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# A meta-analysis of heart rate variability in major depression

Celine Koch[1], Marcel Wilhelm[1], Stefan Salzmann[1], Winfried Rief[1] and Frank Euteneuer[2,1]

[1]Clinical Psychology and Psychotherapy, Philipps Universität, Marburg, Germany and [2]Clinical Psychology and Psychotherapy, Medical School Berlin, Berlin, Germany

**Review Article**

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**Author for correspondence:**
Frank Euteneuer, E-mail: frank.euteneuer@medicalschool-berlin.de

## Abstract

**Background.** Major depression (MD) is a risk factor for cardiovascular disease. Reduced heart rate variability (HRV) has been observed in MD. Given the predictive value of HRV for cardiovascular health, reduced HRV might be one physiological factor that mediates this association.

**Methods.** The purpose of this study was to provide up-to-date random-effects meta-analyses of studies which compare resting-state measures of HRV between unmedicated adults with MD and controls. Database search considered English and German literature to July 2018.

**Results.** A total of 21 studies including 2250 patients and 1982 controls were extracted. Significant differences between patients and controls were found for (i) frequency domains such as HF-HRV [Hedges' $g = -0.318$; 95% CI (−0.388 to −0.247)], LF-HRV (Hedges' $g = -0.195$; 95% CI (−0.332 to −0.059)], LF/HF-HRV (Hedges' $g = 0.195$; 95% CI (0.086–0.303)] and VLF-HRV (Hedges' $g = -0.096$; 95% CI (−0.179 to −0.013)), and for (ii) time-domains such as IBI (Hedges' $g = -0.163$; 95% CI (−0.304 to −0.022)], RMSSD (Hedges' $g = -0.462$; 95% CI (−0.612 to −0.312)] and SDNN (Hedges' $g = -0.266$; 95% CI (−0.431 to −0.100)].

**Conclusions.** Our findings demonstrate that all HRV-measures were lower in MD than in healthy controls and thus strengthens evidence for lower HRV as a potential cardiovascular risk factor in these patients.

## Introduction

Depression has a lifetime prevalence of 19% in industrialized nations and affects approximately 322 million people worldwide (World Health Organization, 2008, 2017). In middle- and high-income countries, depression and cardiovascular disease (CVD) are the leading causes for impairments in quality of life and CVD is also a primary cause for mortality (Wittchen *et al.*, 2010; Christopher and Murray, 2016).

Depression and CVD are interrelated (Shaffer *et al.*, 2012). For example, meta-analyses of longitudinal prospective studies strengthen the assumption that depressive symptoms are an independent risk factor for the development of CVDs, such as hypertension (Meng *et al.*, 2012), myocardial infarction (van der Kooy *et al.*, 2007; Gan *et al.*, 2014; Wu and Kling, 2016) and coronary heart disease (Rugulies, 2002; Nicholson *et al.*, 2006*a*, 2006*b*; van der Kooy *et al.*, 2007; Gan *et al.*, 2014; Wu *and* Kling, 2016). In addition, depressive symptoms are frequently observed in patients with CVD: in survivors of acute myocardial infarction, major depression (MD) was prevalent in nearly 20% shortly after the acute medical event (Thombs *et al.*, 2014). Clinically relevant depressive symptoms occur in around one-third of patients after stroke (Hackett and Pickles, 2014). Depressive symptoms are also predictive for morbidity and mortality in coronary heart disease (Goldston and Baillie, 2008).

Heart rate variability (HRV) refers to variations between two successive heartbeats which ensures optimal adaption to environmental challenges. HRV is influenced by parasympathetic autonomic activation including the vagus nerve (which slows down heart rate) and via sympathetic activation (which accelerates heart rate). HRV is frequently quantified using time-domain measures such as the standard deviation of NN intervals (SDNN) and the root mean square of successive differences between normal heartbeats (RMSSD), which is more influenced by vagal activity than SDNN. HRV is also often described in terms of frequency-domain measures. High-frequency (HF)-HRV primarily reflects parasympathetic vagal activity. Low-frequency (LF)-HRV is more complex and may include both sympathetic and parasympathetic influences. Very-low-frequency (VLF)-HRV might reflect long-term regulation mechanisms (e.g. thermoregulation or hormonal factors). A third category of HRV is respiratory sinus arrhythmia (RSA), which reflects heart rate variations via the vagus nerve related to the respiratory cycle (Task Force of The European Society of Cardiology and The North American & Society of Pacing and Electrophysiology, 1996; Shaffer *et al.*, 2014; Shaffer and Ginsberg, 2017).



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Chronically reduced HRV indicates an autonomic imbalance. A substantial body of research suggests that reductions in HRV predict poor cardiovascular health outcomes in both populations without baseline CVD and clinical samples (Buccelletti *et al.*, 2009; Hillebrand *et al.*, 2013; Kubota *et al.*, 2017). Previous meta-analyses suggest that HRV is lower in patients with MD than in healthy controls across all age groups (Kemp *et al.*, 2010; Rottenberg, 2007; Koenig *et al.*, 2016; Brown *et al.*, 2018). Importantly, reduced HRV is not a specific feature of MD but rather a transdiagnostic factor which relates to several stress-related states, conditions and behavioral factors, as well as to several medical conditions and medications (Gidron *et al.*, 2018). Nevertheless, HRV might be an important mediator between depression and CVD (Sgoifo *et al.*, 2015; Shaffer and Ginsberg, 2017).

The latest meta-analysis investigating HRV in MD in (apart from late-life depression, see Brown *et al.*, 2018) was conducted by Kemp and colleagues in 2010 and included 11 studies (published until July 2009) (Kemp *et al.*, 2010). Results indicated that several HRV measures are lower in MD compared to controls by medium to large effect sizes. In the last decade, many studies have investigated HRV in MD. While some of them have also reported reductions in HRV (e.g. Berger *et al.*, 2011; Berger *et al.*, 2012; Kemp *et al.*, 2012; Brunoni *et al.*, 2013; Kemp and Quintana, 2013) others did not find significant differences or have attributed alterations in HRV to antidepressant treatment (Licht *et al.*, 2008; O'Regan *et al.*, 2015).

The purpose of this study is to provide up-to-date random-effects meta-analyses of studies that compare resting-state measures of HRV between unmedicated adults with MD (as defined by DSM-III-R, DSM-IV, DSM-IV-TR or DSM-5) and controls. Effects of antidepressants on HRV have been the subject of controversy and HRV alterations in MD may result in part from antidepressants, in particular tricyclic antidepressants (Kemp *et al.*, 2010, 2011, 2016; Licht *et al.*, 2011; Huang *et al.*, 2016). To avoid confounded or overestimated results, we therefore exclusively focus on studies that include participants without antidepressants, and also without cardiac drugs and CVD. Different from an earlier meta-analysis in this field, which has combined interrelated measures of HRV (Kemp *et al.*, 2010), our meta-analysis provides separate results for specific measures of HRV. This approach was facilitated by the increasing availability of HRV data from samples with MD and may enable a more differentiated understanding of HRV disturbances in MD. Further, the literature is inconclusive regarding equivalence and the approach of treating interrelated HRV measures equivalent, in particular when measures derived from short-term recordings (Task Force of The European Society of Cardiology and The North American & Society of Pacing and Electrophysiology, 1996; Berntson *et al.*, 2005; Kemp *et al.*, 2010; Shaffer and Ginsberg, 2017). Finally, this study considers appropriate methods to control for publication bias and investigates if ECG recording length and study quality moderate magnitudes of effect sizes.

## Methods

### Literature search and inclusion criteria

This meta-analysis was conducted according to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analysis' (PRISMA) guidelines (Moher *et al.*, 2009). Online Supplement 1 includes the PRISMA-Checklist. Because this meta-analysis did not aim to compare intervention effects, it was not preregistered and no review protocol exists.

A systematic literature search was performed up to 10 July 2018. Two investigators (CK & FE) independently searched on PubMed and PsychINFO for publications using the terms [(depress*) AND (heart rate variability) OR HRV OR (cycle length variability) OR (RR variability) OR (heart period variability) OR vagal OR (autonomic nervous system) OR (ANS)]. Studies published since 1 January 1987 (the year of publication of DSM-III-R) were considered with no filters applied. Email alerts notified the investigators of potentially relevant studies published during the process of study selection. The ClinicalTrials.gov database was searched for unpublished studies. Disagreements between the investigators were solved by discussion. The search in PubMed and PsychINFO yielded 6121 and 1779 results, respectively. After removal of duplicates, 7104 titles and abstracts were screened. The search on ClinicalTrials.gov yielded 29 unpublished studies on depressive patients with HRV assessment. Reviews, meta-analyses, abstracts from conference proceedings and single-case studies were excluded. In particular, studies including patients with CVD, cardiac medication and antidepressants were excluded. Also, studies with samples of patients with diabetes and neurological disorders were excluded. Exclusion criteria for each study are outlined in online Supplement 2 (Table S1).

To be eligible for full-test screening, abstracts had to report a comparison of HRV in adults (⩾18 years) in MD to healthy controls.

Studies were included if they:

(1) reported a resting state time-or frequency domain measure of HRV in both (i) unmedicated adults with MD (as defined by DSM-III-R, DSM-IV, DSM-IV-TR or DSM-5) and (ii) age-matched healthy controls.
(2) were published in a peer-reviewed journal
(3) were written in English or German.

### Data extraction

A data extraction sheet was developed based on inclusion criteria, previous meta-analyses (e.g. Tak *et al.*, 2009; Kemp *et al.*, 2010; Koenig *et al.*, 2016) and common study characteristics usually extracted in meta-analyses (e.g. year and country of publication). During the process of study extraction, the sheet was continually adapted. Information on the year and country of publication, matching, inclusion and exclusion criteria, sample size, mean age of participants, diagnostics (i.e. diagnosis assessment tool, medical and psychiatric comorbidities), as well as ECG recording length was extracted from all included studies. If data were not extractable (i.e. only provided in graphs), authors were contacted and asked for additional information. If the data could not be provided on time (Bär *et al.*, 2004; Chang *et al.*, 2015) a plot digitizer (Rohatgi, 2012, Web Plot Digitizer, available at https://automeris.io/WebPlotDigitizer/) was used to estimate the mean and standard deviation (s.d.). When standard errors were reported instead of standard deviations, the standard deviation was estimated in accordance to an earlier meta-analysis, by using the following formula: $SD = SE \times \sqrt{n}$ (Higgins and Green, 2011; Koenig *et al.*, 2016). Absolute values as well as logarithmically transformed values but not normalized values were included in the meta-analysis (Rottenberg, 2007; Tak *et al.*, 2009).

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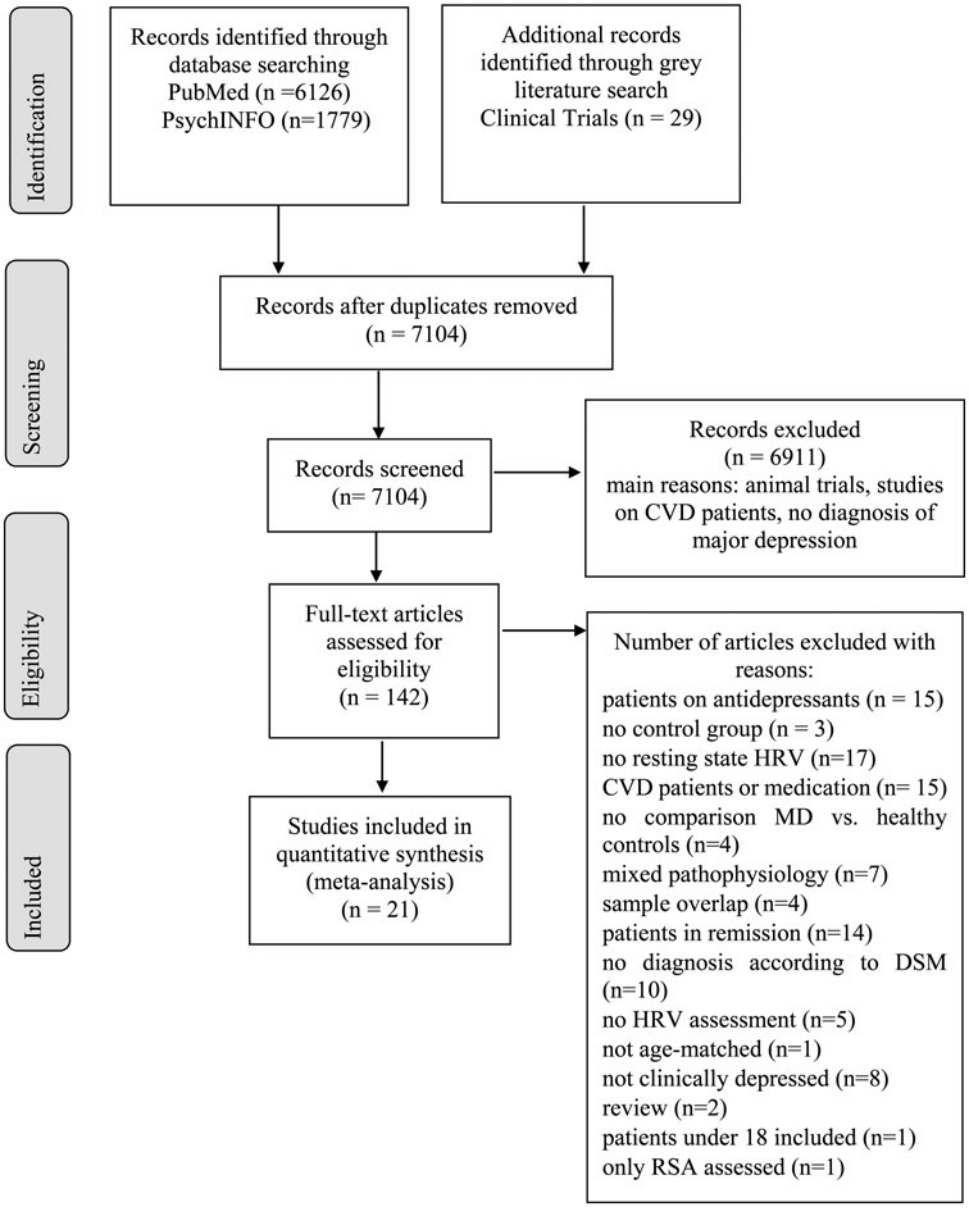


**Fig. 1.** PRISMA flow diagram.

### *Statistical analyses*

The Comprehensive Meta-Analysis (CMA; Version 3) statistical software package (Borenstein *et al.*, 2014) was used to aggregate individual studies. Since sample sizes varied between studies and between samples with MD and controls within the same study, the adjusted mean difference (Hedges' *g*) was chosen as the primary summary measure and 95% confidence intervals were computed. Effect sizes of 0.2, 0.5 and 0.8 were considered as low, moderate and large effects (Cohen, 1988). Several study characteristics varied between studies (e.g. sample size, mean age and gender distribution). Therefore, non-random-variance in effect-sizes was assumed and random-effects models were chosen to compute the overall effect sizes for HRV-measures (Borenstein *et al.*, 2009). Heterogeneity was assessed using the $I^2$ index (Higgins and Thompson, 2002), which quantifies the amount of variation between studies that can be attributed to true variation in effect sizes (e.g. an $I^2$ of 23% indicates that 23% of the variation in effect sizes between studies can be explained by true variation in effect sizes and not by sampling error). An $I^2$ of 25, 50 and 75% is considered as low, moderate and high heterogeneity, respectively. $I^2$ does not depend on the number of studies included in the meta-analysis or the metric of the effect size (Higgins *et al.*, 2003). To assess publication bias, funnel plots were visually inspected to discover possible asymmetry that might occur due to the selective publication of smaller studies reporting large effect sizes (Higgins and Green, 2008). Additionally, the trim and fill method was used as a statistical procedure as an estimate of the unbiased effect size (Duval and Tweedie, 2000). Meta-regression was performed on each of the HRV measures to test if the ECG recording length and study quality moderated the effect size. Two researchers (MW and SS) independently rated study quality using a slightly

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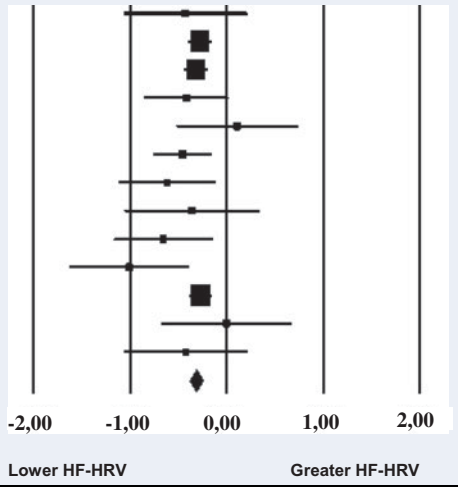
**Table 1.** Random-effects meta-analysis forest plot for HF-HRV: Comparison between patients with Major Depression (MD) and healthy controls (HC).

| | Sample Size | | | | | |
|---|---|---|---|---|---|---|
| Study | MD | HC | weight % | Hedges´g | CI, lb. | CI, ub. |
| Berger *et al.* (2012) | 18 | 18 | 1.17 | -0.426 | -1.072 | 0.221 |
| Chang *et al.* (2015) | 591 | 421 | 26.51 | -0.277 | -0.403 | -0.152 |
| Chang *et al.* (2012) | 498 | 462 | 25.88 | -0.319 | -0.447 | -0.192 |
| Chen *et al.* (2017) | 40 | 40 | 2.53 | -0.417 | -0.856 | 0.021 |
| Dawood *et al.* (2007) | 24 | 15 | 1.23 | 0.111 | -0.521 | 0.743 |
| Kemp *et al.* (2012) | 73 | 94 | 5.04 | -0.458 | -0.766 | -0.150 |
| Khandoker *et al.* (2017) | 32 | 29 | 1.89 | -0.614 | -1.122 | -0.106 |
| Kikuchi *et al.* (2009) | 15 | 15 | 1.00 | -0.359 | -1.061 | 0.343 |
| Shinba (2014) | 22 | 47 | 1.86 | -0.657 | -1.169 | -0.144 |
| Shinba (2017) | 14 | 41 | 1.25 | -1.010 | -1.637 | -0.383 |
| Yeh *et al.* (2016) | 618 | 506 | 29.41 | -0.270 | -0.388 | -0.152 |
| Yeragani *et al.* (2002) | 14 | 18 | 1.06 | 0.000 | -0.681 | 0.681 |
| Yeragani *et al.* (2000) | 18 | 18 | 1.17 | -0.424 | -1.071 | 0.222 |
| Overall ES | | | | -0.318 | -0.388 | -0.247 |




modified rating scale adapted from Tak *et al.* (2009). Interrater reliability for independent ratings was in the range of almost perfect agreement ($\kappa = 0.823$). As the next step, any disagreements were resolved through discussion to obtain consistent values. Rating criteria and results are shown in online Supplement 4.

## Results

The database search yielded 197 articles to be full-text screened. The gray literature search on ClinicalTrials.gov yielded no additional results since all potentially relevant studies were still recruiting. After full-text screening, 21 studies remained to be included in the meta-analysis, with $N = 2250$ patients and $N = 1982$ controls ($N = 4235$). Figure 1 illustrates results of the selection procedure. Characteristics of the included studies and HRV recording lengths for each study ($M = 10.68$ min, S.D. = 9.66 min, range = 28.33 min) are shown in online Supplementary Table S1. Separate meta-analyses were conducted for HRV frequency- and time-domains. We provide no meta-analysis for RSA, because only two studies were extracted, which differ in RSA calculation (Lehofer *et al.*, 1997; Berger *et al.*, 2012).

### *Meta-analysis 1 – frequency domain: high-frequency heart rate variability (HF-HRV)*

Compared to control groups ($N = 1724$), depressed samples ($N = 1977$) showed a significant reduction in HF-HRV [$Z = -8.860$, $p < 0.001$; Hedges' $g = -0.318$; 95% CI (−0.388 to −0.247); $k = 13$, $N = 3701$], as illustrated in Table 1. There was no evidence for heterogeneity across studies ($\tau^2 = 0.00$, $\chi^2(13, N = 3701) = 12.513$, $p = 0.405$; $I^2 = 4.103\%$). The visual inspection of the funnel plot indicated slight asymmetry (online Supplement 3, Fig. S2). Using trim and fill did not change the effect size Hedges' $g = -0.318$; 95% CI (−0.388 to −0. 247).

### *Meta-analysis 2 – frequency domain: low-frequency heart rate variability (LF-HRV)*

Compared to control groups ($N = 1640$), depressed samples ($N = 1939$) showed a significant reduction in LF-HRV ($Z = -2.803$, $p = 0.005$; Hedges' $g = -0.195$; 95% CI (−0.332 to −0.059); $k = 12$, $N = 3579$), as illustrated in Table 2. Heterogeneity across studies was low ($\tau^2 = 0.02$, $\chi^2(11, N = 3579) = 26.07$, $p = 0.009$; $I^2 = 26.12\%$). The visual inspection of the funnel plot indicated slight asymmetry (Supplement 3, Fig. S3). Using trim and fill attenuated the effect size to Hedges' $g = -0.158$; 95% CI (−0.297 to −0.019).

### *Meta-analysis 3 – frequency domain: very-low frequency heart-rate variability (VLF-HRV)*

Compared to control groups ($N = 992$), depressed samples ($N = 1273$) showed a significant reduction in VLF-HRV [$Z = -2.263$, $p = 0.024$; Hedges' $g = -0.096$; 95% CI (−0.179 to −0.013); $k = 5$, $N = 2265$], as illustrated in Table 3. There was no evidence for heterogeneity across studies ($\tau^2 = 0.00$, $\chi^2(4, N = 2265) = 2.05$, $p = 0.726$; $I^2 = 0.00\%$). The visual inspection of the funnel plot indicated slight asymmetry (online Supplement 3, Fig. S4), but using trim and fill did not change the magnitude of the effect size.

### *Meta-analysis 4 – frequency domain: LF/HF ratio*

Compared to control groups ($N = 2189$), depressed samples ($N = 1929$) exhibited a significantly higher LF/HF ratio ($Z = 3.525$, $p < 0.001$; Hedges' $g = 0.195$; 95% CI (0.086; 0.303); $k = 19$, $N = 4118$), as illustrated in Table 4. Heterogeneity across studies was low to moderate ($\tau^2 = 0.02$, $\chi^2(18, N = 4118) = 32.232$, $p = 0.021$; $I^2 = 44.16\%$). The visual inspection of the funnel plot indicated slight asymmetry (online Supplement 3, Fig. S5), but using trim and fill did not change the magnitude of the effect size.

### *Meta-analysis 5 – time domain: root mean square of successive differences between normal heartbeats (RMSSD)*

Compared to control groups ($N = 337$), depressed samples ($N = 356$) showed a significant reduction in RMSSD [$Z = -6.037$, $p < 0.001$; Hedges' $g = -0.462$; 95% CI (−0.612 to −0.312); $k = 9$, $N = 692$], as illustrated in Table 5. There was no evidence for heterogeneity across studies [$\tau^2 = 0.00$, $\chi^2(8, N = 692) = 2.67$, $p = 0.954$;

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**Table 2.** Random-effects meta-analysis forest plot for LF-HRV: Comparison between patients with Major Depression (MD) and healthy controls (HC).

| Study | Sample Size MD | HC | weight % | Hedges´*g* | CI, lb. | CI, ub. |
|---|---|---|---|---|---|---|
| Berger *et al.* (2012) | 18 | 18 | 3.72 | 0.446 | -0.201 | 1.093 |
| Chang *et al.* (2015) | 591 | 421 | 19.01 | -0.030 | -0.154 | 0.095 |
| Chang *et al.* (2012) | 498 | 462 | 18.90 | -0.281 | -0.408 | -0.154 |
| Chen *et al.* (2017) | 40 | 40 | 6.75 | -0.463 | -0.903 | -0.023 |
| Dawood *et al.* (2007) | 24 | 15 | 3.86 | 0.106 | -0.526 | 0.739 |
| Khandoker *et al.* (2017) | 32 | 29 | 5.58 | -0.416 | -0.918 | 0.086 |
| Kikuchi *et al.* (2009) | 15 | 15 | 3.02 | -0.878 | -1.609 | -0.147 |
| Schulz *et al.* (2010) | 57 | 57 | 8.63 | 0.186 | -0.179 | 0.552 |
| Shinba *et al.* (2017) | 14 | 41 | 4.15 | -0.498 | -1.103 | 0.107 |
| Yeh *et al.* (2016) | 618 | 506 | 19.36 | -0.190 | -0.308 | -0.072 |
| Yeragani *et al.* (2002) | 14 | 18 | 3.35 | -0.407 | -1.095 | 0.281 |
| Yeragani *et al.* (2000) | 18 | 18 | 3.67 | -0.578 | -1.230 | 0.075 |
| Overall ES | | | | -0.195 | -0.332 | -0.059 |

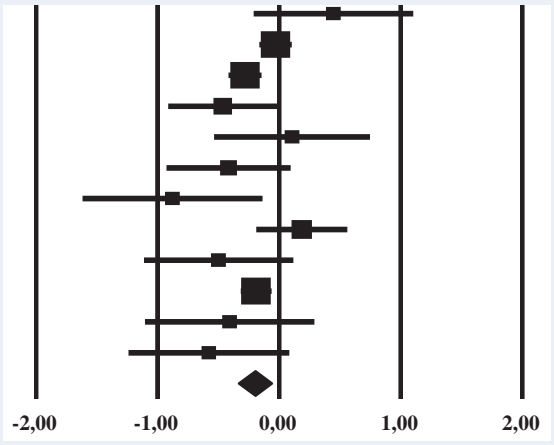
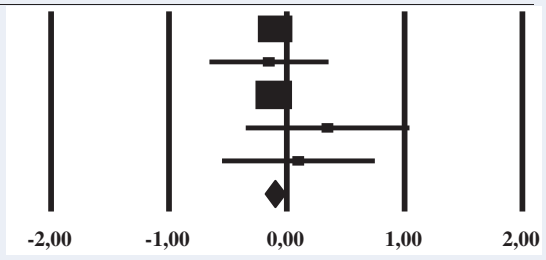



**Table 3.** Random-effects meta-analysis forest plot for VLF-HRV: Comparison between patients with Major Depression (MD) and healthy controls (HC).

| Study | Sample Size MD | HC | weight % | Hedges´*g* | CI, lb. | CI, ub. |
|---|---|---|---|---|---|---|
| Chang *et al.* (2015) | 591 | 421 | 44.14 | -0.098 | -0.223 | 0.026 |
| Khandoker *et al.* (2017) | 32 | 29 | 2.79 | -0.152 | -0.648 | 0.345 |
| Yeh *et al.* (2016) | 618 | 506 | 49.92 | -0.110 | -0.227 | 0.008 |
| Yeragani *et al.* (2002) | 14 | 18 | 1.46 | 0.346 | -0.340 | 1.032 |
| Yeragani *et al.* (2000) | 18 | 18 | 1.69 | 0.098 | -0.541 | 0.738 |
| Overall ES | | | | -0.096 | -0.179 | -0.013 |




$I^2 = 0.00\%$]. The visual inspection of the funnel plot indicated slight asymmetry (online Supplement 3, Fig. S6). Using trim and fill changed the effect size to Hedges' g =−0.480; 95% CI (−0.623 to −0.339).

### *Meta-analysis 6 – time domain: standard deviation of the intervals between normal beats (SDNN)*

Compared to control groups ($N = 271$), depressed samples ($N = 289$) presented a significant reduction of small effect size in SDNN [$Z = -3.142$, $p = 0.002$; Hedges' $g = -0.266$; 95% CI (−0.431 to −0.100); $k = 9$, $N = 560$], as illustrated in Table 6. There was no evidence for heterogeneity across studies [$\tau^2 = 0.00$, $\chi^2(5, N = 560) = 4.469$, $p = 0.484$; $I^2 = 0.00\%$]. The visual inspection of the funnel plot (online Supplement 3, Fig. S7) indicated no asymmetry and using trim and fill did not change the magnitude of the effect size.

### *Meta-analysis 7 – time domain: interbeat interval (IBI)*

Compared to control groups ($N = 1855$), depressed samples ($N = 1535$) showed a significant reduction of small effect size in IBI [$Z = -2.267$, $p = 0.023$; Hedges' $g = -0.163$; 95% CI (−0.304 to −0.022); $k = 7$, $N = 3390$], as illustrated in Table 7. Heterogeneity across studies was moderate [$\tau^2 = 0.02$, $\chi^2(6, N = 3390) = 16.629$, $p = 0.011$; $I^2 = 63.92\%$]. The visual inspection of the funnel plot indicated slight asymmetry (online Supplement 3, Fig. S8). Using trim and fill attenuated the effect size to Hedges' $g = -0.141$; 95% CI (−0.275 to −0.007).

### *Meta-regression 1 – impact of ECG recording length*

Recording length did not moderate the differences between depressed samples and controls in HRV measures, except for the interbeat interval [$\beta = -0.0172$, 95% CI (−0.026 to−0.008)]. Here, greater recording length resulted in lower effect sizes. Results of the other meta-regressions are shown in online Supplement 5 (Table S2).

### *Meta-regression 2 – impact of study quality*

Study quality did not moderate the differences between depressed samples and controls in any of the HRV measures. Results of meta-regressions are shown in online Supplement 6 (Table S3).

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**Table 4.** Random-effects meta-analysis forest plot for LF/HF Ratio: Comparison between patients with Major Depression (MD) and healthy controls (HC).

| Study | Sample Size MD | HC | weight % | Hedges´*g* | CI, lb. | CI, ub. |
|---|---|---|---|---|---|---|
| Bär *et al.* (2004) | 18 | 18 | 2.47 | -0.058 | -0.697 | 0.518 |
| Berger *et al.* (2011) | 30 | 30 | 3.71 | 0.005 | -0.495 | 0.504 |
| Berger *et al.* (2012) | 18 | 18 | 2.36 | 0.655 | -0.002 | 1.311 |
| Chang *et al.* (2015) | 591 | 421 | 14.18 | 0.088 | -0.037 | 0.213 |
| Chang *et al.* (2012) | 498 | 462 | 14.11 | 0.125 | -0.001 | 0.252 |
| Chen *et al.* (2017) | 40 | 40 | 4.59 | 0.112 | -0.322 | 0.546 |
| Kemp *et al.* (2012) | 73 | 94 | 7.25 | 0.418 | 0.110 | 0.726 |
| Khandoker *et al.* (2017) | 32 | 29 | 3.74 | 0.148 | -0.349 | 0.645 |
| Kikuchi *et al.* (2009) | 15 | 15 | 2.04 | -0.593 | -1.306 | 0.119 |
| Schulz *et al.* (2010) | 57 | 57 | 5.86 | 0.124 | -0.241 | 0.489 |
| Schumann *et al.* (2017) | 29 | 29 | 3.59 | 0.214 | -0.295 | 0.723 |
| Shinba (2014) | 22 | 47 | 3.57 | 0.628 | 0.116 | 1.139 |
| Shinba (2017) | 14 | 41 | 2.67 | 0.647 | 0.037 | 1.258 |
| Terhardt *et al.* (2013) | 44 | 28 | 3.90 | 0.730 | 0.246 | 1.213 |
| Udupa *et al.* (2007) | 40 | 40 | 4.43 | 0.620 | 0.176 | 1.065 |
| Voss *et al.* (2011) (f ) | 18 | 18 | 2.47 | -0.067 | -0.706 | 0.572 |
| Voss *et al.* (2011) (m) | 18 | 18 | 2.47 | 0.115 | -0.524 | 0.754 |
| Yeh *et al.* (2016) | 618 | 506 | 14.49 | 0.160 | 0.042 | 0.278 |
| Yeragani *et al.* (2002) | 14 | 18 | 2.12 | -0.630 | -1.328 | 0.068 |
| Overall ES | | | | 0.195 | 0.086 | 0.303 |

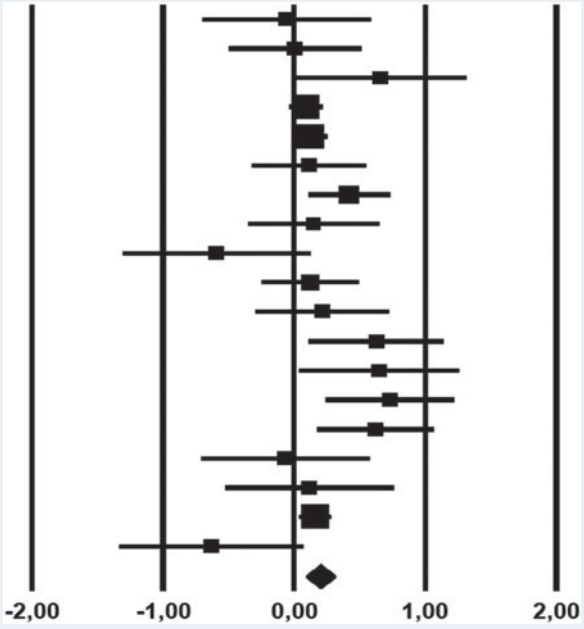
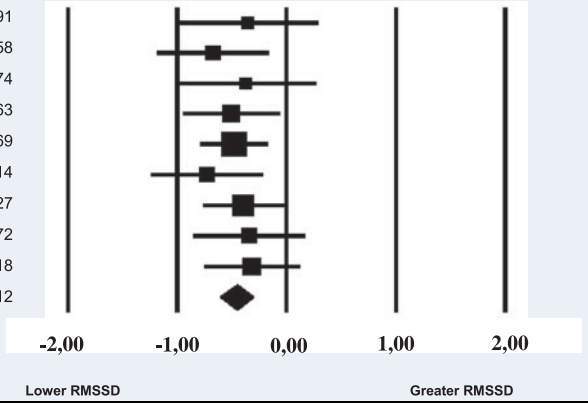



**Table 5.** Random-effects meta-analysis forest plot for RMSSD: Comparison between patients with Major Depression (MD) and healthy controls (HC).

| Study | Sample Size MD | HC | Weight % | Hedges´*g* | CI. lb. | CI. ub. |
|---|---|---|---|---|---|---|
| Bär *et al.* (2004) | 18 | 18 | 5.42 | -0.352 | -0.997 | 0.291 |
| Berger *et al.* (2011) | 30 | 30 | 8.52 | 0.672 | -1.186 | -0.158 |
| Berger *et al.* (2012) | 18 | 18 | 5.41 | -0.371 | -1.015 | 0.274 |
| Chen *et al.* (2017) | 40 | 40 | 11.56 | -0.504 | -0.945 | -0.063 |
| Kemp *et al.* (2012) | 73 | 94 | 23.06 | -0.478 | -0.786 | -0.169 |
| Khandoker *et al.* (2017) | 32 | 29 | 8.56 | -0.727 | -1.240 | -0.214 |
| Schulz *et al.* (2010) | 57 | 57 | 16.57 | -0.396 | -0.764 | -0.027 |
| Schumann *et al.* (2017) | 29 | 29 | 8.59 | -0.339 | -0.851 | 0.172 |
| Udupa *et al.* (2007) | 40 | 40 | 11.78 | -0.319 | -0.755 | 0.118 |
| Overall ES | | | | -0.462 | -0.612 | -0.312 |




## Discussion

The purpose of this study was to provide up-to-date meta-analyses of studies that compare resting-state measures of HRV between unmedicated adults with MD and controls. Results suggest that patients with MD are likely to display small reductions in several measures of HRV such as HF-HRV, LF-HRV, SDNN and IBI and an increase in LF/HF ratio. The largest effect size was found for RMSSD, a time domain measure of HRV, suggesting that reductions in patients with MD in this measure are of small to moderate magnitude. The reduction in VLF-HRV was minimal but still statistically significant. Our findings thus strengthen evidence that MD is not associated with alteration in specific indicators of HRV but rather with abnormalities in several time- and frequency-domain measures, although the effect sizes for these alterations differ. In this context, it is noteworthy that several time- and frequency-domain measures, rather than specific indicators, have predictive value for poor cardiovascular health outcomes in populations without known baseline CVD (Hillebrand *et al.*, 2013). A further important feature of our meta-analyses is that we found no evidence for a moderating role of study quality. This negative finding strengthens robustness of the observed HRV alterations in MD.

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**Table 6.** Random-effects meta-analysis forest plot for SDNN: Comparison between patients with Major Depression (MD) and healthy controls (HC).

| Study | Sample Size MD | HC | weight % | Hedges´*g* | CI. lb. | CI. ub. |
|---|---|---|---|---|---|---|
| Chen *et al.* (2017) | 40 | 40 | 13.90 | -0.621 | -1.066 | -0.177 |
| Kemp *et al.* (2012) | 73 | 94 | 29.35 | -0.289 | -0.595 | 0.017 |
| Khandoker *et al.* (2017) | 32 | 29 | 11.16 | -0.009 | -0.505 | 0.487 |
| Schulz *et al.* (2010) | 57 | 57 | 20.41 | -0.311 | -0.677 | 0.056 |
| Schumann *et al.* (2017) | 29 | 29 | 10.60 | -0.198 | -0.707 | 0.311 |
| Udpa *et al.* (2007) | 40 | 40 | 14.58 | -0.063 | -0.497 | 0.371 |
| Overall ES | | | | -0.266 | -0.431 | -0.100 |

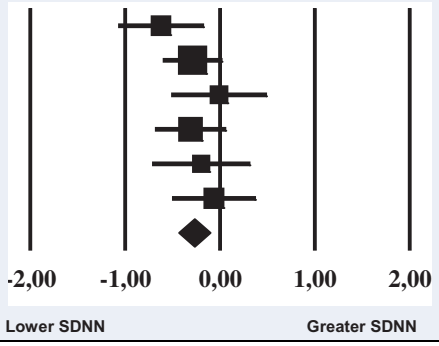
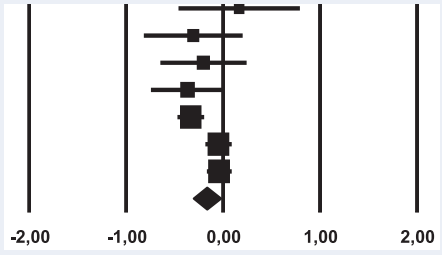



**Table 7.** Random-effects meta-analysis forest plot for IBI: Comparison between patients with Major Depression (MD) and healthy controls (HC).

| Study | Sample Size MD | HC | weight % | Hedges´*g* | CI, lb. | CI, ub. |
|---|---|---|---|---|---|---|
| Chang *et al.* (2015) | 591 | 421 | 23.81 | -0.047 | -0.172 | 0.078 |
| Chang *et al.* (2012) | 498 | 462 | 23.63 | -0.333 | -0.460 | -0.206 |
| Chen *et al.* (2017) | 40 | 40 | 7.73 | -0.203 | -0.638 | 0.233 |
| Khandoker *et al.* (2017) | 32 | 29 | 6.27 | -0.308 | -0.807 | 0.191 |
| Schulz *et al.* (2010) | 57 | 57 | 9.79 | -0.366 | -0.733 | 0.002 |
| Yeh *et al.* (2016) | 618 | 506 | 24.34 | -0.040 | -0.157 | 0.077 |
| Yeragani *et al.* (1991) | 19 | 20 | 4.44 | 0.165 | -0.451 | 0.782 |
| Overall ES | | | | -0.163 | -0.304 | -0.022 |




Given the controversies about unfavorable effects of antidepressants on HRV (Kemp *et al.*, 2010, 2011, 2016; Licht *et al.*, 2010, 2011; Huang *et al.*, 2016), this meta-analysis with unmedicated samples clearly demonstrates that reductions in HRV are prevalent in depressed patients without antidepressants. However, effect sizes for differences in HRV measures between depressed patients and controls are substantially smaller than effects sizes for the reduction of HRV when starting the use of tricyclic or noradrenergic antidepressants (Licht *et al.*, 2010). These observations strengthen the assumption that HRV alterations in MD may be overestimated when studying patients who use antidepressants. In addition, although our findings result from cross-sectional analyses, the small to moderate effect sizes observed in this work may suggest that lower HRV does not completely explain the risk of CVD associated with MD. This is in line with previous research indicating that no single biological or behavioral factor accounts for more than a fraction of the total risk of CVD associated with depression (Carney and Freedland, 2017).

Our findings mostly support the results of a previous meta-analysis by Kemp *et al.* (2010), although these authors report a larger elevation in LF/HF ratio in MD than in our analysis. A further difference is that our study indicates a significant reduction in LF-HRV in MD while Kemp *et al.* (2010) found no evidence for differences in LF-HRV between patients and controls. Importantly, a recent meta-analysis focusing on late-life depression (Brown *et al.*, 2018) did not observe alterations in HF-HRV in MD but, consistent with our findings, a significant reduction in LF-HRV in MD (Brown *et al.*, 2018). Another recent meta-analysis of HRV alterations in childhood and adolescent depression suggests that HF-HRV was lower in children with depression than in controls, but the authors did not analyze LF-HRV alterations (Koenig *et al.*, 2016). A possible reason why the present and previous meta-analyses (Kemp *et al.*, 2010; Koenig *et al.*, 2016) found differences in HF-HRV between MD and nondepressed controls while the meta-analysis including patients with late-life depression and older nondepressed participants did not (Brown *et al.*, 2018), may be because HF-HRV declines with aging (Jandackova *et al.*, 2016). Further reasons for partly differing results are speculative but it is important to note that our work considers a substantially larger number of patients with MD for analyses than previous publications. Our findings might thus provide more robust results.

Given the increased risk of patients with MD for CVD (Rugulies, 2002; Nicholson *et al.*, 2006*a*, 2006*b*; van der Kooy *et al.*, 2007; Meng *et al.*, 2012; Shaffer *et al.*, 2012; Gan *et al.*, 2014; Wu and Kling, 2016), reduced HRV has been considered an indicator of autonomic imbalance and one potential mediator in the relationship of depression and other stress-related states and conditions with poor health outcomes (Kop *et al.*, 2010; Kemp *et al.*, 2017). Reduced HRV and other indicators of autonomic dysfunction interact with peripheral inflammation, a further potential pathway between MD and CVD (Howren *et al.*, 2009; Dowlati *et al.*, 2010; Rief *et al.*, 2010; Haarala *et al.*, 2011; Euteneuer *et al.*, 2012; Jarczok *et al.*, 2014; Halaris, 2016). Reduced HRV is not a specific feature of depression but rather a transdiagnostic marker of health and well-being which can be

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affected by several medical, psychosocial and behavioral factors (e.g. medical conditions, drugs, nutrition, smoking, physical activity) (Rozanski *et al.*, 2005; Eller *et al.*, 2011; Nemeroff and Goldschmidt-Clermont, 2012; Elderon and Whooley, 2013; Shaffer *et al.*, 2014; Cohen *et al.*, 2015; Pieritz *et al.*, 2016; Kemp *et al.*, 2017; Gidron *et al.*, 2018; Young and Benton, 2018).

One important question in the context of HRV and depression is, whether interventions that aim to reduce depressive symptoms can also improve HRV in these patients. There is a large debate on whether antidepressants affect HRV. While tricyclic antidepressants seem to reduce HRV, findings for Serotonin Reuptake Inhibitors (SSRIs) or specific subgroups of SSRIs respectively are not clear or mainly result from cross-sectional studies which allow no causal assumptions (Kemp *et al.*, 2010, 2016, 2011; Licht *et al.*, 2011; Huang *et al.*, 2016). The impact of psychological interventions on HRV in patients with MD without CVD is understudied and may be a promising aim for future studies. In an ongoing randomized controlled trial of our research group, we intend to address this issue by examining whether cognitive behavioral therapy, a standard treatment for depression, improve HRV in patients with MD (Euteneuer and Rief, 2016). Previous research indicates that cognitive behavioral therapy has beneficial effects on HRV in depressed patients with CVD and in older patients with manifest cardiovascular risk factors (Carney *et al.*, 2005; Taylor *et al.*, 2009). Moreover, a recent preliminary study with a small sample of female college students with MD suggests that combining HRV biofeedback with psychotherapy reduces not only depressive symptoms but also increases HRV (Caldwell and Steffen, 2018). Therefore, from a translational perspective, future studies should examine (i) which kind of interventions improve HRV in MD and (ii) whether a potential increase in HRV reduces risk for CVD or possibly, reduces other biological risk factors for CVD (e.g. inflammation). In this context, it may be of relevance which mechanisms may underlie a potential increase in HRV during psychological treatments. Although speculative, potential mechanisms may include several interrelated factors such as cognitive-affective mechanisms (e.g. mood changes, better cognitive skills to cope with stressors) and behavioral factors (e.g. increased physical activity, relaxation).

This study has important strengths. To determine HRV alternations in MD this set of meta-analyses considered a total of $N = 4220$ subjects. We further conducted separate meta-analyses for specific HRV measures providing a more comprehensive picture for HRV alterations in MD. Finally, we examined the moderating role of study quality, which is *per se* an important contribution to the existing literature. This study also has limitations. A conservative approach was taken in the process of study selection. For example, studies, in which only a very few of the participants did not entirely fulfill our inclusion criteria (e.g. in one study some patients received a low dose of Lorazepam and in another, a low dose of benzodiazepines) were excluded from analyses. On the one hand, this procedure may draw a clear picture of the impact of MD on HRV in the absence of any medication effects. On the other hand, excluding samples with medication may also bias meta-analytic findings in terms of an underestimation of HRV alterations in MD. In addition, our meta-analyses based on cross-sectional studies and do not provide any causal explanation of the relationship between MD and HRV. In this context, it is important to note that we are not able to identify potential mediators between MD and reduced HRV, for example differences between patients and controls in lifestyle factors such as smoking or nutrition.

To conclude, this set of meta-analyses strengthens evidence that MD is associated with alterations in several measures of HRV, a transdiagnostic indicator of stress and cardiovascular health with potential predictive value for poor health outcomes.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S0033291719001351.

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**Author contributions.** C.K. and F.E. conceptualized the study and extracted the data. F.E. and C.K. wrote the original draft. All authors reviewed and revised the original draft. C.K. performed statistical analysis. S.S. and M.W. rated the study quality.

**Conflict of interest.** None.

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