B, Parvaresh A, Palamarchuk I, De Koninck J, et al. Using heart rate profiles during sleep as a biomarker of depression. BMC Psychiatry 2019 Jun 07;19(1):168 [FREE Full text] [doi: 10.1186/s12888-019-2152-1] [Medline: 31174510]

Abbreviations

ApEn: approximate entropy
ANS: autonomous nervous system
CVC: cardiac vagal control
CVDs: cardiovascular diseases
DFA: detrended fluctuation analysis
DSM: Diagnostic and Statistical Manual of Mental Disorders
ECG: electrocardiogram
ES: effect size
HRV: heart rate variability
LLE: largest Lyapunov exponents
MDD: major depressive disorder
MSE: multiscale entropy
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
SampEn: sample entropy
ShanEn: Shannon entropy

Edited by J Torous; submitted 16.06.22; peer-reviewed by C Massaroni, S Jonas; comments to author 09.11.22; revised version received 28.11.22; accepted 06.12.22; published 17.01.23

Please cite as:
Čukić M, Savić D, Sidorova J
When Heart Beats Differently in Depression: Review of Nonlinear Heart Rate Variability Measures
JMIR Ment Health 2023;10:e40342
URL: https://mental.jmir.org/2023/1/e40342
doi: 10.2196/40342
PMID: